Table 11
Outcome by site/isolate
Candida albicans

	Complete success	Partial success	Failure ALL	IR	S	UN	D
Blood		1	2	1		1	
Cerebral			1	1			
Pulmonary	1		2	1	1		
Skin							
Bone		1					
Bile			1	1			
OPC		1*					
Esophageal			1	1			
Tonsil		1					
Hepato/splenic			1	1			
Peritoneal			1	1			

*** = Relapse**
IR = Insufficient Response, D = Death, S = Stable, UN = Unevaluable

Candida krusei:
(N = 13 isolates from 10 patients):

Subjects with *Candida krusei infections* primarily suffered from hematologic malignancies (60%, 6/10). The remaining subjects had other malignancy, aplastic anemia with profound neutropenia, an unspecified hematologic disease, and unknown in 1 subject. 9 subjects had definite infection and 1had a probable infection. 3 subjects had 2 sites of infection (31201110001: cerebral, blood, 604106861109: blood, OPC, 60650190024: blood, skin). 1subject had a mixed infection and outcome can be seen in the following table:

Subject Number	Baseline Pathogens	Site(s)	Outcome
312-01110001 (salvage)	*C. albicans*	Brain	Failure
	C. glabrata	Brain	
	C. krusei	Brain and blood	
	Rhizopus spp.	Brain	

All subjects received prior antifungal treatment with a mean duration of prior treatment of 20.1 days and a median of 21 (range 1, 31).

Mean age of the subjects was 32.4 (median 29 range 12 – 69) and there were 7 males and 3 females.

8 subjects had blood isolates, and there were also cerebral, skin, oropharyngeal, tonsil, and UT isolates (1 each).

Mean duration of voriconazole treatment was 37.3 days (median 19.5 days).

Overall per patient success rate was 6/10 or 60% at the EOT and there were no relapses. 1 of the failures was in the mixed infection subject. The most common cause of failure was insufficient response (2), followed by failure due to death in 1 and to intolerance in 1.

Global response was assessed as complete success in 3/10 (30%) subjects, as partial success in 3/10 (30%), as failure in 3 subjects (30%), and was not assigned in 1 (10%).

Mycologic response was unknown in 8 subjects because it was not a protocol requirement and indeterminate in 2.

Of 3 subjects with a documented risk factor there were 3 with allogeneic BMT. 1 had a UT isolate and was a complete success, 1 had a blood isolate and was a complete success, and 1 had blood and cerebral isolates as well as a mixed infection and was a failure due to insufficient response. Of the subjects with profound neutropenia, 1 had a blood isolate alone and was a partial success, one had blood and OPC and was a partial success, 1 had blood and skin infections and was a failure due to insufficient response, and 1 had a blood infection but discontinued due to intolerance,

A total of 4 subjects died during the study period or follow-up, and all deaths were due to underlying disease.

1 case had a follow-up assessment (#3120111000). This subject with mixed infection died at day 8 post-treatment.

Mean calculated survival day from the start of treatment was 39.8 days (sd 40.3), median 28, (range 5, 121).

In conclusion, voriconazole appeared effective in the treatment of refractory infections due to *Candida krusei*. Given the increasing frequency of this isolate as a significant pathogen in immunosuppressed subjects, the relative lack of available efficacious products for the treatment of these infections, and the high mortality associated with infections due to *Candida krusei*, the MO recommends approval for the use of voriconazole in the treatment of such infections in subjects who have failed or are intolerant of other conventional antifungal therapies if the risk/benefit analysis supports this usage.

Table 12
Outcome by site/isolate
Candida krusei

	Complete success	Partial success	Failure ALL	IR	S	UN	D
Blood	2	2	4	2		1	1
Cerebral			1	1			
UT	1						
Skin			1	1			
Tonsil		1					

IR = Insufficient Response, D = Death, S = Stable, UN = Unevaluable

Candida glabrata
(N = 17 isolates from 12 patients):

Subjects with *Candida glabrata* primarily suffered from hematologic malignancies (5/12, 42%) followed by 3 subjects with transplant (25%). The remaining subjects had other malignancy, aplastic anemia with profound neutropenia, CGD, and surgery. 11 subjects had definite infection and 1 had a probable infection (30104780001, lung).

5 subjects had 2 sites of infection (30103140001: probable prosthetic valve and definite blood; 30104990002: biliary tract and ascitic fluid; 60410016163 blood, urine; 60410336151: blood, kidney; 60650050038: probable lung, definite hepatosplenic). 1subject 31201110001 had a mixed infections and outcome can be seen in the following table:

Subject Number	Baseline Pathogens	Site(s)	Outcome
312-01110001 (salvage)	*C. albicans*	Brain	Failure
	C. glabrata	Brain	
	C. krusei	Brain and blood	
	Rhizopus spp.	Brain	

All subjects received prior antifungal treatment with a mean duration of prior treatment of 24 days and a median of 26 (range 8, 31).

Mean age of the subjects was 52 (median 53.5 range 24 – 73); 8 were males and 4 were females.

6 subjects had blood isolates, 2 had pulmonary, and there was 1 each cerebral, hepatosplenic, sinus, urine, kidney, prosthetic valve, bile, biliary tract, and ascitic fluid.

Mean duration of voriconazole treatment was 22.8 days (median 16 days).

Overall per patient success rate was 4/12 or 34% at the EOT and there were no relapses. 1 of the failures was the in the subject with mixed infection.

The most common cause of failure was insufficient response (6), followed by failure due to intolerance in 2.

Global response was assessed as complete in 4/12 (34%) and failure in 8 subjects (67%).

