Clinical Response rOPC
MITT and EE/C/I97-330
Per Applicant

Efficacy Outcome	Protocol Version Enrollment		
	Original	Amended	Total
MITT	**n=89**	**n=87**	**n=176**
Responder (Cure and Improved)	67 (75.3)	65 (74.7)	132 (75.0)
Non-Responder	21 (23.6)	21 (24.1)	42 (23.9)
Missing Post-Baseline Evaluation	1 (1.1)	1 (1.1)	2 (1.1)
EE	**N = 81**	**N = 77**	**N=158**
Responder	66 (81.5)	63 (81.8)	129 (81.6)
Non-Responder	15 (18.4)	14 (18.2)	29 (18.4)

Responders=number of subjects who achieved a cure (absence of plaques or ulcers and no or minimal symptoms) + number of subjects who improved (partial resolution of pre-treatment signs and symptoms of *Candidiasis*).

Comment: An analysis of the all treated population revealed that of the 199 subjects, 42 had an imputed response (21.1%). In all, 102 subjects were considered cured (51.2%), 42 were considered improved (21.1%), 26.1% were considered failures and 3 subjects had missing data. Of these subjects the failures were imputed responses. Generally it would appear that posaconazole is effective in at least 51% of subjects with refractory disease.

In Study P00298, 85.6% (77/90) of subjects in the MITT subset and 88% (66/75) of subjects in the efficacy-evaluable subset were clinical responders at the end of the 3-month acute treatment period. There was a higher clinical response in the previously treated with posaconazole group as compared to the posaconazole naïve group.

Comment: *The 80 % success rate in the posaconazole naïve group is approximately the expected response rate based on the results in study 330.*

Table 40
Clinical Response rOPC
MITT and EE/P0298
Per Applicant

Efficacy Outcome	Enrollment Strata		
	POS Treated	POS Naive	Total
MITT	**n=59**	**n=31**	**n=90**
Responder	52 (88.1)	25 (80.7)	77 (85.6)
Non-Responder	5 (8.5)	4 (12.9)	9 (10)
Missing	2 (3.4)	2 (6.5)	4 (4.4)
EE	**N = 50**	**N = 25**	**N=75**
Responder	46 (92)	20 (80)	66 (88)
Non-Responder	4 (8)	4 (16)	8 (10.7)

Missing	1 (4)	1 (1.3)

Response = 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*).
POS treated = Subjects who were enrolled and treated under the previous POS protocol
POS naïve = Subjects who had not received POS prior to enrollment. Also includes one subject (Subject No. 37/100) who was previously treated under

Clinical Response Rates at the End of the Acute Treatment Period by Baseline Fluconazole or Itraconazole Minimum Inhibitory Concentration (C/I97-330, P00298)

In vitro susceptibility testing at baseline demonstrated that a large number of MITT subjects in both C/I97-330 and P00298 had *Candida* isolates that were of reduced susceptibility to azoles by current NCCLS criteria at Baseline (baseline fluconazole MIC_{50} = 64 µg/mL for any *Candida* species and baseline itraconazole MIC_{50} values = 0.5 µg/mL for any *Candida* species (n=195) and 0.25 µg/mL for *C. albicans*);.

For subjects in the MITT subset in Study C/I97-330, clinical response rates by baseline fluconazole and/or itraconazole MICs (microbiological resistance) were analyzed using the following breakpoints:
• Fluconazole: susceptible (≤8 µg/mL), dose dependent (>8 µg/mL to ≤32 µg/mL), and resistant (>32 µg/mL).
• Itraconazole: susceptible (≤0.125 µg/mL), dose dependent (>0.125 µg/mL to <1.0 µg/mL), and resistant (≥1.0 µg/mL).

Comment: The MIC breakpoints were based on the current CLSI MIC breakpoints. In addition, data for the dose-dependent population were analyzed separately from those for the resistant population. As per the NCCLS guidance, 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.

Among subjects in the MITT subset of study 330, 19% (33/170) of subjects had a *Candida* isolate that was susceptible to fluconazole at Baseline and 24% (41/169) had a *Candida* isolate that was susceptible to itraconazole at Baseline

Comment: *These findings supported the fact that the subjects enrolled in this study were subjects with refractory disease that required higher azole doses or alternative suppressive treatments for their OPC. However as noted above not all subjects had clinically refractory disease and/or resistant isolates. The determination of refractory diease or not was more of a clinical decision based on previous treatment and in the appropriate clinical setting.*

For subjects in the MITT subset with any *Candida* isolate at Baseline, 73% (67/92) with baseline fluconazole resistance, 74% (49/66) with baseline itraconazole resistance, and 73% (42/57) with resistance to both azole antifungals were clinical responders (1month assessment).

Comment: *Of note in this analysis were the decreasing response rates as the MIC increased.*

For those subjects with *C. albicans*, 68% (25/37) with baseline resistance to both fluconazole and itraconazole were clinical responders.

Comment: These response rates correlated with the overall clinical response rate for subjects in the MITT population (75%, 132/176).

Table 41
Clinical Response Rates for Any *Candida* and *Candida albicans* Baseline Isolates
Number (%) of Clinical Responders by Baseline Fluconazole and/or Itraconazole MIC Values Based on the CLSI MIC Breakpoints
Modified Intent-to-Treat Subset
Protocol No. C/I97-330

		Any *Candida*		*Candida albicans*	
MIC Breakpoints (μg/mL)[a]		**n_b**	**Number (%) of Responders**	**n_b**	**Number (%) of Responders**
Fluconazole:					
Susceptible	≤8	33	30 (91)	37	35 (95)
Dose Dependent	>8 to ≤32	45	37 (82)	45	35 (78)
Resistant	>32	92	67 (73)	71	51 (72)
Total		170	134 (78.8%)	153	(79%)
Itraconazole:					
Susceptible	≤0.125	41	37 (90)	46	41 (89)
Dose Dependent	>0.125 to <1.0	62	47 (76)	62	48 (77)
Resistant	≥1.0	66	49 (74)	44	31 (70)
Combination of Fluconazole and Itraconazole:					
Dose Dependent or Resistant	Fluconazole >8, Itraconazole >0.125	115	84 (73)	93	66 (71)

Resistant	Fluconazole >32 Itraconazole ≥1.0	57	42 (73)	37	25 (68)

a: Results other than a standard concentration value are assigned to the next higher standard concentration value. If a subject has multiple values within an organism, the maximum value within that species was used.
b: Number of subjects with a baseline MIC value that met the specified criteria.

***Comment**: Clinical response rates for subjects with other azole-resistant Candida species identified at Baseline can be seen below. Only for Candia glabrata were there enough isolates to make any substantive statements. For subjects with C. glabrata at Baseline, 67% (12/18) with baseline resistance to fluconazole, 76% (19/25) with baseline resistance to itraconazole, and 71% (12/17) with baseline resistance to both azoles were clinical responders. There were too few subjects with azole-resistant C. krusei or C. tropicalis at Baseline to draw any conclusions but clinical success rates were consistent with those obtained overall in subjects with these isolates.*

Table 42
Clinical Response Rates for other *Candida* spp. Baseline Isolates
Number (%) of Clinical Responders by Baseline Fluconazole and/or Itraconazole MIC Values Based on the CLSI MIC Breakpoints
Modified Intent-to-Treat Subset
Protocol No. C/I97-330

MIC Breakpoints (µg/mL)[a]	*Candida glabrata*		*Candida dublinensis*		*Candida tropicalis*		*Candida Inconspicua*		*Candida krusei*		*Candida Norvegensis*	
Fluconazole												
Susceptible ≤8	11	9 (82)	2	2 (100)	1	1 (100)	0	0	0	0	0	0
DD >8 to ≤32	10	8 (80)	0	0	0	0	1	1 (100)	2	2 (100)	0	0
Resistant >32	18	12 (67)	0	0	4	3 (75)	0	0	7	6 (86%)	1	1 (100)
Total	39	29 (74)	2	2 (100)	5	4 (80)	1	1 (100)	9	8(89)	1	1 (100)
Itraconazole												
Susceptible ≤0.125	3	2 (67)	2	2 (100)	2	2 (100)	1	1 (100)	0	0	1	1 (100)
DD >0.125 to <1.0	11	8 (73)	0	0	1	0	0	0	5	4 (80)	0	0
Resistant ≥1.0	25	19 (76)	0	0	2	2 (100)	0	0	4	4 (100)	0	0
Total	39	29 (74)	2	2 (100)	5	4 (80)	1	1 (100)	9	8(89)	1	1 (100)
DD or Resistant Fluconazole >8, Itraconazole >0.125	27	20 (74)			3	2 (67)			9	8 (89)		
Resistant Fluconazole >32 Itraconazole ≥1.0	17	12 (71)			2	2 (100)			4	4 (100)		

Clinical Relapse Rate During The 4 Week Post-Treatment Follow- Up Period

In study C/I97-330, a 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. At Week 4 of Follow-up (defined as 23 through 37 days after the last dose of study drug), 28.8% (38/132) of all MITT subjects who were responders at Treatment Endpoint relapsed: there was difference in the number of subjects that relapsed between the original and amended protocols (32.8% (22/67O) and 24.6% (16/65A). Conversely, 10.4% (7/67) versus 18.5% (12/65) of subjects treated under the original versus amended protocols, respectively, had a sustained clinical response..

Comment: *The post treatment follow-up visit may have occurred at different times during the study for subjects enrolled in the original protocol (after acute treatment or maintenance) or amended protocol (after acute treatment). However, many of these latter subjects did not enter the follow-up period at all, as they were enrolled immediately into Study P00298. More than half of the subjects who were clinical responders at Treatment Endpoint were not assessed in the post treatment follow-up period. The findings suggest that the higher dose of posaconazole is more effective in this population.*

Table 43
Relapse Rate
MITT Study C/I97-330

	Protocol Version Enrollment		
Relapse Rate MITT	**Original (n=67)**	**Amended (n=65)**	**Total (n=132)**
Non-Relapse	7 (10.4)	12 (18.5)	19 (14.4)
Relapse	22 (32.8)	16 (24.6)	38 (28.8)
Not Assessed (cultures not obtained)	38 (56.7)	37 (56.9)	75 (56.8)

In study 0298, 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. Relapse was defined as the recurrence after discontinuation of therapy following a complete response or improvement. However, the majority of MITT subjects were not assessed for clinical relapse 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. An additional 4 subjects 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.

Mycological Response

In Study C/I97-330, mycological cultures were not required at the EOT assessment for subjects who were clinical responders or for those continuing posaconazole in Study P00298 for long-term therapy. Cultures were not obtained for 50 of 176 (28.4%) subjects in the MITT subset and 37 of 158 (23.4%) subjects in the EE subset.

At Week 4, 36.5% (46/126) of MITT subjects and 38.0% (46/121) of efficacy-evaluable subjects were mycological responders (mycological success, ≤20 CFU/mL for all *Candida* species isolated at Baseline. Mycological success rates were similar for subjects treated under the original and amended protocols (35.4%, 23/65 versus 37.7%, 23/61, respectively).

Comment: *The lack of a successful mycologic response in 62% of subjects may be related to the subjects' underlying immunosuppression as well as to the development of posaconazole tolerant isolates.*

Table 44
Mycologic Response week 4
MITT study 330

Mycological Response	Protocol Version Enrollment		
	Original (n=65)	Amended (n=61)	Total (n=126)*
Responder	23 (35.4)	23 (37.7)	46 (36.5)
Non-Responder	41 (63.1)	37 (60.6)	78 (61.9)
Missing Post-Baseline Clinical Evaluation	1 (1.5)	1 (1.6)	2 (1.6)

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.
*Fifty subjects (24 in Original + 26 in Amended Protocol) were not assessed (cultures were not obtained)

Of the 126 MITT subjects in C/I97-330 with mycological cultures at the EOT, 116 subjects were clinical responders. The correlation between clinical and mycological response rates was low: 39.7% (46/116) of MITT subjects who were clinical responders were also mycological responders at Week 4. The percentages of subjects who were both clinical and mycological responders were similar for subjects treated under the original and amended protocols: 34.3% (23/60) in the original protocol and 35.4% (23/56) in the amended protocol.

Comment: The low correlation between clinical and mycological response rates may be explained by the expected continued Candida oropharyngeal colonization and the inability to sterilize the OP cavity. The absence or the improvement of signs and symptoms, despite a persistent positive culture result may be a better indicator of effectiveness in the population under study.