Mycological response was persistence in 4 subjects with 5 isolates, unknown in 5 subjects because it was not a protocol requirement, eradication in 1(blood) and indeterminate in 2.

Of 3 subjects with a documented risk factor there were 3 with GVHD. 1 had a blood infection and was a failure due to insufficient response with documented persistence, 1 had a sinus infection and was a failure due to insufficient response with documented persistence, and 1 had a blood isolate and was a complete success. Of the subjects with profound neutropenia, 1 had a blood isolate and was a failure due to insufficient response and one had blood and urine infections and was a failure due to insufficient response.

A total of 7 subjects died during the study period or follow-up, and all deaths were due to underlying disease.

2 patients had a follow-up assessment: one with blood and urine infections was stable at 28 days post-treatment; the other with a blood infection alone was a cure at 33 days.

Mean calculated survival day from the start of treatment was 32.1 days (SD 38.7), median 19 range 2, 138.

In conclusion, voriconazole appeared marginally effective in the treatment of refractory infections due to *Candida glabrata* with a large number of failures from the blood, one of the most common foci of infection with this isolate. The MO does not recommend approval for the use of voriconazole in the treatment of infections due to *Candida glabrata.*

Table 13
Outcome by site/isolate
Candida glabrata

	Complete success	Partial success	Failure ALL	IR	S	UN	D
Blood	2	-	4	3	-	1	-
Cerebral	-	-	1	1	-	-	-
Kidney	1	-	-	-	-	-	-
Urine	-	-	1	1	-	-	-
Pulmonary	1	-	1	-	-	1	-
Hepato/splenic	-	-	1	-	-	1	-
Prosthetic valve	-	-	1	-	-	1	-
Sinus	-	-	1	1	-	-	-
Bile	-	-	1	1	-	-	-
Biliary Tract	1	-	-	-	-	-	-
Ascitic fluid	1	-	-	-	-	-	-

IR = Insufficient Response, D = Death, S = Stable, UN = Unevaluable

Candida tropicalis
(N = 7 isolates from 6 patients):

Subjects with *Candida tropicalis* primarily suffered from hematologic malignancies (5/6, 83%)and one subject had other malignancy. All subjects had definite infection and 1 had 2 sites of infection (60410366025 blood, skin). There were no subjects with mixed infection in this group.

All subjects received prior antifungal treatment with a mean duration of prior treatment of 20.3 days and a median of 21.5 (range 8, 29).

Mean age of the subjects was 45.6 (median 51.5 range 9 – 70); 2 were male and 4 were female.

5 subjects had blood isolates, and there were 1 each skin and muscle isolates.

Mean duration of voriconazole treatment was 64 days (median 62.5 days).

Overall per patient success rate was 3/6 or 50% at the EOT and there were no relapses.

The most common cause of failure was insufficient response (2), followed by failure due to intolerance in 1.

Global response was assessed as partial in 4/6 (67%) and as failure in 2 subjects (33%).

Mycologic response was persistence in 1 subject, indeterminate in 3 subjects with 4 isolates, and unknown because it was not a protocol requirement in 2.

Of 5 subjects with a documented risk factor there were 3 with profound neutropenia. 1 of these had a blood infection and was a failure due to insufficient response with documented persistence, and 1 had a blood infection and was a partial success. The remaining subject with profound neutropenia had a muscle infection and was a partial success. One subject had a relapsing hematologic malignancy with skin and blood infections, both partial successes. The final patient with a known risk factor had an autologous BMT, a blood infection, and a failure due to insufficient response.

A total of 2 subjects died during the study period or follow-up, and all deaths were due to underlying disease.

None of the cases had a follow-up assessment.

Mean calculated survival day from the start of treatment was 118.6 days (SD 117.1), median 105.5 range 10, 247.

In conclusion, voriconazole appeared somewhat effective in the treatment of refractory infections due to *Candida tropicalis.* However given the very small number of isolates, the MO does not recommend an approval for voriconazole as treatment of infections due to *Candida tropicalis.*

Table 14
Outcome by site/isolate
Candida tropicalis

	Complete success	Partial success	Failure ALL	IR	S	UN	D
Blood	-	2	3	2	-	1	-
Muscle	-	1	-	-	-	-	-
Skin	-	1	-	-	-	-	-

Candida parapsilosis
(N = 2 isolates from 2 patients):

Both subjects with *Candida parapsilosis* suffered from malignancies (1 hematologic and 1 other) and both had definite infections. There were no subjects with mixed infection.

Both subjects received prior antifungal treatment with a mean duration of prior treatment of 21.5 days and a median of 21.5 (range 12, 31).

Mean age of the subjects was 17.5 (median 17.5 range 16, 19); both were males.

1 subject had a blood infection and 1 a sinus infection.

Mean duration of voriconazole treatment was 60 days (median 60 days).

Overall per patient success rate was 2/2 or 100% at the EOT and there were no relapses.

Global response was assessed as complete in both subjects.

Mycologic response was eradication in both.

1 subject was s/p BMT and had a complete resolution of his sinus infection. The other had no known risk factor.

Neither of the subjects died during the study period or follow-up.

One of the cases (fungemia) had a follow-up assessment at 22 days and was classified as a cure.

Mean calculated survival day from the start of treatment was 83 days (SD 76.3), median 83 range 29, 137.

In conclusion, voriconazole appeared effective in the treatment of refractory infections due to *Candida parapsilosis.* However given the very small number of isolates, the MO does not recommend an approval for voriconazole as treatment of such infections.

Table 15
Outcome by site/isolate
Candida parapsilosis

	Complete success	Partial success	Failure ALL	IR	S	UN	D
Blood	1	-	-	-	-	-	-
Sinus	1	-	-	-	-	-	-

***Candida* spp.**
(N = 10 isolates from 8 patients):

Subjects with *Candida* spp. infections primarily had underlying hematologic malignancies (6, 75%). 1 patient was immunosuppressed and one had another malignancy. 4 subjects had definite infection and 4 had probable infections. 1 subject with a definite skin and blood infection also had a probable hepatosplenic infection (30120100001). All subjects received prior antifungal treatment with a mean duration of prior treatment of 21.1 days and a median of 26 (range -1, 31).

Mean age of the subjects was 44.8 (median 50.5, range 2, 65); 4 were male and 4 were female.

1 subject had 3 isolates and the remaining 7 subjects had 1 isolate each. 1 subject had a mixed infection and that subject's outcome is in the following table:

Subject Number	Baseline Pathogens	Site(s)	Outcome
312-03040001 (salvage)	*A. fumigatus* *Candida* sp.	Pulmonary Mediastinum	Failure

2 subjects had blood isolates, 1 had a pulmonary isolate, 3 had skin isolates, 2 had hepatosplenic isolates, and 1 had a mediastinal infection.

Mean duration of voriconazole treatment was 84.2 days (median 66.5 days).

Overall per patient success rate was 6/8 or 75% at the EOT. And there was 1 relapse; therefore the complete and partial success rate was 5/8 (63%) at follow-up. 1 of the failures was in a mixed infection patient and the other in the patient with 3 isolates, was due to insufficient response.

The most common cause of failure was insufficient response in both subjects. Relapse was seen in a patient with hepatosplenic candidiasis who initially was classified as a complete success.

Global response was assessed as partial in 4 (50%), as failure in 2 subjects (25%), and was not assigned in 2 (50%).

Mycologic response was unknown in 5 subjects because it was not a protocol requirement, indeterminate in 2, and not evaluable in 1.

Of 3 subjects with a documented risk factor, 2 with profound neutropenia had skin infections and were partial successes and one with autologous BMT had a pulmonary infection and was also a partial success.

1 subject died during the study period or follow-up, and the death was due to underlying disease.

1case had a follow-up assessment at 90 days post-treatment and was determined to have had a relapse of hepatosplenic disease.

Mean calculated survival day from the start of treatment was 44.8 days (sd 20.5) median 50.5, range 2, 65.

In conclusion, voriconazole appeared effective in the treatment of refractory infections due to *Candida* spp. however, the MO does not recommend an approval because of the absence of speciation and the varying sensitivity patterns of the members of the *Candida* family

Table 16
Outcome by site/isolate
***Candida* spp.**

	Complete success	Partial success	Failure ALL	IR	S	UN	D
Blood	-	1	1	1	-	-	-
Pulmonary	-	1	-	-	-	-	-
Skin	-	2	1	1	-	-	-
Mediastinum	-	-	1	1	-	-	-
Hepato/splenic	1*	1	1	1	-	-	-

*** = Relapse**
IR = Insufficient Response, D = Death, S = Stable, UN = Unevaluable

Outcome by Previous Treatment:

36 of the subjects were prior efficacy failures, 4 were intolerant, and 3 received salvage treatment for unknown reasons. 26 of the 36 subjects who failed prior treatment, were fluconazole failures, 18 of whom had also received AMP B.

Reproduced below is the sponsor's table (modified by MO) of outcome in subjects who received prior fluconazole treatment:

Table 17
Duration of Prior Fluconazole and Outcomes for 26 Patients Receiving Voriconazole as Salvage Therapy.

Duration of prior fluconazole	Voriconazole Success/ Total
< 1 week	5/9 (56%)
> 1 week	4/9 (44%)
> 2 weeks	½ (50%)
> 3 weeks	0/1
> 4 weeks	2/5 (40%)
ALL	12/26 (46%)

Of these 26 fluconazole failures, 12/26 (46%) subjects who failed fluconazole treatment were treated successfully with voriconazole.

16/43 (37%) of salvage patients had failed prior AMP B therapy and 9 (56%) were successfully treated with voriconazole. The duration of prior AMP B treatment (all formulations) and

outcomes for patients receiving salvage therapy with voriconazole are shown below in the sponsor's table copied and modified by the MO.

Table 18
Duration of Prior Amphotericin B Treatment and Outcomes for Patients Receiving Voriconazole as Salvage Therapy

Duration of prior amphotericin B	Voriconazole Success/ Total
≤ 1 week	2/4 (50%)
> 1 week	¼ (25%)
> 2 weeks	3/3 (100%)
> 3 weeks	1/1 (100%)
> 4 weeks	2/4 (50%)
ALL	9/16 (56%)

One other patient had received prior itraconazole treatment for 285 days and had failed this regimen, but was a success on voriconazole therapy.

Conclusion: Voriconazole was effective in the successful treatment of *Candida* infections in 12/26 subjects who had failed previous fluconazole treatment and in 9/16 (56%) of subjects who had failed AMP B treatment. The sample size was too small however to allow for any comments regarding the relationship between duration of previous treatment and outcome.

General efficacy by underlying disease:

Table 19
Success rate by Underlying Disease

Underlying Disease	Complete Success	Partial Success	All Success	Failure
Hematologic malignancy	3	7	10	11
Immunosuppression	-	1	1	2
AIDS	-	1	1	-
Transplant	3	-	3	1
CGD		-	-	1
Malignancies (other)	1	2	3	2
Surgery	-	-	-	1
Aplastic Anemia	-	-	-	2
Other	3	1	4	1
ALL	10	12	22	21

Relapses = 2

21/43 (349%) subjects had underlying hematologic malignancies. 3 of these were classified as complete successes, 7 as partial successes, 9 as failures due to insufficient response, 1 as failure/stable, and 1 as a failure due to discontinuation. Thus. The overall success rate was 48%. Of note, of the failures due to insufficient response, 4 had *Candida glabrata* and the remaining 5 had 1each of the other *Candida* species.