Table 45
Correlation between Clinical and Mycologic response Week 4
Study C/I97-330 MITT

Overall Mycological Response at Week 4	Clinical Response at Week 4			
	Responder (n=116)	Non-Responder (n=8)	Total (n=126)	Missing (n=2)
Responder	46 (39.7)	0	46 (36.5)	--
Non-Responder	70 (59.3)	8 (100.0)	78 (61.9)	--
Missing Clinical Evaluation	--	--	2 (1.6)	2 (100.0)

Fifty subjects (16 responders and 34 non-responders) were not assessed (cultures were not obtained).

In Study P00298, cultures were not required at the end of the 3-month acute treatment period for subjects who were clinical responders. Cultures were only required for subjects considered treatment failures, relapses, or as clinically indicated. Cultures were not

obtained for 39 of the 90 subjects in the MITT subset at the end of 3-month acute treatment period, and the majority of subjects continued immediately into the maintenance period. Mycological assessments at the end of the 3-month acute treatment period were available for only 57% (51/90) of subjects in the MITT population. At the end of the 3-month acute treatment period, 17.6% (9/51) of MITT subjects with mycological assessments were mycological responders (≤20 CFU/mL). 8 of the 9 (89%) mycological responders in the MITT subset were clinical responders. For the other mycological responder, the clinical response was missing/unknown

Mycological response rates by baseline fluconazole and/or itraconazole MICs (microbiological resistance) were analyzed in Study C/I97-330 based on the current CLSI MIC breakpoints for subjects in the MITT subset.

Among subjects in the MITT subset, 21% (26/125) of subjects had a *Candida* isolate that was susceptible to fluconazole at Baseline and 24% (30/124) had a *Candida* isolate that was susceptible to itraconazole.

For subjects in the MITT subset with any *Candida* isolate at Baseline, 31% (19/61) with baseline resistance to fluconazole, 22% (11/49) with baseline resistance to itraconazole, and 25% (10/40) with baseline resistance to both fluconazole and itraconazole were mycological responders. For those subjects with *C. albicans*, 28% (8/29) with baseline microbiological resistance to both fluconazole and itraconazole were mycological responders.

Table 46
Mycological Response: Number (%) of Mycological Responders by Baseline Fluconazole and/or Itraconazole MIC Values Based on CLSI MIC Breakpoints
Modified Intent-to-Treat Subset
Protocol No. C/I97-330

		Any *Candida*		*Candida albicans*	
MIC Breakpoints (μg/mL)[a]		**n_b**	**Number (%) of Responders**	**n_b**	**Number (%) of Responders**
Fluconazole:					
Susceptible	≤8	26	12 (46)	29	12 (41)
Dose Dependent	>8 to ≤32	38	9 (24)	38	9 (24)
Resistant	>32	61	19 (31)	48	16 (33)
Total		125	40 (32)	115	37 (32.1)
Itraconazole:					
Susceptible	≤0.125	30	17 (57)	33	16 (48)
Dose Dependent	>0.125 to <1.0	45	12 (27)	45	12 (27)
Resistant	≥1.0	49	11 (22)	36	9 (25)
Total		124	40 (32)	114	37 (32)
Combination of Fluconazole and Itraconazole:					
Dose Dependent or Resistant	Fluconazole >8, Itraconazole >0.125	84	20 (24)	71	19 (27)
Resistant	Fluconazole >32 Itraconazole ≥1.0	40	10 (25)	29	8 (28)

Table 47
Clinical Response Rates for other *Candida* spp. Baseline Isolates
Number (%) of Clinical Responders by Baseline Fluconazole and/or Itraconazole MIC Values Based on the CLSI MIC Breakpoints
Modified Intent-to-Treat Subset
Protocol P0298

MIC Breakpoints (µg/mL)[a]	*Candida glabrata*		*Candida dublinensis*		*Candida tropicalis*		*Candida Inconspicua*		*Candida krusei*		*Candida Norvegensis*	
Fluconazole												
Susceptible ≤8	9	2 (22)	1	0	1	0	0	0	0	0	0	0
DD >8 to ≤32	6	0	0	0	0	0	1	0	2	0	0	0
Resistant >32	12	1 (8)	0	0	2	1 (50)	0	0	4	1 (25%)	1	1 (100)
Total	27	3 (1)	1	0	3	1 (33)	1	0	6	1 (16.6)	1	1 (100)
Itraconazole												
Susceptible ≤0.125	2	1 (50)	1	0	2	1 (50)	1	0	0	0	1	1 (100)
DD >0.125 to <1.0	9	1 (11)	0	0	0	0	0	0	3	0	0	0
Resistant ≥1.0	16	1 (6)	0	0	1	0	0	0	3	1 (33)	0	0
	27	3 (1)	1	0	3	1 (33)	1	0	6	1 (16.6)	1	1 (100)
DD or Resistant Fluconazole >8, Itraconazole >0.125	18	1 (6)			3	2 (67)			6	1 (17)		
Resistant Fluconazole >32 Itraconazole ≥1.0	11	1 (9)			2	2 (100)			3	1 (33)		

Comment: Mycologic success rates were very low independent of the spp.

Mycological Response Rates for Subjects With a Final Clinical Response of Failure or Relapse at Any Time During Study 330

Final culture results were evaluated for all MITT subjects with a final clinical response of either failure or relapse at any time during the treatment, maintenance, or follow-up phases. Twenty-three MITT subjects were considered failures. Seventy-seven MITT subjects who had initially responded to therapy had a final clinical response of relapse at another later point in the study. The majority of the relapses/failures occurred following study drug discontinuation. *Candida* species isolated at Baseline for the subjects in Study C/I97-330 were predominantly microbiologically resistant to both fluconazole and itraconazole. Final culture results in about one fourth of relapses or failures showed a 4-fold increase in MIC values to posaconazole of one or more *Candida* species present at Baseline.

There were 21 subjects whose final culture demonstrated the emergence of a *Candida* species that was not present at Baseline; 11 *C. glabrata*, 6 *C. albicans*, 1 each of *C. dublinensis*, *C. parapsilosis*, *C. tropicalis*, and *C. krusei*. Ten strains remained susceptible to posaconazole (MIC ≤1.0 mcg/mL) and eleven strains had increased MIC values to posaconazole (MIC ≥2.0 mcg/mL). Subjects had received posaconazole from 20 to 129 days prior to the emergence of the new organism; median of 95 days.

Additional Agency Analyses:

As per the Applicant, "Most 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.

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 protocol:

- 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 refractory disease from relapse or recurrence off of treatment.

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.

LIST:

C97330	30	00001	28	DIFLUCAN	200MG | PO | QD
C97330	10	000003	47	FLUCONAZOLE	400MG | PO | QD
I97330	4	000003	376	ITRACONAZOL	200 MG | PO | QD
I97330	4	000006	20	ITRACONAZOLE	200 MG | PO | QD
I97330	4	000008	34	ITRACONAZOLE	200MG. | P.O | Q.D
I97330	4	000010	25	ITRACONAZOLE	200 MG | PO | QD
I97330	11	000005	365	FLUCONAZOLE	100MG | PO | QD

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.

Clinical and Mycologic efficacy by patient were assessed at week 4 of treatment (the end of the acute treatment phase, CR330WK4, the primary endpoint; all patients had this visit either on the last day of treatment or on the day before maintenance), at follow-up 4 weeks after the end of treatment (CR330FU4, this visit occurred 4 weeks after the last dose and in subjects and is an OFF treatment evaluation in those subjects that had this assessment; subjects who did not have this assessment were those that were lost to follow-up). A final evaluation off of any treatment was also provided (Follow-up EOT) this was an earlier EOT assessment that was primarily performed in subjects who relapsed. The value of this asessement was 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.

Table 48
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 questionable as a repeat culture was not required and were obtained in few subjects.

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.

7. Dosing, Regimen, and Administration Issues

The applicant is currently seeking approval for the 200 mg PO loading dose followed by the 100 mg PO QD x 13 days dose for OPC and for the 400 mg PO BID dose for refractory disease.

In support of the former OPC regimen, the applicant submitted the results of a dose-response study in subjects with azole-susceptible OPC (C/I96-209) that suggested that although no clear clinical dose response was observed for posaconazole 50 mg, 100 mg, 200 mg, or 400 mg QD, that both the 400 mg and the 100 mg doses were efficacious. Issues that may have led to the lack of a dose response included the use of a high loading dose (400 BID) at all dose levels and the long half life of the drug with some resultant prolonged treatment effect of the loading dose. Although statistical conclusions could not be drawn, it appeared as if the 400 and 100 mg doses were clinically comparable between them and each was also comparable to fluconazole in the MITT and PP populations. The 50-mg dose of posaconazole was numerically inferior to fluconazole.

No dose-response was observed for posaconazole 50 mg, 100 mg, 200 mg, and 400 mg based on mycological success rates (≤20 CFU/mL) in Study C/I96-209 at the EOT and the mycologic eradication results were numerically inferior to those attained on the fluconazole arm.

Posaconazole 100 mg QD was confirmed as effective as fluconazole in treating subjects with azole-susceptible OPC in Study C/I97-331. A loading dose was utilized on both treatment arms. The higher success rates in this study as compared to the Phase II study may have been due to the topical effects of the oral suspensions used on both treatment arms and to the somewhat greater bioavailibity of the oral posaconazole formulation.

In the refractory disease study C/I97-330, the comparison of posaconazole dosing regimens between protocol versions (400 mg BID for 3 days, followed by 400 mg QD for 25 days in the original protocol and 400 mg BID for 28 days in the amended protocol) allowed a comparison of the clinical response rates among subjects enrolled under the two protocol versions. Clinical success rates were similar for subjects in the original and amended protocols (75.3%, 67/89 and 74.7%, 65/87, respectively but 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 a more sustained response at the higher dose.

These clinical results in conjunction with the high baseline MIC_{50} values of most of the *Candida albicans* isolates versus fluconazole (> 32 µg/mL) revealed that in an HIV infected population of subjects with severe immunosuppression that has received previous courses of fluconazole treatment and that has isolates that are less susceptible to traditional fluconazole treatment regimens, a dose of 400 mg PO BID is necessary to achieve and maintain a clinical response.

Of 239 unique subjects treated with posaconazole in the two azole-refractory OPC (Study C/I97-330 and Study P00298), the majority of subjects were immediately enrolled in a 12-month maintenance period as most investigators felt that continued suppressive therapy was clinically warranted in this population.

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) of subjects took posaconazole for at least 12 months. The mean duration of treatment was 154 days, and the maximum duration of exposure was 18 months. 67% (10/15) of subjects treated with posaconazole for at least 12 months had continued clinical success (cure or improvement) at the last assessment.

Safety as it pertains to the OPC/rOPC indication:

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 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%).

Of note, 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 however a concomitant effect of POS could not be ruled out. 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				
	Controlled OPC Pool				Refractory OPC Pool
	POS		FLZ		POS
Adverse Event	n=557		n=262		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)

SAEs:

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 compromised 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.

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 rIFI 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.

Discontinuations and Deaths:

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 CRFs. 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.

Patient 40/003: 43YO received 14 days of FLU 100 QD. 3 weeks after treatment found dead, sudden death.

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.

Cases synopses for the 2 neutropenic subjects are reproduced below:

Patient 15/002 Sex: Male Age: 41
Treatment and Regimen Assigned: Posaconazole 400 mg QD: Group 1
Reason for Summary: Death; Serious Adverse Event: Neutropenia, Cerebral Hemorrhage, Pulmonary Infiltration
Summary: 41-year-old HIV (+) male subject with a history of neutropenia, cerebral toxoplasmosis and herpes zoster initiated posaconazole 400 mg QD on 18 JUN 1998 for OPC. The subject had a Grade 2 neutropenia on 15 JUN 1998, a Grade 3 neutropenia on 25 JUN 1998 and a Grade 4 neutropenia on 06 JUL 1998. Study medication was discontinued after the 06 JUL 1998 dose. On 09 JUL 1998, the subject recovered without any intervention; Neupogen SC every 2 days was initiated ongoing from 15 JUL 1998. Study drug was restarted on 27 JUL 1998 without Sponsor approval, and the investigator was advised by the Sponsor's monitor that the study medication should be discontinued. Antiretroviral therapy was changed to didanosine, efavirenz, hydroxvurea, indinavir, and ritonavir. The last dose of posaconazole was taken on 13 AUG 1998. On —— the subject complained of headaches lasting a few hours without associated visual changes or photophobia. The subject had one episode of vomiting. The subject also reported a 2-week history of speech and memory problems. Later that same day, he was found lying on the floor, not fully responsive and limbs were shaking. The subject was verbalizing incomprehensible sounds, but no incontinence or tongue biting occurred. The subject was hospitalized. Angiography results revealed no aneurysm or signs of vasculitis. Intraventricular hemorrhage was diagnosed. The subject received extensive concomitant medical treatment, including multiple antibiotics, pain medication and intravenous fluids but died in hospital on —— due to intraventricular hemorrhage. An autopsy was not performed. The investigator considered all of the events and the death to be unlikely related to study medication.
MO agreed with investigator/sponsor determination of death but disagreed regarding attribution of worsening neutropenia.