3/43 (7%) subjects had immunosuppression due to disease or drugs. Of these, 1 subject (33%) was a partial success (*Candida albicans)* and the remainder were failures (1 unevaluable (*Candida albicans*) and 1 due to insufficient response (*Candida* spp.).

1/43 (2%) subject had AIDS/HIV as the underlying disease process and was classified as partial success (*Candida albicans*).

4/43 (9.3%) subjects had a history of transplant. Of these, 3 were classified as complete successes (75%) and 1 as a failure due to insufficient response. 2 of the patients with complete successes had liver transplants and infection due to *Candida glabrata.* 1 patient with a kidney transplant and *Candida albicans* was a failure and 1 patient with a lung transplant and *Candida albicans* was a complete success.

1/43 (2%) subject with CGD and *Candida glabrata* was classified as a failure due to discontinuation.

5/43 (12%) subjects had other malignancies with a complete and partial success rate of 3/5 (60%). 2 patients were failures 1 with *Candida albicans* and 1 with *Candida tropicalis.*

1/43 (2%) subject with a history of surgery and *Candida glabrata* was classified as a failure due to discontinuation.

2/43 (5%) subjects had aplastic anemia both of whom were failures due to insufficient response (one each *Candida glabrata* and *Candida krusei*).

5/43 (4%) subjects (6 isolates) had other underlying diseases. 3 were classified as successes; 2 complete (*Candida krusei, Candida parapsilosis*); 1 partial (*Candida albicans*) and 1 was classified as a failure/stable (*Candida* spp.).

Conclusion: The sample size was too small to draw valid conclusions. It appeared as if subjects with underlying hematologic malignancies had a lower success rate that those with a history of trauma or other underlying diseases.

Analysis by Risk Factor:

8/43 (19%) of subjects had documented profound neutropenia. 3 (38%) of these subjects were classified as partial successes after voriconazole treatment and the remaining 5 (62%) subjects were failures including failure due to insufficient response in 4, and failure due to discontinuation in 1. Of note, of the four neutropenic patients with documented *Candida krusei* infection, two had successful outcomes

Table 20
Outcome in Neutropenic subjects with *Candida krusei*

PID	Site of infection	Underlying Condition	Outcome
604 1068 6119	Blood	Hematologic malignancy	Success
301 0330 0001	Disseminated (blood, skin)	Hematologic malignancy	Success
606 5003 0001	Blood	Hematologic malignancy	Failure
606 5019 0024	Disseminated (blood, skin)	Hematologic malignancy	Failure

35/43 (81%) of subjects were non-neutropenic. 19 (54.%) were considered successes at the end of voriconazole therapy. 6 of these subjects had *Candida krusei* infections and 4 had successful outcomes.

1/42 (2%) subjects with autologous BMT was a partial successes.

5/43 subjects (12%) with allogeneic BMT were classified as complete success in 2 and failure due to insufficient response in 3.

4/43 (9%) subjects had GVHD. 1 of these were classified as partial success and 2 were failures, one stable and one due to insufficient response.

1(2%) subject had a risk factor of relapsed hematologic malignancy. This subject was a partial success.

23/43 subjects (53%) had no known risk factor. 7 (30%) of these subjects had a partial response and 6 (26%) a complete response. The remaining 10 (47%) subjects were failures due to insufficient response in 7, failure/stable in 1, intolerance in 1, and unevaluable in 1.

1 subject was classified as a post BMT and was a complete success.

Conclusion: 20/43 (47%) subjects had a documented risk factor. This number was too small to allow for valid conclusions. 3/8 (38%) of subjects with profound neutropenia including 2 with *Candida krusei* and 19/35 (54%) without neutropenia including 4 subjects with *Candida krusei* were treated successfully with voriconazole.

Analysis by site of Infection:

6 subjects had hepatosplenic candidiasis, 3 with *Candida* spp. and 1 each with *Candida glabrata* and *Candida albicans.* There was 1 subject with hepatosplenic disease due to an unspecified

yeast. 4 subjects failed treatment, 2 due to insufficient response and 1 was a failure/stable. 1 patient discontinued treatment. There were 2 successes, one complete due to *Candida* spp. that later relapsed, and 1 partial due to *Candida* spp.

24 subjects had fungemia, 2 with *Candida albicans* (both failures), 6 with *Candida glabrata* (3 failures due to insufficient response, 1 failure due to discontinuation, and 2 complete responses), 8 with *Candida krusei* (2 complete success, 2 partial success, 3 failures due to insufficient response and 1 due to discontinuation), 1 due to *Candida parapsilosis* (complete success), 2 due to *Candida* spp. (1 partial success and 1 failure due to insufficient response), and 5 due to *Candida tropicalis* (2 failures due to insufficient response, 1 due to discontinuation, and 2 partial successes).

6 subjects had skin/subcutaneous infections, 3 due to *Candida* spp., and 1 each due to *Candida albicans, Candida tropicalis,* and *Candida krusei.* 4 were partial successes (*Candida albicans, Candida tropicalis,* and *Candida* spp. x 2) and 2 were failures due to insufficient response (1 due to *Candida krusei* and 1 due to *Candida* spp.)

6 subjects had pulmonary infections due to *Candida albicans in* 3, *Candida glabrata* in 2 and *Candida spp.* in 1. 2 subjects were complete successes (1 each *Candida albicans* and *Candida glabrata*) and 1 was partial success *Candida* spp.). The remaining subjects were failures (1 each stable, insufficient response, and discontinuation).

3 subjects had cerebral disease and all were failures due to insufficient response. Etiologic agents included *Candida albicans, Candida krusei,* and *Candida glabrata.*

15 subjects had other sites infected with *Candida.* 4 of these had a complete response (UT: *Candida krusei,* kidney, biliary tract, and ascitic fluid: Candida glabrata). 5 had a partial response (OPC and tonsil: *Candida albicans,* tonsil: *Candida krusei,* muscle: *Candida tropicalis,* OPC: *Candida krusei*).

Finally there was 1 bone infection (partial success due to *Candida albicans*), 2 sinus infections (1 failure due to *Candida glabrata* and 1 success due to Candida parapsilosis and 1 esophageal infection due to *Candida albicans* (failure).

Conclusion: The sample size was too small to allow for valid conclusions regarding the outcome of refractory *Candida* infections by site of infection. 2/6 subjects with hepatosplenic candidiasis, 10/24(17%) with candidemia, 4/6 (67%) with skin infections, 2/6 with pulmonary infections, and 9/15 subjects with other sites of infection were treated successfully with voriconazole. All subjects with cerebral disease failed.

D. Efficacy Conclusions

Voriconazole appeared relatively effective as salvage therapy in the treatment of refractory Candida infections due to Candida albicans and Candida krusei. Success rates were 5/12 (42%) or 4/12 with relapse (33%) in a by patient analysis of *Candida albicans* (by pathogen: 5/14 (36%) or 4/14 (29%) with relapses) and 6/10 (60%) in a by patient analysis for *Candida krusei*

(by pathogen 7/13 (54%). Although the success rates are not high especially for *Candida albicans* spp. infections, the mortality associated with these infections can be very high and thus the success rates obtained with voriconazole are of significance for patients with these refractory infections.

Voriconazole was marginally effective in the treatment of infections due to *Candida glabrata* with a large number of failure in patients with candidemia (success by patient 4/12 (33%) and by pathogen 6/17 (35%). As the success rates versus *Candida glabrata* are similar to those attained versus *Candida albicans*, a final decision regarding approval can only be made based on the bulk of the evidence of voriconazole's effectiveness versus this pathogen in a population with non-refractory but with disseminated disease.

Conclusions regarding the efficacy of voriconazole in the treatment of infections due to *Candida tropicalis* and *Candida parapsilosis* could not be drawn due to the small number of isolates.

The total sample size of 43 subjects was too small to draw valid conclusions regarding the efficacy of voriconazole depending on the underlying disease process. It appeared as if subjects with underlying hematologic malignancies had a lower success rate that those with a history of trauma or other underlying diseases.

20/43 (47%) subjects had a documented risk factor. This number was too small to allow for valid conclusions. 3/8 (38%) of subjects with profound neutropenia including 2 with *Candida krusei* and 19/35 (54%) without neutropenia including 4 subjects with *Candida krusei* were treated successfully with voriconazole.

Total by patient success rate was 22/43 (51%) or 20/43 (46.5%) excluding relapses. Total by pathogen rate was 30/64 (47%) or 28/64 (44%) excluding relapses.

The sample size was too small to allow for valid conclusions regarding the outcome of refractory *Candida* infections by site of infection. 2/6 subjects with hepatosplenic candidiasis, 10/24(17%) with candidemia, 4/6 (67%) with skin infections, 2/6 with pulmonary infections, and 9/15 subjects with other sites of infection were treated successfully with voriconazole. All subjects with cerebral disease failed.

VI. Dosing, Regimen, and Administration Issues

The following table presents the recommended dosing regimen for voriconazole.

	Intravenous	Oral	
		Patients 40 kg and above	Patients less than 40 kg
Loading Dose Regimen	Two doses of 6 mg/kg separated by 12hour interval in first day	Two doses of 400 mg separated by 12-hour interval on first day	Two doses of 200 mg separated by 12-hour interval on first day
Maintenance Dose	3 mg/kg every 12 hours***	200 mg BID**	100 mg BID*
Dosage Adjustment: If inadequate patient response, increase dose up to: *** 4 mg/kg every 12 hours ** 300 mg BID * 150 mg BID If subjects are unable to tolerate treatment at these higher doses, reduce dose by 1 mg/kg IV or 50 mg oral steps to original dose.			

VII. Use in Special Populations

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

Of the 98 subjects included in the FDA dataset, 65 subjects were male (66%) and 33 (34%) were female. There did not appear to be a gender effect regarding efficacy. 27 of the treated males (41%) were complete or partial successes as compared to 17 of the women (52%). However, the sample sizes were too small to allow for valid comparisons.

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

Of the 98 subjects in the dataset, 10 (10%) were < 16 and 7 (7%) were > 65 years of age. No specific comments could be made based on age, as the sample size was too small to allow for valid conclusions.

83/98 (85%) of subjects were white. No conclusions could be drawn regarding the effects of race on the efficacy of voriconazole given the small sample size and the skewed population evaluated.

C. Evaluation of Pediatric Program

The MO defers to the primary medical reviewer for comment.

D. Comments on Data Available or Needed in Other Populations

Voriconazole was not adequately studied in non-Caucasians with rare or refractory fungal infections and data of its effects in other ethnic groups and races should be compiled at a later date. Additionally, data on the efficacy and effects of voriconazole in both the geriatric and pediatric populations should be compiled in the post-approval phase. There were no additional populations to be studied within the rare infections indication, however the sample size of patients with rare fungal infections was small. In addition, the lack of a comparative study makes

it difficult to draw valid conclusions. It is strongly suggested that data on efficacy in these infections continue to be collected in the post-approval phase.