Subject: 09-100 **Sex:** Male **Age:** 44
Treatment and Regimen Received: Posaconazole 800 mg/day
Reason for Summary: Serious Adverse Events: fever, *Enterococcus faecalis* endocarditis, meningitis, Grade-4 neutropenia, cytomegalovirus retinitis, tuberculosis pneumonia, end stage AIDS Death
Summary: 44-year-old HIV (+) male subject with a history of *PCP*, adrenal insufficiency, anemia, neutropenia, tuberculosis, CMV retinitis and esophagitis, *Clostridium difficile* colitis, HIV enteropathy, and vancomycin-resistant Enterococcus (+) stool, initiated study drug on 27 MAR 2001 for refractory OPC. Concomitant medications included Bactrim DS, Sustiva (efavirenz), Combivir (lamivudine/zidovudine), Neupogen, rabeprazole, and ganciclovir. On —— , he was hospitalized for evaluation of fevers. Blood cultures were positive for *Enterococcus faecalis.* CXR showed bilateral, bibasilar opacities. He was treated with ampicillin and gentamicin. The subject was diagnosed on 27 APR 2001 with CMV retinitis. Ganciclovir was administered. Transesophageal echocardiogram performed on —— showed mitral valve endocarditis. He was also diagnosed with meningitis. During hospitalization, Grade-4 neutropenia developed. Neupogen was given. On —— , the subject was discharged. The neutropenia had resolved. On —— , he was hospitalized for pneumonia, r/o TB. He was discharged to hospice and died on —— due to complications of end-stage AIDS. The last documented dose of study drug was

06 JUN 2001, although doses were missed throughout the study due to multiple hospitalizations. The investigator considered the neutropenia to be probably related to study drug. The remainder of the events and the death were considered unlikely related to study drug.

Grade 3 or Grade 4 AEs

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).

In the Controlled OPC Pool, there were no treatment related Grade 4 AEs for subjects in either treatment pool. Treatment related Grade 3 AEs reported for more than one subject in either treatment pool were headache, neutropenia, and nausea (each reported for 3 subjects on posaconazole and no subject on fluconazole) and abdominal pain (reported for 2 subjects on posaconazole and no subject on fluconazole).
Comment: Of note were the 7 Grade 3 reports of neutropenia in the POS treated controlled OPC population as compared to the 2 reports in the FLU treated subjects.

In the Refractory OPC Pool 138/239 (58%) subjects reported Grade 3 AEs and 60/239 (25%) of subjects reported Grade 4 AEs. The most commonly reported Grade 3 AEs were neutropenia (8%), fever (6%), asthenia (5%), anemia (5%), and vomiting (5%). The most commonly reported Grade 4 AEs were neutropenia and AIDS (5% each).

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).

Grade 3 and Grade 4 Treatment-Emergent Adverse Events by Dose

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.

Comment: Neutropenia was reported in 7% of the < 800 mg subjects and in 9% of the ≥ 800 mg/day subjects and there were 4 (3%) reports of hepatic enzymes increased, hepatitis and SGOT increased at the higher dose as compared to none at the lower doses. The potential for a dose related increase in AEs (both those events strongly associated with POS as well as other azoles such as nausea, vomiting, as well as for more significant events such as neutropenia and liver dysfunction) appears to exist although many of these events may also be related to the underlying disease.

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).

Comment: Although there were fewer episodes of treatment related Grade 4 neutropenia at the proposed ≥ 800 mg dose, there were an increased number of Grade 3 events at this dose level.

Grade 3 and Grade 4 Treatment-Emergent Adverse Events by Time Interval

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 if 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" Neither of these events was considered by the investigator to be treatment related. Below are pertinent case synopses.

Subject I96209-08/001, a 35-year-old man, had an AE of QTc/QT prolongation reported on Day 8, which was considered by the investigator to be unlikely related to treatment with posaconazole. The machine-read QTc interval increased by 50 msec from baseline on Day 8 (from 370 msec to 420 msec), and by 60 msec from baseline on Day 10 (corresponding increases using the QTcF calculation were 41 msec and 51 msec). Two months after completing the study, the QTc interval remained at about 440 msec.

Subject C97330-02/018, a 45-year old man, had an AE of ECG abnormal (literal event term was "prolonged QT interval") reported on Day 15; the QTc interval increased by 36 msec from baseline (424 msec to 460 msec). The subject also had bradycardia, which along with the abnormal ECG, resulted in study discontinuation. Both events for this subject were considered by the investigator to be treatment related.

Comment: The posaconazole treated controlled OPC subjects with abnormal ECGs were reviewed. In all cases subjects had atrial abnormalities including AV block, atrial extrasystoles etc. Treatment was discontinued in only one subject C96209/34/010) who developed a first degree AV block considered related to treatment.

However there appeared to be difference between treatment arms regarding the frequency of ECG abnormalities in the controlled OPC group of subjects.

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.

Comment: The MO reviewed all subjects with changes of at least 60 msec from baseline as well as any male subject with a QT greater than 450 or 500 msec. No subject developed ventricular arrhythmias and generally the abnormalities were non specific. Based on the review of the data, it appears 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.

Baseline data were available in approximately 90% of subjects in both the controlled and refractory OPC pools. In the controlled pool, more than half of the subjects had abnormal baseline values (Grade 1 or higher) for hematocrit and hemoglobin; one-third to one-half of the subjects had abnormal baseline neutrophil counts and leukocyte counts; and approximately 10% to 15% of subjects had abnormal baseline platelet counts. In the Refractory OPC Pool two thirds of subjects had abnormal values for hematocrit,

hemoglobin, and leukocyte counts at baseline; approximately one-half of subjects had abnormal values neutrophil counts; and approximately one-quarter of subjects had abnormal values for platelet counts at baseline.

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.

46/557 posaconazole-treated subjects (8%) and 24/262 fluconazole-treated subjects (9%) developed AEs classified as disorders of blood and lymphatic system, and 11 posaconazole-treated subjects (2%) and 4 fluconazole-treated subjects (2%) had AEs classified as platelet, bleeding and clotting disorders. The most commonly reported hematologic/lymphatic AE was neutropenia (4% with posaconazole and 3% with fluconazole) and 2% on each arm of were classified as treatment-related. Anemia was reported for 2% of both POS treated and FLU treated subjects, and was classified as treatment-related in less than 1% of subjects on each arm. Neutropenia and anemia were considered Grade 3 or Grade 4 events in < 1% of subjects on each arm.

Comment: Seven subjects reported AEs of the blood and lymphatic system that resulted in discontinuation/death (6 POS [1%] and 1 FLU [<1%]), and one POS subject had a platelet, bleeding and clotting disorder that resulted in discontinuation/death.

Three POS subjects (2%) and four FLU subjects (2%) experienced SAEs that were classified as disorders of the blood and lymphatic system, all of which were considered unlikely related to treatment. There were no SAEs classified as platelet, bleeding and clotting disorders.

In the Refractory OPC Pool, 34% of subjects developed AEs classified as disorders of blood and lymphatic system, and 13% had treatment related events. Eight percent (8%) of subjects had AEs classified as platelet, bleeding and clotting disorders, and 4% of subjects had treatment related events. The most commonly reported hematologic AEs were neutropenia (16%), anemia (14%), thrombocytopenia (5%), anemia aggravated (3%), and leukopenia (3%). 15% of subjects had Grade 3 and 6% of subjects had Grade 4 disorders of the blood and lymphatic system, and 3% of subjects had Grade 3 and 1% of subjects had Grade 4 platelet, bleeding, and clotting disorders.

In the Refractory OPC pool, 3% of subjects developed AEs classified as disorders of the blood and lymphatic system and 3% of subjects had platelet, bleeding, and clotting disorders that resulted in discontinuation/death. The more commonly reported of these events were anemia, neutropenia, and thrombocytopenia. In the Controlled OPC Pool, one case of neutropenia was treatment related. In the Refractory OPC Pool, treatment related neutropenia and thrombocytopenia each resulted in discontinuation/death in two subjects (1%). All other events that led to discontinuation/death were reported by one subject each (<1%). A case of fatal disseminated intravascular coagulation (DIC) was reported for one subject in the Refractory OPC Pool, and was considered by the investigator to be unlikely related to treatment.

In the Refractory OPC pool, 38 subjects (16%) experienced an SAE classified as a disorder of the blood and lymphatic system and 7 subjects (3%) experienced SAEs classified as platelet, bleeding and clotting disorders. The events were considered treatment related for 13 (5%) and 2 (1%) subjects, respectively. The SAEs reported by at least 2% of subjects were neutropenia (10%), anemia (4%), anemia aggravated (2%), and thrombocytopenia (2%). Treatment related SAEs reported were neutropenia (5%, n=11), and anemia, anemia aggravated, leukopenia, prolonged prothrombin time, and thrombocytopenia, each reported for one subject.

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.

Comment: In the controlled OPC pool, thrombocytopenia was reported in 4/557 (1%) patients in the posaconazole arm and in 1/262 (<1%) in the fluconazole arm. There were no reports of DIC in the controlled OPC pool.

In the refractory OPC pool, thrombocytopenia was reported in 12/239 (5%) patients. One case of DIC was reported in the refractory OPC pool and was considered by the investigator to be unlikely related to posaconazole. The patient died; however, the death was attributed to the underlying HIV/AIDS with progressive respiratory failure.

There were no cases of TTP or HUS in with pool of OPC subjects.

There were 2 cases of neutropenia (2/557) in the posaconazole OPC treated subjects that were determined to be treatment related. One subject received 50 mg/day and the other received 200 mg/day of POS. In both cases the event was noted 2 -3 days after the EOT and slowly resolved. The lowest counts were 380 and 590 neutrophils per cubic mm.

There were 18 subjects with neutropenia possibly related to treatment in the refractory pool. 9 subjects received the 400 mg QD dose and 9 received 800 mg QD. The event began as early as the seventh treatment day and as late as the 154th day. In 8 cases the counts were 1000 but in none were they less than 200 cells/mm'3.

An explanation for the high incidence of neutropenia in these subjects was difficult given the multiple confounding factors.

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.

8. Use in Special Populations

A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation

No differences were found between treatments arms and across studies regarding efficacy by sex.

B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

No differences were found between treatments arms and across studies regarding efficacy by race or ethnicity. In both studies, the ages of subjects in the posaconazole 100 mg group fell within the range of 18 to 65 years; therefore, no meaningful conclusions could be drawn regarding age-related trends for subjects <18 years or ≥65 years of age.

Table 49
Clinical Response by Gender and Race
MITT OPC

	C/I96-209				C/I97-331			
	POSA 100 QD		FLU 100 QD		POSA 100 QD		FLU 100 QD	
	N	# Responders	N	# Responders	N	# Responders	N	# Responders
Sex								
Female	16	13 (81.3)	20	17 (85.0)	44	39 (88.6)	41	40 (97.6)
Male	75	66 (88.0)	63	57 (90.5)	125	119 (95.2)	119	112 (94.1)
Race								
Caucasian	45	43 (95.6)	36	31 (86.1)	61	56 (91.8)	59	55 (93.2)
Non-Caucasian	46	36 (78.3)	47	43 (91.5)	108	102 (94.4)	101	97 (96.0)

Clinical response rates by baseline demographic characteristics (age, sex, and race), location were also examined in the MITT subjects with refractory disease (Study C/I97-330 at the EOT and in Study P00298 at the end of the acute treatment period (3 months). Only one subject was ≥65 years of age and no subject in either study was <18 years of age; therefore, no meaningful conclusions could be drawn for either study regarding age-related trends for subjects <18 years or ≥65 years of age. Little variation in response was noted among the other subgroups in either study

Table 50
Clinical Response by Gender and Race
MITT rOPC

	C/I97-330a		P00298a	
Subgroup	**N**	**Number (%) of Responders**	**N**	**Number (%) of Responders**
Sex				
Female	21	16 (76.2)	14	12 (85.7)
Male	155	116 (74.8)	76	65 (85.5)
Race				
Non-Caucasian	45	31 (68.9)	25	21 (84.0)
Caucasian	131	101 (77.1)	65	56 (86.2)

a: Number (%) of clinical responders at Week 4 in C/I97-330 and at the End of the 3-month Acute Treatment Period in P00298.

Safety: Age-related comparisons could not be made for this population because there was only one subject in each of the OPC pools (controlled and refractory) who was at least 65 years of age.