VIII. Conclusions and Recommendations

A. Conclusions

Voriconazole appeared relatively effective as salvage therapy in the treatment of refractory Candida infections due to *Candida albicans* and *Candida krusei*. Success rates were 5/12 (42%) or 4/12 with relapse (33%) in a by patient analysis of *Candida albicans* (by pathogen: 5/14 (36%) or 4/14 (29%) with relapses) and 6/10 (60%) in a by patient analysis for *Candida krusei* (by pathogen 7/13 (54%). Although the success rates are not high especially for *Candida albicans* spp. infections, the mortality associated with these infections can be very high and thus the success rates obtained with voriconazole are of significance for patients with these refractory infections.

Voriconazole was marginally effective in the treatment of infections due to *Candida glabrata* with a large number of failure in patients with candidemia (success by patient 4/12 (33%) and by pathogen 6/17 (35%). As the success rates versus *Candida glabrata* are similar to those attained versus *Candida albicans*, a final decision regarding approval can only be made based on the bulk of the evidence of voriconazole's effectiveness versus this pathogen in a population with non-refractory but with disseminated disease.

Conclusions regarding the efficacy of voriconazole in the treatment of infections due to *Candida tropicalis* and *Candida parapsilosis* could not be drawn due to the small number of isolates.

The total sample size of 43 subjects was too small to draw valid conclusions regarding the efficacy of voriconazole depending on the underlying disease process. It appeared as if subjects with underlying hematologic malignancies had a lower success rate that those with a history of trauma or other underlying diseases.

20/43 (47%) subjects had a documented risk factor. This number was too small to allow for valid conclusions. 3/8 (38%) of subjects with profound neutropenia including 2 with *Candida krusei* and 19/35 (54%) without neutropenia including 4 subjects with *Candida krusei* were treated successfully with voriconazole.

Total by patient success rate was 22/43 (51%) or 20/43 (46.5%) excluding relapses. Total by pathogen rate was 30/64 (47%) or 28/64 (44%) excluding relapses.

The sample size was too small to allow for valid conclusions regarding the outcome of refractory *Candida* infections by site of infection. 2/6 subjects with hepatosplenic candidiasis, 10/24(17%) with candidemia, 4/6 (67%) with skin infections, 2/6 with pulmonary infections, and 9/15 subjects with other sites of infection were treated successfully with voriconazole. All subjects with cerebral disease failed.

B. Recommendations

The MO recommends approval for use of voriconazole in the treatment of serious fungal infections caused by *Candia albicans* and *Candia krusei*. in subjects intolerant of or refractory to other therapy. The MO does NOT recommend approval for other *Candida* species as requested by the applicant as the sample size studied was small and the outcomes inconclusive. The recommendation for approval for *Candida albicans* is based on the bulk of evidence within the NDA that supports the activity of voriconazole versus *Candida albicans* and on the fact there is no other currently approved oral antifungal with a refractory candidiasis indication and that the severity of the infections as well as the underlying diseases in the patients studied indicate the medical need for an oral antifungal for this indication.

It is recommended that the applicant's proposed labeling be revised from:

VFEND™ is indicated in the treatment of refractory infections

The MO does NOT recommend approval for the following requested indication:

This non-approval is recommended because of the broadness and the lack of specificity of the proposed indication. The issuance of such a generalized approval is not feasible given the vastly different clinical responses (depending upon underlying disease and presence or absence of risk factors) that can be seen as well as the varying efficacy rates between the different species of *Candida*.

AMENDMENT to MOR of VORICONAZOLE NDAs 21-266 and 21-267

Indication: Refractory Candidiasis

Background:

Pfizer submitted 2 new drug applications (NDA) 21-266 and 21-267 for the use of the intravenous and oral solution formulations of voriconazole in the treatment of a variety of fungal infections including serious fungal infections caused by *Candida* spp. in patients intolerant of, or refractory to, other therapy.

After a review of 43 subjects with 64 isolates the MO recommended approval for use of voriconazole in the treatment of serious fungal infections caused by *Candida albicans* and *Candida krusei* in subjects intolerant of or refractory to other therapy. The MO did NOT recommend approval for other *Candida* species as requested by the applicant, as the sample size studied was small and the outcomes inconclusive. The recommendation for approval for *Candida albicans* was based on the bulk of evidence within the NDA that supported the activity of voriconazole versus *Candida albicans* and on the fact there is no other currently approved oral antifungal with a refractory candidiasis indication and that the severity of the infections as well as the underlying diseases in the patients studied indicate the medical need for an oral antifungal for this indication.

Success rates by pathogen and by patient can be seen below:

Table 1
Complete and Partial Success Rates by Pathogen and by Subject

Complete and Partial Success Rate by Pathogenic Organism	Pathogen	Subjects
Candida albicans	5/14 (36%)* 4/14 ((29%) excluding relapses	5/12 (42%)* 4/12 (33%) excluding relapses
Candida tropicalis	4/7 (57%)	3/6 (50%)
Candida krusei	7/13 (54%)	6/10 (60%)
Candida glabrata	6/17 (35%)	4/12 (34%)
Candida parapsilosis	2/2 (100%)	2/2 (100%)
***Candida* spp.**	6/10 (60%)	6/8 (75%)*
Yeast Unspecified	0/1	0/1
ALL	30/64 (47%)	22/43 (51%)

* = Relapse (1 *Candida albicans*, 1 *Candida* spp.)

Table 2
Complete and Partial Success Rate By Patient and By Pathogen

Complete and Partial Success Rate	By Patient	By Pathogen
FDA	22/43 (51%)	30/64 (47%)

NOTE 2 relapses: 20/43 (47%), 1each *Candida* spp. and C*andida albicans*

On 8/31/01 the sponsor submitted jmp datasets of an additional 22 subjects (24 isolates) with refractory candidiasis. 20 subjects had 1 isolate each and 2 subjects had 2 isolates each, (*Candida albicans, Candida glabrata* 309 20471782: blood and 604 10786079: hand). 15 subjects were from study 309 and 7 were from study 604. 20 subjects had failed previous treatment and 2 were intolerant. 13subjects were male and 9 were female. 9 subjects had *Candida albicans,* 7 had *Candida glabrata,* 2 had *Candida krusei* and there was 1 each: *Candida parapsilosis, Candida tropicalis, Candida famata,* Candida spp., and 1 unspecified fungus as well as 1 yeast suggestive of *Candida albicans.*

2 subjects had AIDS, 3 were immunocompetent, 12 were immunocompromised, and 5 were neutropenic. Mean age was 48.3 (SD 15.6) and median age was 50 (17, 87). Mean duration of treatment was 68.9 days (standard deviation: 31.4), and the median was 64 days (17, 115). Mean duration of IV treatment was 19 days (SD 17.4), and the median was 12.5 days (1, 69). The mean duration of oral treatment was 55.9 days (SD 30.8) with a median of 55 days (6, 110).

By patient global response was complete in 7, partial in 3, failure in 7, stable in 4 and unknown in 1 (died).

By isolate responses included: *Candida albicans*: complete in 2, partial in 1, failure in 3, stable in 2 and unknown in 1; *Candida glabrata*: complete in 2, failure in 2, partial in 1, stable in 1, and unknown in 1; and *Candida krusei:* complete in 1 and failure in 1(both blood isolates).

Conclusion: The addition of 22 subjects with refractory candidal infections due to a variety of species did not add or detract from the MO's original conclusions.

Table 3
Complete and Partial Success Rates by Pathogen and by Subject

Complete and Partial Success Rate by Pathogenic Organism	Pathogen
Candida albicans	8/23 (35%)* 7/23 (30%) excluding relapses
Candida tropicalis	4/8 (50%)
Candida krusei	8/15 (53%)
Candida glabrata	9/24 (38%)
Candida parapsilosis	3/3 (100%)
***Candida* spp.**	6/11 (55%) or 5/11 (45%)
Candida famata	1/1
Yeast Unspecified	1/3
ALL	40/88 (45%) or 38/88 (43%)

* = Relapse (1 *Candida albicans*, 1 *Candida* spp.)

Table 4
Complete and Partial Success Rate By Patient and By Pathogen

Complete and Partial Success Rate	By Patient	By Pathogen
FDA	32/65 (49%)	40/88 (45%)

NOTE 2 relapses: 30/65 (46%), 1 each *Candida* spp. and *Candida albicans or 38/88 (43%)*

Regina Alivisatos, MD
DSPIDP, HFD-590

Concurrence only:
HFD-590/DIVDir/MGoldberger

Cc:
Orig. NDA 21-266 and 21-267
HFD-590
HFD-590/DIVDir/MGoldberger
HFD-590/MTL/CavailleCOle
HFD-590/MO/CoxE
HFD-590/MO/PowersJ
HFD-590/MO/TiernanR
HFD-590/CSO/SalibaJ
HFD-590/Micro/Gosey
HFD-725/Biostat/HigginsK
HFD- 725/DixonC
HFD-520/Biopharm/

9/6/01

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

/s/

Regina Alivisatos
11/29/01 11:51:05 AM
MEDICAL OFFICER

Marc Cavaille Coll
1/3/02 02:14:40 PM
MEDICAL OFFICER

Renata Albrecht
2/7/02 10:57:19 AM
MEDICAL OFFICER

EXECUTIVE SUMMARY
VORICONAZOLE NDAs 21-266 and 21-267

Indication: Voriconazole in the treatment of serious fungal infections caused by *Scedosporium* or *Fusarium* spp. and of other serious fungal infections in patients intolerant of, or refractory to, other therapy.

Background:

Pfizer submitted 2 new drug applications (NDA) 21-266 and 21-267 for the use of the intravenous and oral solution formulations of voriconazole in the treatment of a variety of fungal infections including serious fungal infections caused by *Scedosporium* or *Fusarium* spp. and of other serious fungal infections in patients intolerant of, or refractory to, other therapy. The proposed dosing schedule can be seen in the applicant's table below.

	Intravenous	Oral	
		Patients 40 kg and above	**Patients less than 40 kg**
Loading Dose Regimen	Two doses of 6 mg/kg separated by 12hour interval in first day	Two doses of 400 mg separated by 12-hour interval on first day	Two doses of 200 mg separated by 12-hour interval on first day
Maintenance Dose	3 mg/kg every 12 hours***	200 mg BID**	100 mg BID*
Dosage Adjustment: If inadequate patient response, increase dose up to: *** 4 mg/kg every 12 hours ** 300 mg BID * 150 mg BID If subjects are unable to tolerate treatment at these higher doses, reduce dose by 1 mg/kg IV or 50 mg oral steps to original dose.			

The indication(s) as it appears in the proposed label is as follows:

[redacted]

Clinical Studies:

The clinical data in the applicant's NDA submission were derived from 4 phase 2/3 open, multicenter, non-comparative studies (150-303, 150-304, 150-309, and 150-604) as well as from 4 compassionate use studies (150-301, 150-303a, 150-304a, and 150-606). Studies 150-309 and 150-604 (open, non-comparative trials in subjects intolerant have or failing other therapies or with infections for which there is no approved therapy (interim analyses) were the primary studies from which data were collected.