In the Controlled OPC pool, AEs were reported in 280/448 (63%) of POS treated males and in 76/109 (70%) of POS treated females as compared to 132/200 (66%) of FLU treated males and 43/62 (69%) of FLU treated females. In the refractory pool 193/206 (93%) of males reported an AE vs. 28/33 (85%) of females.

Comment: The increased rate of AEs seen in both sexes in the refractory group appeared consistent with the more severe underlying disease in this group.

In the controlled group, the incidences of individual AEs were similar between the sexes. In the refractory pool the following differences were seen:

- Asthenia was more often reported for women (24%, 8/33)than for men (11%, 23/206);
- Fatigue was more often reported for men (14%, 29/206) than for women (6%, 2/33).
- Anemia was reported in a higher proportion of women than men (21%, 7/33 for women versus 13%, 27/206 for men)
- Pruritus was more often reported for women than for men (12%, 4/33 for women versus 5%, 11/206 for men).
- Increased sweating (mostly "night sweats") was reported for 11% (22/206) of men and 3% (1/33) of women.
- Neutropenia was reported more frequently in men (35/206 (17%) vs. women (4/33 (12%).
- Dysphagia was reported more frequently in women (4/33, 12%) than men 14/206 (7%).
- Vomiting was reported more frequently in women (12/33, 36%) than men 55/205 (27%).
- Bilirubinemia was reported in 3/33 (9%) of women vs. 3/206 (1%) of men.
- Anxiety and Depression were more common in men (10% and 9%) men vs. 6% women.
- Convulsions were reported for 1% (3/206) of men and 9% (3/33) of women.

Comment: A clear explanation for the increased frequency of convulsions in the refractory OPC pool of women was not identified. Possible causes of seizure activity in this population included CNS lesions including PML as well as toxic or metabolic etiologies.

The proportions of men and women with treatment related AEs were similar for POS and FLU: 27% (119/448) for men and 28% (31/109) for women on POS and 27% (53/200) for men and 27% (17/62) for women on FLU> There were no differences in the types or incidences of treatment related AEs reported for men and women between the two treatments in the controlled OPC pool.

In the refractory OPC pool, the proportions of subjects with treatment related AEs were similar for men (57%, 117/206) and for women (55%, 18/33). Treatment related asthenia and convulsions were more often reported for women than for men: 9% (3/33) and 1% (3/206), respectively, for asthenia; and 6% (2/33) and no subjects, respectively, for convulsions.

Treatment-related neutropenia was more often reported for men (9%, 19/206) than for women (3%, 1/33). Other treatment related AEs that were reported with at least a 5% difference in incidence rates between men and women included headache (12% women, 7% men), abdominal pain (9% women, 4% men), pruritus (6% women, 1% men).

In the Controlled OPC Pool, the proportions of subjects with AEs in each race category were similar for posaconazole and fluconazole. The proportions observed for Hispanics (47% in each treatment pool (60/128 POS, 33/70 FLU) were lower than those observed for Caucasians (164/238 (69%) and 81/108 (75%) on POS and FLU, respectively) and Blacks (97/149 (65%) and 38/56 (68%), respectively). There was a higher proportion of Asian subjects with AEs independent of treatment arm (30/34 (88%) and 18/19 (95%) for subjects on POS and FLU, respectively)

There were no differences in the controlled OPC studies, in the proportions of subjects with treatment-related AEs between posaconazole and fluconazole for any race category. However as expected, on both treatment arms, Asians had more treatment-related AEs (50%, 17/34 on posaconazole; 68%, 13/19 on fluconazole) than Caucasians (33%, 78/238 on posaconazole; 38%, 41/108 on fluconazole), Blacks (20%, 30/149 on posaconazole; 18%, 10/56 on fluconazole), and Hispanics (17%, 22/128 on posaconazole; 9%, 6/70 on fluconazole).

Comment: The higher incidence of AEs in Asians in both the controlled OPC pool as well as the rIFI pool is of note. In both populations, there were relatively few Asian subjects so an adequate assessment is difficult. There was no one event that contributed to the higher incidence, rather the increase was due to the relative increase in AEs of all types compared to the other races in the face of small patient numbers. Possible these differences are due to different metabolism of POS in this population.

In the Refractory OPC Pool, the proportions of Hispanics (10/14, 71%) with AEs was lower than those observed for Caucasians (165/176, 94%) and Blacks (45/48, 94%). As above these differences were not caused by any one event and again the number of Hispanic subjects was too small to allow for valid conclusions.

C. Evaluation of Pediatric Program

No pediatric subjects with OPC or rOPC were assessed. Pending determination of appropriate studies, a pediatric program could be further discussed.

10. Conclusions and Recommendations

A. Conclusions

Posaconazole was non-inferior to an approved comparator regimen in the treatment of OPC in HIV infected subjects at a dose of 200 mg PO on the first day followed by 100 mg PO QD for 13 days. Posaconazole was also effective in a subpopulation of highly immunosuppressed subjects with HIV disease who had azole-refractory OPC at a dose of 400 mg PO BID for 28 days.

B. Recommendations:

An approval is recommended for the indication of OPC and azole-refractory OPC.

APPENDIX A INDIVIDUAL TRIALS

Study C99-331: Randomized, Controlled Trial of SCH 56592 (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. 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.

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

The dose of fluconazole is the approved dose for OPC.

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

posaconazole 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.

A total of 366 subjects were randomized in the study; 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 MITT subset: 169 subjects treated with posaconazole and 160 subjects treated with fluconazole. Demographic and other baseline characteristics were comparable between the two treatment groups.

Study Design: see section 6

Table 50
Study Flow chart/study 331:

Evaluation/Procedure	**Treatment**			**Follow-Up**
Visit	1	2	3	4
Study Day	1	8a	15a	42b
Signed Consent	X			
HIV Confirmation	Xc			
Medical History	X			
Complete Physical Exam	X			
Clinical Evaluation for Efficacy		X	X	X
Vital Signs (blood pressure, pulse)	X	X	X	X
Concomitant Medications	X	X	X	X
Electrocardiogram	X			
Complete Blood Count				
Blood Chemistry	X	X	X	Xd
Urinalysis	X	X	X	Xd
Pregnancy Test	Xe			
KOH Prep/Fungal Stain	X	Xf	Xf	Xf
Mycologic Culture	X	X	X	X
Study Medication Dispensed/returned	X	X	X	
Adverse Events		X	X	X
Posaconazole Plasma Drug Levels			Xg	

a: Patients who are clinically unchanged from Baseline or failures are dropped and final evaluations done.
b: Follow-up evaluations are done on Visit 3 cures/improvements only.
c: ELISA positive antibody test and either Western blot confirmation or other confirmatory tests unless prior documentation is available.
d: Done if abnormal at the prior visit.
e: Performed in women of child-bearing potential. Negative urine result must be available before study enrollment.
f: Only for clinical failures or relapses.
g: Done at selected study sites.

Inclusion and Exclusion Criteria
Subjects (18 years of age or older) who provided written informed consent

and adhered to protocol specifications were allowed to participate in this study if they met the following inclusion criteria:

• HIV infection, documented by any licensed ELISA test kit and confirmed by either Western Blot, HIV antigenemia, HIV culture, or another antibody test other than ELISA
• Clinical evidence of pseudomembranous OPC at time of enrollment into the study
• Laboratory evidence of candidiasis documented by fungal stain of scraping positive for yeasts, hyphae or pseudohyphae that was consistent with Candida species, and subsequently confirmed by a positive mycologic culture
• Females of childbearing potential, including subjects taking oral contraceptives who used a reliable barrier-type method of contraception throughout this study
• Expected survival greater than two months

Comment: Only subjects with HIV/AIDs were enrolled in this study. There had to be mycologic documentation of disease at the time of enrollment.

Subjects who met any of the following exclusion criteria were not allowed to participate:

• Medications excluded at enrollment:

- Any systemic therapy (eg, amphotericin, 5-flucytosine, or azole antifungals) within 1 week before enrollment into the study; any topical oral mucosal therapy (eg, Nystatin, clotrimazole, or oral amphotericin) within 2 days of study enrollment.

Comment: The applicant excluded subjects with refractory disease from this study.

- First time use of protease inhibitors 30 days before study enrollment, use of astemizole within 10 days of starting study drugs
- Medications, which may interact with azoles to cause life-threatening side effects: terfenadine, astemizole, cisapride, ebastine, triazolam, and midazolam)
- Medications which lower the serum concentration/efficacy of azoles: INH, rifampin, rifabutin, phenytoin, carbamazepine, barbiturates, and H2 blockers within 10 days of enrollment into the study

- Vinca alkaloids, and supraphysiologic doses of corticosteroids within 10 days before enrollment into the study

• Excluded Concomitant Medications:

- Medications excluded at study enrollment were prohibited during the 2-week treatment period.

Comment: Subjects already taking protease inhibitors for a period exceeding 30 days were allowed to continue taking these drugs. The continued use of these regimens would not be expected to alter the immune response of subjects.

Also of note was the exclusion of subjects with

- cancer and OPC due to chemotherapeutic regimens
- a documented or suspected fungal esophagitis.
- A history of treatment failure with FLZ (100 mg/day for 2 weeks in the last 3 months)
- Prior use of POZ in the preceding 3 months
- Any of the following laboratory abnormalities:
- ALT, AST, or alkaline phosphatase levels greater than 5 times the upper limit of normal (ULN)
- Total bilirubin levels greater than 2.5 times the ULN (greater than 5 mg/dL for subjects on Indinavir)
- Prothrombin time greater than 5 seconds over control or INR greater than or equal to 2.0
- Serum creatinine greater than 3 times the ULN, platelet count less than 75,000/mm3
- electrocardiogram (ECG) with prolonged QTc interval (greater than 10%).

Randomization:
The study drug for each subject was assigned using a randomization schedule generated by the Biostatistics Department at SPRI. Randomization was performed in appropriately sized blocks generated by a validated computer program using the SAS random number

Selection of Doses in the Study
The selection of dose for POZ or FLZ suspension was based on the recommended dose of FLZ for oral candidiasis in the United States, i.e., 200 mg, given on the first day, followed by 100 mg given once daily for 1 to 2 weeks.

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.

Blinding

This was an evaluator-blinded study, i.e., the evaluators were unaware of the subject's assigned regimen. The same person was used at each site to evaluate clinical response throughout the trial. These evaluators included licensed physicians, dentists, or registered nurses with experience in evaluating oral candidiasis of the patient's treatments regimen.

Comment: This study was not double blinded, that is the investigators were aware of the patient's treatments regimen.

Prior and Concomitant Therapy
All medications and other treatments taken by subjects during the study were recorded on the CRF. This included over-the-counter medications and medication/treatment that was initiated within 30 days before entry into the study.

Concomitant Medications
Prophylactic medications (eg, trimethoprim-sulfamethoxazole, inhaled pentamidine for *Pneumocystis carinii* pneumonia prophylaxis, and acyclovir for Herpes Simplex Virus) were permitted as long as they were not included in the list of prohibited medications.

Prohibited Medications
Systemic antifungal agents as well as medications known to interact with the azoles were prohibited during study drug treatment and follow-up phases: amphotericin compounds

Treatment Compliance
Subjects recorded treatment compliance on a diary card, which was kept at the study site as part of the subject's study record. The study staff reviewed diary card data and transferred data from this card onto the CRF. In addition, the physician or his/her designee questioned each subject regarding his/her use of study medication and recorded this information on the CRF.

. **Clinical Evaluation:** Obtained at Visits 2, 3, and 4. The investigator examined the oral cavity and questioned the subject to identify any signs/symptoms of infection and categorize clinical response to treatment at Visits 2, 3, and 4.

. **Mycologic Quantitative Culture, Identification of Species and Susceptibility Testing:** Obtained at each visit. Quantitative cultures were obtained using the oral swish technique. Identification of species and susceptibility testing were performed at 1 of 4 selected laboratories. Sites were notified if culture results were negative at Visit 1. No other culture results were provided until the end of the study.

. **KOH Prep/Fungal Stain:** This test was performed within 24 hours before the initiation of treatment. It was repeated at Visit 2 if no improvement was observed in OPC at Visit 3 for subjects with persisting plaques, and at the time of discontinuation and relapse for treatment failures (Visit 4). A specimen was obtained by scrapping or swabbing the oropharynx lesions while using a tongue depressor. A wet prep using 10% KOH, Chlorazol Black E fungal stain (Delasco), or a Gram stain was performed and specimens were examined for the presence of yeasts, hyphae, or pseudohyphae that were consistent with *Candida* species. If both fungal microscopic examination and quantitative culture were performed at the same time, the swish samples for quantitative culture were taken before the scraping was obtained for fungal microscopic exam.

. **Clinical Laboratory**

Laboratory assessments were performed at Visit 1 (or within 48 hours before initiation of treatment) and at Visits 2 and 3, and 4. Tests were repeated as clinically indicated and at Visit 4, if Visit 3 findings were abnormal and clinically significant.

A central laboratory (——————— . performed all clinical laboratory tests, except for prothrombin time, whenever possible. Tests performed included a CBC, an ECG (visit 1), Blood chemistries (sodium, potassium, chloride, bicarbonate, glucose, BUN, creatinine, calcium, inorganic phosphorous, uric acid, aspartate aminotransferase

(AST/SGOT), alanine aminotransferase (ALT/SGPT), alkaline phosphatase, cholesterol, total bilirubin, direct bilirubin, total protein, albumin, and lactate dehydrogenase (LDH), a UA, pregnancy test, and a CD4 count was performed within 3 months before randomization or at Visit 1.

In addition, a blood sample was collected at selected sites on Day 15 (Visit 3) for determination of plasma POZ concentrations.

Early Termination
Subjects were discontinued from the study whenever it was considered necessary for their health and well being, as judged by the investigator or at their request. If the subject discontinued the study before Visit 3, all procedures and evaluations that were scheduled for Visit 3 were performed at the time of study discontinuation. If a subject discontinued before study completion, the reason for, date of discontinuation, and date of the last dose of study medication were obtained.

Events or circumstances that required permanent discontinuation of the subject from the study included:

- . Baseline (Visit 1) evaluations and procedures outside of the range required by the protocol
- . Negative cultures at Visit 1
- Conditions requiring the administration of systemic or oral topical antifungals at any time during the study, including the post-treatment follow-up
- . Conditions requiring treatment with any medication that is prohibited
- First time initiation of protease inhibitors within 30 days before enrollment or during the study period
- . Enrollment in an investigational drug (unlicensed new chemical entity) study at any time during the study
- . The occurrence of a serious or life-threatening AE
- . Worsening of OPC at Visit 2 or inadequate clinical response, as judged by the investigator at any time. In the event that this occurred, appropriate antifungal therapy was recommended
- . Clinical failure at Visit 3
- Onset of pregnancy during the treatment phase
- . Noncompliance with study dosing (missed greater than 4 days of dosing) and evaluation requirements

Comment: *The applicant did not provide information on how early discontinuations were managed. The MO elected to assess all such subjects as failures in the MITT analysis.*

Primary Efficacy Variable(s)

The primary efficacy variable was defined as the proportion of subjects who were clinically cured/improved after 14 days of therapy.

Comment: Please see previous comments regarding efficacy assessment. The agency analysis also included an analysis of therapeutic success defined as clinical cure with mycologic eradication.

A 95% confidence interval (two-sided) for the difference in the clinical cure and improvement rates between treatments (POZ-FLZ) was constructed using the asymptotic normality of the binomial distribution. Posaconazole was considered equivalent to FLZ if the lower limit of the confidence interval for the difference in the corresponding response rates (POZ-FLZ) exceeded a delta of -15%, if the observed rate for FLZ was greater than 80% and exceeded a delta of -20%, and if the observed rate for FLZ was 80% or less. Any subject who failed to improve after 7 consecutive days of therapy was considered as a clinical failure for this analysis.

Secondary Endpoint

The clinical cure/improvement rate achieved after 7 days of POZ treatment was compared to that achieved after 14 days of FLZ treatment. The secondary efficacy variables, which were summarized by treatment arm included:
. Relapse rate 4 weeks after the last dose of study drug
. Mycologic response rate by visit

Data Quality Assurance

- A central IRB or EC approved the study protocol and the informed consent before study initiation. The investigator or designee recorded data obtained for each subject on a CRF. The steps taken to ensure that the data collected during this study was accurate and reliable included:

- Selection of an established investigator and study center

- Review of protocol procedures with the principal investigator and associated personnel assisting with the study conduct at study initiation

- Regular monitoring of study center to ensure that the study was being conducted according to protocol specifications, SPRI's SOPs, and regulatory requirements

- Use of a central laboratory for the processing of laboratory samples, whenever possible

- The steps taken to ensure that the database was created and maintained in accordance with quality controls included:

- Study Monitor compared subject data recorded on the CRF against information in source documents (patient files, hospital records and charts, original recordings, laboratory notes and slips, and raw data from clinical and laboratory findings) for consistency

- Resulting database underwent a standard checking program, which included range checks and checks for inconsistencies and logical errors

- This program was supplemented by an additional set of study specific checks

- Data fields in the database were verified against supporting documentation in the CRF, and errors detected were corrected and rechecked before finalizing the database. A random sampling of key efficacy and safety data was 100% audited before database lock and checked against the CRFs and data discrepancy documentation.

- Detected errors were corrected and rechecked before finalization of the database

- Data handling and reporting conventions (i.e., for efficacy and safety definitions and calculations, laboratory data, and database quality assurance procedures) were performed as specified in The sponsor's Worldwide Research Quality Assurance (WRQA) group conducted GCP audit(s) according to WRQA written SOPs.

Statistical Methods Planned in the Protocol and Determination of Sample Size

Data Sets Analyzed
The analyses and tables presented in this report were based on the following data subsets.

Randomized, Not Treated Subjects
The randomized but not treated subject subset included 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
The all-treated subject subset included all randomized subjects who received at least one dose of study medication. All summaries of safety data were based on this subset of subjects.

Intent-to-Treat Subjects
The intent-to-treat (ITT) subject subset included all randomized subjects.

Modified Intent-to-Treat Subjects
The modified Intent-to-treat (MITT) subject subset included all randomized subjects who received at least one dose of study drug and had a positive culture for *Candida* species at Baseline. The primary efficacy analysis was based on this subset of subjects.

Protocol Evaluable Subjects

The subset of protocol evaluable subjects included 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.

Demographic and Baseline Characteristics
Demographic and Baseline characteristics were summarized by treatment arm to allow for a comparison of these data between treatments at Baseline.

Secondary Endpoint
The clinical cure/improvement rate achieved after 7 days of POZ treatment was compared to that achieved after 14 days of FLZ treatment. The secondary efficacy variables, which were summarized by treatment arm included:

- Relapse rate 4 weeks after the last dose of study drug
- Mycologic response rate by visit

Changes in the Conduct of the Study or Planned Analyses
The original protocol dated June 23, 1998 was amended on October 20, 1998 (Amendment No. 1). A brief description of relevant to the analyses changes is summarized **below:**

- Clarified that clinical evidence was based on an examination for pseudomembranous oropharyngeal candidiasis.

- Clarified that either oral azole antifungal therapy given 1 week before study enrollment or any topical oral mucosal therapy (eg, nystatin, clotrimazole, or oral amphotericin) given within 2 days of study enrollment would exclude a subject from entering this study

- Specified that H2 blockers when given within 10 days of study enrollment would also exclude a subject from entering this study.

- Specified that supraphysiologic doses of corticosteroids when given within 10 days before study enrollment would also exclude a subject from entering this study

- Added an excluded concomitant medication section. This section specified that medications excluded at enrollment were prohibited during the 2-week treatment period, except that subjects already taking protease inhibitors for greater than 30 days were allowed to continue taking these drugs.

- Added an excluded concomitant condition section, which specified that cancer requiring the use of chemotherapeutic agents known to cause oral mucositis would exclude a subject from entering this study.

- Redefined superinfection as A *Candida* species present for the first time at Visits 2 and 3. Also defined indeterminant as extenuating circumstances that precluded classification.

- Clarified that a two-sided 95% confidence interval would be used to determine the difference in the clinical cure/improvement rates between POZ and FLZ.

- In response to comments from the Food and Drug Administration (FDA) concerning the refractory OPC development program, another analysis of the data was performed using cutoff values of greater than zero (cfu) to define evidence of candida infection. Two additional patients in the POZ arm fit the criteria for inclusion in the MITT subset when this alternative definition was used. This modification had minimal impact on outcome for the primary and secondary efficacy endpoints.

Study Subjects: Disposition and Demographics:
See Section 6
One subject in the MITT subset (Subject No. 161/I-19; POZ) took one dose of study drug that had expired during treatment, and one subject in the Protocol Evaluable subset (Subject No. 162/I-18; FLZ) took eight doses of study drug that had expired during treatment.

Comment: Subject 161 was a posaconazole recipient classified as a cure at the initial visit with relapse at follow-up and subject 162 was also a cure with a subsequent relapse. It is unlikely that the exclusion of with of these cases would have an effect on the efficacy analysis.

Fifteen subjects violated entry criteria but were allowed to enroll in this study. Five of these subjects (3 FLZ; 2 POZ) took prohibited medications, and four subjects (3 FLZ; 1 POZ) had platelet counts of less than 75,000/mm3. The remaining six subjects had serum creatinine levels 3 times higher than the upper limit of normal (ULN; 1 FLZ), prolonged QTc interval of 0.5 sec (1 POZ), SGOT greater than 5 times the ULN (1 FLZ), elevated alkaline phosphatase levels (2 FLZ), and elevated liver enzymes (1 FLZ).

Comment: The inclusion of these subjects could have had an effect on safety but did not appear to affect the efficacy analyses and was allowed.

The principal investigator from Study Site Number 33 signed the Test Article Accountability Ledger (TAAL) for seven subjects (Subject No. 458/I-33 through 463/I-33 and Subject No. 472/I-33) at Visit 3 (primary endpoint). Thus, treatment assignment for these subjects was unblinded to the investigator before database lock. Six of these subjects (3 in each treatment arm) were assigned to the protocol evaluable data subset, and one (Subject No. 461/I-33; POZ) was assigned to the all-treated data subset.

Comment: The MO reviewed the subjects from site 33. subjects 458, 459 and 462 received fluconazole and were classifies as cure, improvement and failure respectively, and subjects 460, 463, and 472 received posaconazole were classified as cure, cure, and failure respectively. Subject 461 was a posaconazole recipient also classified as a failure. Given the equal distribution of subjects between the treatment arms, the exclusion of

these subjects from the efficacy analyses would have had minimal to no impact on outcome.

The CRF for Subject No. 044/C-06 (FLU).was not collected until after database closure. This subject received 2 days of treatment but developed viral meningitis and study drug was discontinued. FLYU was resumed at a later timepoint but this patient would have been excluded from the PE and included in the MITT as a failure. The database was not re-opened to include this data in the analyses.

Subjects excluded because they did not have the disease under study (2 POSA re-included per FDA criteria)

Prot/Site	Subject	Tx	Baseline cultures
C9733104	0016	POS	No growth
C9733107	0085	POS	No growth
I9733107	0051	POS	10 CFU/ml
I9733118	0145	POS	No baseline culture
I9733118	0199	POS	No growth
I9733119	0157	POS	No growth
I9733120	0169	POS	No baseline culture
I9733133	0461	POS	Assumed incorrect CFU D1 culture Candida albicans, D8 culture 3.90 x 102 CFU/ml
I9733142	0639	POS	No growth
C9733104	0013	FLU	No growth
C9733107	0086	FLU	No growth
C9733121	0152	FLU	No growth
I9733110	0326	FLU	No growth
I9733115	0596	FLU	No Candida growth
I9733118	0146	FLU	No culture D1
I9733118	0147	FLU	No culture D1
I9733118	0196	FLU	No appropriate source, no culture
I9733118	0203	FLU	No growth
I9733127	0416	FLU	No growth
I9733130	0397	FLU	No culture D1
I9733139	0444	FLU	No growth

EFFICACY (see Section 6)

Clinical Response at the EOT by other parameters (Original MITT/Study 331):

Table 51

Clinical Response by demographic MITT study 331

	POSA	FLU

MITT	N= 169	N = 160
Sex Male	N = 125	N = 119
Success	119	112
Failure	6	7
Sex Female	N = 45	N = 41
Success	39	40
Failure	5	1
Race White	N= 61	N = 59
Success	56	55
Failure	5	4
Race Other	N = 59	N = 50
Success	55	48
Failure	4	2
Race Hispanic	N = 49	N = 51
Success	47	49
Failure	2	2
Baseline Sx Sum 0	N = 36	N = 24
Success	35	22
Failure	1	2
Baseline Sx Sum 1	N = 35	N = 28
Success	32	27
Failure	3	1
Baseline Sx Sum 2 – 3	N = 44	N = 54
Success	41	52
Failure	3	2
Baseline Sx Sum 4 – 5	N = 23	N = 16
Success	21	15
Failure	2	1
Baseline Sx Sum 6 -7	N = 16	N = 23
Success	14	23
Failure	2	0
Baseline Sx Sum > 8	N = 15	N = 15
Success	15	13
Failure	0	2

Study C/I96 –Study 209: A Multicenter, Randomized, Double-Blind, Phase II Study to Evaluate the Safety, Tolerance and Efficacy of Multiple Doses of SCH 56592 Versus Fluconazole in the Treatment of Oropharyngeal Candidiasis (OPC) in HIV-positive patients

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

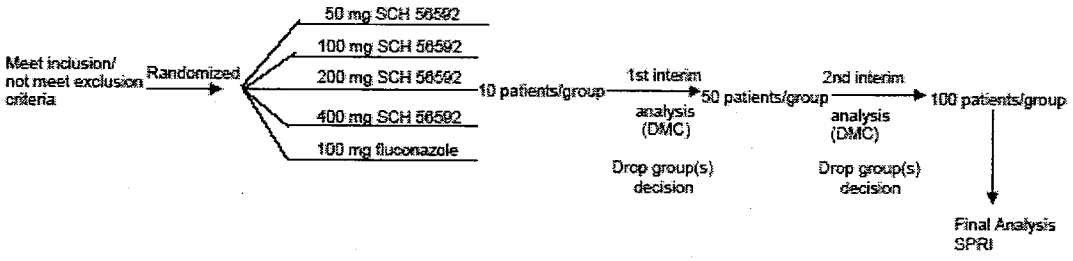
Summary: Randomized (5-arm), active-control, parallel-group, multicenter, double blind, and double-dummy study conducted to evaluate the safety and efficacy of four different dose levels of posaconazole compared to fluconazole in the treatment of azole OPC in HIV-positive subjects.

Subjects were treated an initial loading dose with posaconazole 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.

Study Details:
This was a phase II safety and efficacy study for dose selection, using 2 interim analyses. The protocol was finalized on December 20, 1996 and was amended substantially once on May 20, 1997. The amendment did not change the design of trial but primarily served to clarify procedures and to indicate the applicant's intent to use the study as a Phase III trial is the highest does was retained through final enrollment. The study Design is depicted below:

The comparator fluconazole is approved for the treatment of OPC at the dose used in this study.

Figure 1 Study Design for C/I96-209 Study



Inclusion criteria:

Subjects were eligible for inclusion in this study if they met the following criteria
Subjects were to be between the ages of 18 and 65 years, of either sex of any race.
Subjects had to be HIV seropositive (documented by Western blot or other approved confirmatory test) prior to enrollment.
Pseudomembranous OPC defined as: ≥2 discrete pseudomembranous plaques or a single confluent plaque ≥ 3 cm.
Laboratory results were to show fungal stain of scraping positive for yeasts, hyphae or pseudohyphae, consistent with Candida species, subsequently confirmed by a positive mycological culture.
Subjects must have had a Karnofsky performance score of ≥ 60

Exclusion criteria:
Subjects were excluded if they met any of the following criteria:

- They were using systemic (washout 14 days) or topical a antifungals (washout 1 day)(eg, Nystatin, Mycelex, etc)

- Use of medications that are known to interact with azoles and that may lead to life-threatening side effects: terfenadine, astemizole, cisapride, ebastine, triazolam, midazolam

- Use of medications that are known to lower the serum concentration/efficacy of azole antifungals: rifampin, carbamazepine, phenytoin, rifabutin, barbiturates, isoniazid, H2 blockers

- Use of cytokines (except erythropoeitin), interferon or lymphocyte replacement therapy unless subject was already taking these agents for at least 30 days prior to enrollment.

- Subjects starting protease inhibitors, for the first time, in the 30 days prior to enrollment

- Cytotoxic therapy for cancer

- Excluded were subjects with the following Concomitant Conditions:

  - Any medical condition requiring use of prohibited drugs.
  - Primary HIV seroconversion – related mucosal candidiasis.
  - Systemic candidiasis.
  - All forms of OPC other than pseudomembranous (unless accompanied by
  - pseudomembranous OPC)
  - Documented or suspected fungal esophagitis in subjects with symptoms of esophagitis.

- Also excluded were subjects with a history of prior failed therapy with fluconazole 100 mg/day for 2 weeks in the last 3 months.

Comment: Subjects with azole refractory disease were not specifically excluded.

- Subjects who had the following laboratory abnormalities were also excluded:
  - ANC <750
  - Hepatic function studies: alanine aminotransferase (ALT) and aspartame aminotransferase (AST) > 4 times upper limit of normal (ULN);
  - bilirubin >3 mg/dl.
  - Prothrombin time > 5 seconds over control or INR .1.5

- Renal function: creatinine >2.0 mg/dl
- Platelet count < 75,000/mm3
- EKG with prolonged QTc interval or clinically significant abnormalities.

- Prior enrollment in this study

- Women who were pregnant or nursing.
- Investigational drug (unlicensed new chemical entity) use in the 30 days prior to enrollment.
- Current known drug abuse if in the opinion of the investigator this would interfere with the subject's participation in the study.
- Less than 3 months life expectancy.
- History of hypersensitivity to azole antifungals.

Removal of Patients from Therapy or Assessment

- Subjects had study therapy permanently discontinued under the following
- conditions:
- Subjects with Baseline (Visit 1) evaluations and procedures outside of the
- Range required by the protocol were discontinued from the study as soon as the results were known.
- Subjects with negative Visit 1 cultures.
- Subjects who were required to receive systemic or oral topical antifungals at any time during the study, including the post-treatment follow-up.
- Subjects who required any medication that was prohibited
- Subjects who had started on protease inhibitors, for the first time, within
- 30 days prior to enrollment or during the study period.
- Subjects who had enrolled in an investigational drug (unlicensed new chemical entity) study at any time during the study.
- Subjects who had experienced serious or life threatening AEs.
- Subjects whose OPC had worsened at Visit 2 or clinical response was inadequate in the judgment of the investigator at any time. Appropriate antifungal therapy was instituted.
- Subjects who were considered clinical failures at Visit 3 were dropped from the follow-up phase of the study.
- Subjects who had become pregnant during the treatment phase.
- Subjects who had failed to comply with dosing (missed >4 doses) and evaluation requirements of the study.
- Subjects who no longer wished to continue in the study.
- The investigator had determined that further participation would be detrimental to a subject's health or well being.

At the time of discontinuation prior to Visit 3, all procedures and evaluations scheduled for Visit 3 were performed. If a subject discontinued prior to completion of the study, the reason for and the date of the discontinuation was obtained. The date of the last dose of study medication also was obtained. Discontinued subjects were not replaced.

Comment: *All subjects who discontinued treatment early were assessed. Confirmatory analyses were performed where subjects who discontinued early were categorized as failures.*

Randomization and Treatment:

Subjects from each study site who met the inclusion and exclusion criteria were randomly assigned to one of four posaconazole treatment groups or a fluconazole treatment group. Subjects were assigned treatments using a randomization schedule generated by the Biostatistics Department of Schering-Plough Research Institute. Randomization was performed in appropriately sized blocks generated by a validated computer program using the SAS random number generator (with seed number based on clock time).

Subjects self-administered POSA capsules or fluconazole encapsulated tablets orally with meals. Subjects randomized to one of the 4 doses SCH 56592 received 400 mg BID on Day 1, followed by one of the following 4 QD maintenance regimens on Days 2–14: 50, 100, 200, or 400 mg. Subjects randomized to fluconazole received 200 mg on the first day followed by QD doses of 100 mg for 13 days.

Each treatment box contained sufficient study medication for one subject to receive 14 days of treatment.

On Day 1, subjects were to take 4 capsules in the morning with a meal and 4 capsules in the evening with a meal. Maintenance dosing consisted of 4 capsules once daily, taken with a meal, for 13 days.

In order to maintain the blind, subjects took a combination of active and placebo capsules. During the study, the investigator, study staff, and subjects were blinded to the treatment assignment. A set of sealed envelopes corresponding to the individual treatment units, which contained the identification of the test drug, were maintained by the sponsor. A set of sealed envelopes for each subject was provided to the investigator and was opened only in case of an AE requiring that information in order to provide medical care. Opened envelopes were accompanied by a written explanation. Opening a single envelope did not compromise the blind for the remainder of the subjects. Compliance assessments were made based on the number of blister packages/capsules returned by the subject at each visit

Prior and Concomitant Therapy

As in study 331, the use of prophylactic medications [eg, trimethoprim-sulfamethoxazole (TMP/SMX), and inhaled pentamidine for Pneumocystis carinii pneumonia (PCP) or acyclovir for HSV were allowed. In addition to systemic or oral topical antifungals all of the medications listed in the exclusion criteria were excluded during the study.

Efficacy and Safety Assessments

Subjects were assessed during the study as follows:

- On admission when the inclusion criteria were fulfilled (Visit 1);
- Clinical and mycological response (Visit 2 and Visit 3);
- For cures/improvements (Visit 3), follow-up clinical response (Visit 4).

A Study Flow chart can be seeing below:

Table 52
Study flow chart Study 209

Study Flow Chart	TREATMENT			FOLLOW-UP
VISIT	1	2	3	4
STUDY DAY	1	8	15a	42b
Signed Consent	X			
HIV Confirmation	Xc			
CD4 Count (d)	X			
Medical History	X			
Signs/Symptoms	X	X	X	X
Physical Exam/Vital Signs	X	X	X	Xe
Concomitant Medications	X	X	X	X
ECG	X	X	Xe	Xe
Karnofsky Assessment	X			
Clinical Labs	X	X	X	Xe
Pregnancy Test (f)	X			
Microscopic Exam (Fungal Stain)	X	Xg	Xg	Xg
Quantitative Mycological Culture/ Susceptibility	X		X	X
Study Medication Dispensed/returned	X	X	X	
Adverse Events		X	X	X
SCH 56592 Serum Drug Levels		X	X	
Clinical Response		X	X	X

A: Subjects who are clinically unchanged from baseline or failures are dropped and final evaluations done.
b: Follow-up evaluations are done on Visit 3 cures/improvements only.
c: Documentation reviewed that confirms HIV seropositivity.
d: Within 1 month of entry.
e: To be done if abnormal at the prior visit.
f: To be performed in women of child-bearing potential.
g: On persistent plaques , clinical failures or relapses.
If death occurs within 30 days of last visit, death information to be collected and submitted to SPRI.

Comment: *The general design of this study was the same as that of 331. CD4 counts were assessed prior to treatment. Clinical evaluation included the assessment of the signs and symptoms of OPC as described in study 331. Subjects were classified as cured, improved or failed. Subjects requiring additional treatment at visit 3 were considered failures. Mycologic response was a secondary efficacy endpoint and was determined based on quantitative mycological culture results. The major timepoint for determining mycological efficacy was the end of treatment (Visit 3). As in the original 331 dataset, the following definitions were used:*

Eradication (Mycological success): ≤ 20 CFU/mL Candida species.
Persistence (Mycological failure): >20 CFU/mL Candida species.
Not Assessed: Subject was not cultured.
Comments regarding the 20 colony cutoff from the Agency were provided in the review of study 331. The applicant will be requested to provide similar revised analyses using 0 colonies at the TOC. All further protocol details were the same as in study 331 and will not be described here. Of note there were 2 interim analyses in this trial for which the appropriate statistical penalties were taken.

There were four populations, similar to what was done in study 331.

Intent-to-Treat: All randomized subjects.
Modified Intent-to-Treat: A subpopulation of the ITT population who have a positive Candida culture at Visit 1 and have taken at least one dose of study drug.
Per-Protocol A subpopulation of the Modified ITT population who satisfy all inclusion/exclusion criteria, and:
a) Have 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.
b) Have 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.
c) Have had a clinical assessment at Visit 3 (or at the end of treatment, if the subject discontinues prior to Visit 3).
d) Visit 3 must have been performed between 0 and 3 days after the end of treatment.

The efficacy conclusions were mainly based on the data from the modified ITT subjects.

STUDY PATIENTS
See Section 6

Efficacy analyses:
See Section 6 of MOR.

Studies C/I/97-330 Open-Label, Non-Comparative Trial of SCH 56592 in the Treatment of Azole Refractory Candidiasis in HIV-Infected Subjects: See Section 6 of MOR for Synopsis
Other Protocol details:
Protocol details:

Primary and Secondary Objectives:

The primary objective of this study was to assess the clinical response of treatment of resistant or refractory oral/esophageal candidiasis following treatment with POS oral suspension at Treatment Endpoint (Week 4).

Secondary objectives included the following:
• Assess clinical response after 2 weeks of treatment (Amendment Nos. 1 and 2)
• Assess the rate of clinical relapse during the 1-month post-treatment follow-up period (Amendments No. 1 and 2)
• Determine mycologic response after 2 weeks of treatment (Amendments No. 1 and 2)
• Determine mycologic response after 4 weeks of treatment (Amendments No. 1 and 2)
• Evaluate fungal susceptibility patterns before and after therapy
• Assess the rate of treatment-limiting toxicity

***Comment**: The primary endpoint in this study was clinical. This was deemed reasonable for this population of HIV infected subjects who generally were profoundly immunosuppressed and in whom the signs and symptoms of OPC can be striking including extensive oral plaques, inability to eat or swallow, and significant weight loss.*

Inclusion Criteria

- 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 courses of Fluconazole at standard or increased doses. Of note there was no prespecified amount of time lapsed between the previous treatment and the start of POSA.*

Other inclusion criteria were as follows:

- HIV infection, documented by any licensed enzyme-linked immunosorbant assay (ELISA) test kit and confirmed by either Western Blot, HIV antigen, HIV culture, or another antibody test other than ELISA
- Evidence of OPC at time of enrollment (Original Protocol and Amendments No. 1 and 2), documented by KOH/fungal stain and confirmed by mycologic culture or esophageal candidiasis documented by esophageal brushing or biopsy and culture (Amendments No. 1 and 2)
- Females of childbearing potential and their partners, including subjects taking oral contraceptives, who used a reliable barrier-type method of contraception throughout the study
- Expected survival of ≥6 months

Pertinent Exclusion Criteria included the following:

Use of any systemic antifungal (amphotericin B, 5-flucytosine or oral azole antifungals) therapy within 1 week before enrollment into the study, unless there was clearly no

improvement (Original Protocol and Amendments No. 1 and 2) (or worsening) in candidiasis after at least 7 consecutive days of therapy (Amendments No. 1 and 2)

Use of topical oral antifungals (eg, nystatin, clotrimazole, oral amphotericin) within 2 days of enrollment into the study (Amendments No. 1 and 2), unless there was clearly no improvement (or worsening) in candidiasis

Excluded Concomitant Conditions:

- Presence of systemic fungal infection
- Baseline mycologic culture that was negative for *Candida* species (Amendments No. 1 and 2)
- Allergy or intolerance to azoles
- First time use of protease inhibitors 30 days before enrollment
- Presence of only perioral lesions (angular stomatitis, perleche)

Study Procedures:

The following study procedures were performed:

• **Medical History:** Obtained at Visit 1. A general medical history, including an HIV history, was obtained along with documented evidence of clinical failure to FLZ (Original Protocol) and FLZ and ITZ (Amendments No. 1 and 2).
• **Complete Physical Exam:** Obtained at Visit 1 (Original Protocol) and at Visits 1, 5, and 6 (Amendments No. 1 and 2).
• **Concomitant Medication:** Recorded at each visit. All concomitant medication taken by the subject for 30 days before initiation of study drug and throughout the study was documented.
• **Vital Signs:** Obtained at each visit. Blood pressure and pulse were taken and recorded on the CRF at each study visit.
• **Esophagoscopy:** Performed at Visits 1 and 5 (Original Protocol and Amendment No. 1) and at Visits 1, 3, and 5 (Amendment No. 2). For subjects with suspected esophagitis, an esophagoscopy was performed at Visits 1 and 5 (Original Protocol). This procedure was also performed at Visit 3 only if clinically indicated, i.e., if new, persistent, or worsening symptoms of esophagitis were present.
• **Electrocardiogram:** Obtained at Visit 1.
• **Complete Blood Count:** Obtained at Visits 1, 2, 5, 6, 7, 8, and 9 (Original Protocol) and at Visits 1, 2, 5, and 6 (Amendments No. 1 and 2).
CD4 count (Original Protocol and Amendments No. 1 and 2) and viral load (Original Protocol) were obtained only at Visit 1.
• **Blood Chemistry:** Obtained at Visits 1, 2, 5, and 6.
• **Prothrombin Time:** Obtained at Visit 1 (Amendments No. 1 and 2).
Prothrombin time was determined from the blood sample collected at Visit 1. The analysis was performed at the local laboratory.
• **Urinalysis:** Performed at Visits 1 and 5.
• **HIV Confirmation:** Available or obtained at Baseline.

• **Mycologic Culture:** Obtained at Visits 1, 5, and 8 in all subjects who relapsed at any time and for treatment failures that occurred before Visit 5
(Original Protocol) and at Visits 1, 3, and 5 in all treatment failures that occurred before Visit 5 or relapsed during follow-up (Amendment No. 1) and at Baseline, Visit 3, and Visit 5 in all subjects who relapsed at any time and for treatment failures that occurred before Visit 5 (Amendment No. 2).

***Comment**: As noted above, subjects were clinically. Mycologic response was a secondary endpoint in this study and quantitative cultures were performed at baseline, at visit 3 (14 days) and at visit 5 (week 4, end of acute treatment). Follow-up cultures at week 6 were NOT required. Additionally a number of subjects who were assessed clinically DID NOT have the week 4 cultures (N = 50, 34 failures). In addition 2 subjects did not receive a clinical or a mycologic assessment. Although not an issue in the OPC indication,*

Quantitative cultures were obtained using the oral swish-and-spit technique. Identification of species and susceptibility testing were performed at a selected laboratory. If both microscopic examination and quantitative culture were performed at the same time, the swish samples for quantitative culture were taken before the scraping was obtained for fungal microscopic exam.

Comment: The details of this technique described by Graybill were detailed in the original MOR (presence of < 20 colonies of yeast was considered indicative of eradication). Although the Agency preferred that the definition of eradication be equated with the complete absence of growth, this was not done. As this was a clinically driven study and mycologic assessments were performed only for failures, it seems reasonable to accept the applicant's analyses.

• **KOH Prep/Fungal Stain:** Obtained at Visits 1 and 5 and in all subjects who relapsed at any time and for treatment failures that occurred before Visit 5 (Original Protocol) and at Visit 1 in all treatment failures that occurred before Visit 5 or relapsed during follow-up (Amendments No. 1 and 2).

- • **Clinical Evaluation:** Obtained at all visits. At each visit, the investigator examined the oral cavity and questioned the subject to identify any signs/symptoms of infection and categorize clinical response to treatment.

Treatment:

Subjects took 400 mg (10 mL) of POS oral suspension (40 mg/mL) twice daily for 3 days, followed by 400 mg daily for 25 days (Original Protocol) or 400 mg twice daily for 28 consecutive days (Amendments No. 1 and 2). They were instructed to swish and swallow the study drug with food or immediately after eating.

In the Original Protocol, if at Day 14, a subject was not responding to treatment with study drug, the investigator had the option to increase the POS dose to 400 mg twice daily. The Original Protocol also allowed for a 3-month maintenance period following treatment. During this period, subjects were treated with POS 400 mg twice daily, three times weekly. If a relapse of candidiasis occurred during the maintenance period, subjects could return to the 400 mg twice daily dosing schedule per the investigator's discretion. Per Amendments No. 1 and 2, the maintenance period was eliminated in favor of having the subjects proceed to a new protocol (Protocol No. P00298), where the subjects were treated with 400 mg POS twice daily for 3 months with the option of entering a 12-month maintenance period where they received the same dose of POS.

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 bioavailibity. 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.

Study Procedures (see MOR Section 6):

• **Clinical Evaluation:** Obtained at all visits. At each visit, the investigator examined the oral cavity and questioned the subject to identify any signs/symptoms of infection and categorize clinical response to treatment. The presence of plaques was graded according to the following scale, modified from an AIDs Clinical Trial Group (ACTG) Protocol:

- 0 None = Absent
- 1 Minimal = 1- 5 discrete plaques and/or one confluent plaque < 3 cm in longest length.
- 2 Diffuse = Plaques that were more than minimal extent; or presence of ulcers (Amendments No. 1 and 2).
- 3 Severe plaques that were more than minimal extent, or presence of ulcers (Original Protocol only)
- 4 Worse = Plaques or ulcers were clearly worse than on 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 and led to interference with eating many foods.
- 3 Severe = Symptom(s) were very marked. The subject was unable to eat most foods.

All-Treated Subjects

This subset included all subjects with a diagnosis of OPC who received at least one dose of study drug.

Efficacy Evaluable Subjects

This subset included the subset of All-Treated subjects who satisfied additional key inclusion criteria and received at least 14 consecutive daily doses of study drug. Subjects must have had a clinical assessment at Visit 5 or at least 3 days of treatment before discontinuing study drug before Visit 5 either due to treatment failure or to AEs.

Modified Intent-To-Treat Subjects

This subset included the subset of All-Treated subjects with evidence of an azole-refractory *Candidal* culture at Baseline.

Primary Endpoint

The primary protocol defined primary 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.

Secondary Endpoints
Secondary endpoints were as follows:

- Clinical response at Visit 3 (after 2 weeks of treatment), (Amendments No. 1 and 2)
- Mycologic response at Visit 3 (after 2 weeks of treatment; Amendments No. 1 and 2) and Visit 5 (end of 4-week treatment period)
- Rate of clinical relapse during post-treatment follow-up, maintenance period, and post-maintenance follow-up
- Change in susceptibility pattern of fungal isolates
- AEs during study period (Original Protocol)
- Rate of treatment-limiting toxicity (Amendments No. 1 and 2)

***Comment**: All MITT (azole refractory) subjects were to be assessed after28 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.

Amendments:

The Original Protocol dated November 14, 1997 was amended on February 25, 1999 (Amendment No. 1) and on May 25, 1999 (Amendment No. 2). The primary changes in these amendments were to the dosage regimen because the original protocol treatment regimen was perceived by investigators and study subjects as too complicated (400 mg given twice daily for 3 days, then 400 mg given every day for 25 days, then 400 mg given twice daily three times per week for 3 months). In the amended protocol, the treatment regimen was simplified to 400 mg given twice daily for 28 days.

Changes were also made to the statistical analysis plan:

The clinical response at Week 4 was defined for each subject who had post baseline treatment evaluations available. An imputation rule was derived to estimate the missing clinical evaluation at Week 4.

The correlation between clinical response at Week 4, demographic variables, and baseline CD4 counts were to be explored with summary tables and a logistic regression model.

There were eight *Candida spp.* isolates specified in the CRF data collection: *Candida albicans*, *Candida glabrata*, *Candida tropicalis*, *Candida krusei*, *Candida parapsilosis*, *Candida guilliermondii*, *Candida stellatoidea*, and *Candida pseudotropicalis*. As only a few of the last four *Candida* species were present in the data thus they were pooled into the *Candida* "Others" group. The mycological response was summarized by five groups of *Candida* species: *Candida albicans*, *Candida glabrata*, *Candida tropicalis*, *Candida krusei*, and *Candida* Others.

Only distributions of mycological response rate were provided. However, it was concluded that 95% confidence interval for mycological response rate by each *Candida* isolate was not to be provided, due to the fact that a relatively large number of subjects had no mycological assessment.

In addition to mycological response for each isolate of *Candida* species, an overall mycological response at Week 4 was derived. It was defined as a "response" when all mycological isolates present at Baseline were negative at Week 4, a "nonresponse"if at least one mycological isolate present at Baseline was positive at Week 4, or "not assessed" when no mycological evaluation was performed at Week 4. The overall mycological response rate was summarized by protocol version, by clinical response at Week 4 (primary efficacy variable), and by each mycological isolate present at Baseline.

Changes in susceptibility pattern of fungal isolates were planned to be summarized by the MIC values to FLZ, ITZ and POS at Baseline, Week 2, and Week 4 for each isolate group. The MIC cut-off value was set as 32 mcg/mL for FLZ resistance and was set as 1 mcg/mL for ITZ resistance. Resistance/susceptibility rates to FLZ and ITZ were planned to be summarized at each evaluation time point (Baseline, Week 2, and Week 4) for each isolate. For each isolate, resistance/susceptibility rates to FLZ/ITZ were to be summarized among the subset of subjects susceptible to FLZ/ITZ at Baseline.

Additionally, resistance/susceptibility rates were to be summarized by baseline isolate present and baseline resistance/susceptibility category to FLZ and/or ITZ.

Applicant's analysis
See Section 6

Disposition of subjects: See appendix A for details

Two subjects, who enrolled per the Original Protocol, Subject Nos. 001 and 005 treated at Site I-11, received 123 and 112 days of study drug, respectively. Both subjects re-enrolled per the Amended Protocol approximately 20 and 12 months later, respectively. They were assigned different subject numbers (013 and 012, respectively) and were subsequently analyzed for safety and efficacy as two additional, separate subjects.

Comment: Although at least one treatment course for each of these subjects would be excluded in an efficacy assessment in a comparative trial, this is not necessary in an open label study with the primary objective to show efficacy in refractory disease defined as clinical improvement independent of further treatment.

Documentation was not available to verify the dates of enrollment for four subjects, nor was documentation available to verify that these subjects received at least one dose of study drug. There were, however, AEs reported for each of these subjects and they were included in the All- Treated Subset (Subject Nos. 010, 010, 012, and 009 at Sites C-03, C-09, C-16, and I-19, respectively. Subject No. 012/C-16 was enrolled under the Original Protocol; Subjects Nos. 010, 010, and 009/C-03, C-09, and I-19, respectively, were enrolled under the Amended Protocols).

***Comment**: All discontinuations were previously reviewed*

At Treatment Endpoint, 75.0% (132/176) of all MITT subjects were responders. Response rates were similar independent of the dosing regimen and as expected the response rates were numerically higher in the EE population (81.6% (129/158).

In an analysis of response at study day 14, 93/176 (52.8%) of subjects were classified as responders. Of note, only 26 of 89 subjects treated in the original protocol were included in this analysis with a response rate of 29% as compared to 67/87 amended protocol subjects with a response rate of 77%.

Eighty seven of 176 MITT subjects had isolates resistant to FLZ (MIC $\geq$ 32 mcg/mL) and 66.7% of these subjects had a satisfactory clinical response. Of the 70 subjects with isolates resistant to both fluconazole and itraconazole, 81.9% had a satisfactory clinical response.

Comment: An analysis of the all treated population revealed that of the 199 subjects, 42 had an imputed response (21.1%). In all 102 subjects were considered cured 51.2%, 42 were considered improved (21.1%), 26.1%) were considered failures and 3 subjects had

missing data. Of these subjects the failures were imputed responses. Generally it would appear that posaconazole is effective in at least 51% of subjects with refractory disease.

Clinical Relapse Rate during the 4 Week Post-Treatment Follow- Up Period

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. At Week 4 of Follow-up (defined as 23 through 37 days after the last dose of study drug), 28.8% (38/132) of all MITT subjects who were responders at Treatment Endpoint (Week 4), relapsed: there was difference in the number of subjects that relapses between the original and amended protocols (32.8% (22/67O) and 24.6% (16/65A).

Clinical Response by Baseline CD4 count:

***Comment**: No conclusions could be drawn from this analysis as there was an unequal distribution in the number of subjects with counts > or < 100.*

Table 53
Clinical Response Week 4 by Baseline CD4
MITT Study 330

Response	Baseline CD4			
	CD4 ≤ 100	CD4 > 100	Missing	Total
Responder	108 (73)	11 (78.6)	13 (92.9)	132 (75)
Non Responder	38 (25.7)	3 (21.4)	1 (7.1)	42 (23.9)
Missing	2 (1.4)	-	-	2 (1.1)
Total	148	14	17	176

Mycological Response

***Comment:** Mycologic assessments at the EOT were not required. Approximately 66% of subjects were cultured. In the subset that was cultured after treatment, a much lower percentage of subjects had protocol defined eradication or a "response" as compared to the clinical responders. The reason for this lack of mycologic response was not clear and may be related to the subjects' underlying immunosuppression as well as to the development of posaconazole tolerant isolates.*

Table 54
Mycologic Response week 4
MITT study 330

Mycological Response	Protocol Version Enrollment		
	Original (n=65)	Amended (n=61)	Total (n=126)*
Responder	23 (35.4)	23 (37.7)	46 (36.5)
Non-Responder	41 (63.1)	37 (60.6)	78 (61.9)
Missing Post-Baseline Clinical Evaluation	1 (1.5)	1 (1.6)	2 (1.6)

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.
*Fifty subjects (24 in Original + 26 in Amended Protocol) were not assessed (cultures were not obtained)

At Week 4, 36.5% (46/126) of all MITT subjects were mycological responders (≤20 CFU/mL *Candida* species) (35.4% (23/65O) and 37.7% (23/61A).

Sixty-two percent (78/126) of all subjects were mycological nonresponders (>20 CFU/mL *Candida* species): 63.1% (41/65O) and 60.6% (37/61A).

At Week 4, 40.0% (46/116) of MITT subjects who were clinical responders were also mycological responders. Sixty percent (70/116) of clinical responders at Week 4 were mycological non-responders and 13.8% (16/116) of mycological responders were not assessed (no cultures were obtained).

Table 55
Combined Clinical and Mycologic response Week 4
Study 330 MITT

	Clinical Response at Week 4			
Overall Mycological Response at Week 4	**Responder (n=116)**	**Non-Responder (n=8)**	**Total (n=126)**	**Missing (n=2)**
Responder	46 (40.0)	0	46 (36.5)	--
Non-Responder	70 (60.3)	8 (100.0)	78 (61.9)	--
Missing Clinical Evaluation	--	--	2 (1.6)	2 (100.0)

Fifty subjects (16 responders and 34 non-responders) were not assessed (cultures were not obtained).

For assessed subjects at Week 4 (N = 126), mycological responders to their specific *Candida* species included: 40.2% (47/117) of subjects with *Candida albicans*, 36.0% (9/25) of subjects with *Candida glabrata*, 100.0% (2/2) of subjects with *Candida tropicalis*, 67.0% (4/6) of subjects with *Candida krusei*, and 100.0% (3/3) of subjects with other *Candida* species present at Baseline.

Comment: The following table provides mycologic response rates for the number of subjects tested (66%). Of the mycologic responders (N = 46), 28 had an isolate resistant to fluconazole, of note in this table, subjects with resistance to both azole had a lower response rate than those with only fluconazole resistance.

Table 56

	Mycological Response		
Baseline Resistance	**Responder (n=46)**	**Non-Responder (n=78)**	**Total (n=126)**
Resistant to Fluconazole (FLZ)	28 (60.9)	30 (38.5)	58 (46.0)
Resistant to Itraconazole (ITZ)	4 (8.7)	6 (7.7)	10 (7.9)
Resistant to Both FLZ and ITZ	13 (28.3)	40 (51.3)	53 (42.1)
Missing	1 (2.2)	2 (2.6)	3 (2.4)
Missing Clinical Evaluation	--	--	2 (1.6)

Fifty subjects (4 missing + 29 resistant to FLZ + 17 resistant to both FLZ and ITZ) were not assessed (cultures were not obtained).

Change in Susceptibility Pattern of Fungal Isolates

Due to the small number of subjects with data on baseline organism and MIC, endpoint culture and MIC, endpoint serum drug concentration, and clinical outcome, no correlation

of clinical response and serum concentration or change in susceptibility pattern of fungal isolates could be made.

Additional analyses:

Analyses of clinical response by demographic and baseline disease characteristics, including age groups (18 to 39 years vs. 40 to 64 years vs. ≥65 years), gender (female vs. male), race group (Caucasian vs. non-Caucasian), baseline weight (<65 kg vs. ≥65 kg), and region of enrollment (USA vs. international were inconclusive and little variation in response was noted between subgroups.

Clinical Response by Severity:

Table 57

Response	Total score Range 0 - 22			
	0- 6	7 - 11	12- 16	≥ 17
Responder	42 (72)	39 (76)	28 (80)	23 (72)
Non Responder	16 (28)	12 (24)	7 (20)	9 (28)
Total	58	51	35	32

Study 0298: OPEN-LABEL RE-TREATMENT PROTOCOL FOR HIV-INFECTED PATIENTS WITH AZOLE-REFRACTORY CANDIDIASIS
See section 6
Protocol Details:
Prior episodes of oropharyngeal candidiasis and prior antifungal therapies were reviewed for all subjects.

HIV Confirmation: Available or obtained at Visit 1 or within 1 week prior to enrollment.

Esophagoscopy: Performed at Visit 1 for subjects with symptoms of esophagitis; repeated for subjects with esophagitis who failed therapy or relapsed.

Clinical Response: Assessed at all visits during the treatment phase and at the follow-up visit.

Clinical and Mycologic Evaluations
Signs and symptoms of oral candidiasis and esophagitis and the extent of plaques were assessed. Clinical response to therapy was the primary endpoint. For all definitions see study C/I97-330.

Data Subset Populations: The following populations were assessed:

All-Treated Subjects: All enrolled subjects who received at least one dose of study medication.

Modified Intent-To-Treat Subjects: All treated subjects with a positive culture for *Candida* and evidence of clinical or mycological resistance to *Candida* at Baseline. Efficacy assessments were based on this subset.

Note: The MITT population in this study differed from that in study 330 in that resistance was the determinant of entry into this population as opposed to refractory disease in study 330.

Efficacy Evaluable Subjects: All treated subjects who satisfied all key inclusion and exclusion criteria and received at least 60 days of study medication with no more than 7 consecutive days missed. Subjects must have had a clinical assessment at Visit 4. Confirmatory efficacy analyses were based on this subset.

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.* [redacted].

Clinical response at the end of the treatment phase (month 3) was the primary endpoint for this study.

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 end of treatment 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.

Protocol Deviations:
Subject Nos. 02/002 and 02/003 enrolled after participating in SPRI study C/I97-330 were allowed to continue receiving their previous POS dose, 400 mg once daily (QD), in the present study. Subject No. 33/003 took POS 600 mg every other day (QOD) to avoid a drug interaction with ansetapine.

Per protocol, subjects who had participated in study C/I97-330 were to have been assigned the same subject number for the present study. However, the following 3 subjects from C/I97-330 received new subject numbers upon enrollment into P00298: No. 29/020 (I97-330 No. 11/009), No. 32/027 (I97-330 No. 19/011), and No. 35/001 (C97-330 No. 18/003). Subjects who had not participated in study C/I97-330 were to have been assigned subject numbers beginning with 100. This method was not followed for several subjects who had not participated in C/I97-330:

- Site 01: Subject 008
- Site 17: Subject 007
- Site 19: Subjects 009, 010
- Site 29: Subjects 017, 018, 019, 021
- Site 32: Subjects 015, 016, 017, 018, 019, 020, 021, 022, 023, 025, 026, 028
- Site 33: 008, 009

Baseline laboratory samples were collected prior to the Baseline visit date in three subjects (Subject Nos. 03/102, 03/103, and 10/100); a window of -7 days was considered acceptable.

Based on clinical needs, several subjects were granted exemptions by the SPRI project physician; several subjects were granted exemptions to receive treatment or re-treatment extensions (Subject Nos. 01/002, 01/005, 01/102, 10/006, 10/010, 16/006, 16/007, 16/008, 16/009, 16/010, 33/007, and 35/001) and two subjects (Subject Nos. 18/002 and 18/003) were permitted re-enrollment in the study (as Subject Nos. 18/002R and 18/003R, respectively).

Two subjects at Site 01 were approved by the project physician to continue treatment in this study despite being concurrently enrolled in a protease inhibitor trial.

Subject No. 18/002 was granted a protocol exemption to continue on study while taking the prohibited concomitant medication, phenytoin. A protocol waiver had been granted for this subject to receive concomitant phenytoin while enrolled in study C/I97-330.

Subjects Nos. 09/100, 16/008, and an additional subject from Site 09 (Subject No. not specified), were permitted to enroll or to continue treatment despite Grade 3/4 laboratory values.

Results: Clinical Response at end of Acute Treatment

Conclusions could not be drawn from this study regarding differences in efficacy by demographic characteristics because subjects were primarily Caucasian middle aged males. However, the clinical response at the end of acute treatment for the MITT population was similar in these groups: 85.5% for males (n=65) versus 85.7% for females (n=12) and 86.2% for Caucasians (n=56) versus 84% for non-Caucasians (n=21).

Three subjects included in both the MITT and Efficacy Evaluable subsets were considered to be clinical responders based on response data provided at individual study visits during the acute treatment phase. This differed from the end of- treatment final status of treatment failure conferred by the investigator.

Subject No. 11/101 received POS for 52 days, discontinuing due to treatment failure.

Clinical response on Day 35 was assessed as improved. No assessment was provided at early discontinuation.

Subject No. 32/007 had a Day 58 assessment of cure. A Day 99 assessment of failure was beyond the acute treatment period.

Subject No. 10/032 discontinued study drug on Day 58 with a clinical response of cure. The subject returned on Day 93, still within the acute treatment period but off drug for 35 days, with recurrence of disease and was assessed as a treatment failure.

Considering these three subjects as failures does not substantially alter the clinical response rate in the Efficacy Evaluable, 84% (63/75), or MITT, 82% (74/90), populations.

Table 58
Reanalysis

Clinical response at acute EOT % (#responders/#subjects)	Current analysis EE subset	Reanalysis EE subset	Current analysis MITT subset	Reanalysis MITT subset
All subjects	88% (66/75)	89% (64/72)	86% (77/90)	82% (74/90)
POS-treated	92% (46/50)	94% (45/48)	88% (52/59)	85% (50/59)
POS-naive	80% (20/25)	79% (19/24)	81% (25/31)	77% (24/31)

APPENDIX B

31 Page(s) Withheld

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_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

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