The CRFs of all cases identified by the applicant as having an infection with a rare fungal isolate were reviewed by the MO. Subjects were assessed for key elements including (i) primary underlying condition, (ii) hematological risk factor, (iii) previous antifungal treatment, (iv)

infection details with pathogen, site, and certainty of infection, and (v) outcome. Subjects included in the applicant's database from studies other than 309 and 604, often did not have baseline cultures or histology to document the presence of an infection and were included in the applicant's database based only on investigator comments made when requesting voriconazole for compassionate use. A review of these protocols (301, 303A, 603, 606) revealed that the submission of cultures or other evidence was not an inclusion criterion, that these studies were not monitored, and that the verification of cases was difficult in the absence of culture information. Therefore, the MO determined to exclude any case from these protocols where culture or other evidence of a deep fungal infection was not provided. For studies 309 and 604, where the submission of cultures was an inclusion criterion and where the subjects were monitored, the MO accepted all cases.

The MO requested that the applicant submit any additional cases of *Fusarium* or *Scedosporium* spp. infection not included in the 11/2000 submission, but collected after the original cutoff date. This request was made in order to increase the size of the database for these fungal pathogens and thus to allow for a larger sample size on which to base a regulatory decision.

98 subjects with 147 isolates were included in the FDA database. The primary efficacy variable was the global response (complete, partial, stable, or failure) evaluated by the investigator at EOT/week 16 (for subjects continuing with voriconazole therapy), based on their overall clinical, mycological, radiological, and serological responses. Global response was also assessed 4 weeks after EOT (and compared with EOT) in subjects who stopped voriconazole therapy at or before week 16 and whose global response at EOT was complete, partial, or stable disease. Clinical, radiological, mycological, and serological responses were evaluated at weeks 2, 8, 12, or EOT/week 16 (for those subjects continuing therapy). Clinical response was also evaluated at weeks 1 and 4. When available the applicant's VERA assessments took precedence over the investigators. Those subjects who were in compassionate use protocols did not undergo VERA. Subjects with complete or partial successes were determined to have satisfactory response or a success.

The primary population assessed by the MO was the MITT, defined as subjects that received at least one dose of voriconazole, had a definite or probable diagnosis of systemic or invasive fungal infection at baseline as confirmed by the review of culture or histology reports by the MO, and were recruited on or before 26 May, 1999 (Study 150-604) or May 31, 1999 (Study 150-309). An additional 10 subjects who were treated after the original cut-off date were also included.

The applicant's MITT population consisted of 101 subjects not including subjects counted twice because of mixed infections or 111 including such patients. The applicant's overall success rate by pathogen was 64/137 (47%) and by patient was 45/101 (45%). The by pathogen breakdown included a 59% success rate for *Scedosporium apiospermum* and a 40% success rate for *Fusarium* spp. These rates do not take relapses into account. Relapses were counted as failures by the MO but not by the applicant.

Table 1
Complete and Partial Success Rates for Applicant and FDA Populations by Organism

Complete and Partial Success Rate by Pathogenic Organism	Applicant Isolates	FDA Isolates	Applicant Subjects with Organism	FDA Subjects with Organism
Scedosporium apiospermum/ Pseudoallescheria boydii	24/36 (67%)	22/33 (67%) *5 relapses 17/33 (52%)	16/27 (59%)	15/25 (60%) * 3 relapses 12/25 (48%)
***Fusarium* spp.**	7/23 (30.4%)	12/32 (38%) * 3 relapses 9/32 (28%)	6/15 (40%)	9/21 (43%) * 2 relapses 7/21 (33%)
Scedosporium inflatum/ Scedosporium prolificans	3/10 (30%)	4/12 (33%)	2/8 (25%)	2/8 (25%)

Table 2
Complete and Partial Success Rate By Patient and By Pathogen

Complete and Partial Success Rate	By Patient	By Pathogen
Applicant	45/101 (45%)	64/137 (47%)
FDA	43/98 (44%) or 38/98 (39%) excluding relapses	68/147 (46%) or 60/147 (41%) excluding relapses

As per the FDA analysis, total by patient success rate was 43/98 (44%) or 38/98 (39%) excluding relapses. Total by pathogen rate was 68/147 (46%) or 60/147 (41%) excluding relapses. Voriconazole appeared relatively effective as salvage therapy in the treatment of fungal infections due to *Scedosporium apiospermum/Pseudallescheria boydii* and in those due to *Fusarium solani/Fusarium* spp. in subjects refractory to or intolerant of conventional antifungal treatments. Success rates were 15/25 (60%) or 12/25 (48%) in a by patient analysis of *Scedosporium apiospermun* (by pathogen: 22/33 (67%) or 17/33 (52%) with relapses) and 9/21 (43%) or 7/21 (33%) with relapses in a by patient analysis for *Fusarium* spp. (by pathogen 12/32 (38%) or 9/32 (28%) with relapses. Although the success rates are not high especially for *Fusarium* spp. infections, the mortality associated with these infections can be > 80%, thus the success rates obtained with voriconazole are clearly an improvement and provide an obvious benefit to patients.

Voriconazole was ineffective in the treatment of infections due to *Cryptococcus neoformans/Cryptococcus* spp. including CNS infections and is not recommended for such processes (success by patient 4/13 (31%) and by pathogen 6/21 (29%). Although the success rates versus *Cryptococcus* spp. are similar to those attained versus *Fusarium* spp., the rates that are attainable with conventional antifungal therapies are much higher; thus voriconazole would not be beneficial in such a population. Additionally, voriconazole was ineffective in the treatment of zygomycosis (success 0/4).

Conclusions regarding the efficacy of voriconazole in the treatment of infections due to *Scedosporium prolificans/inflatum* and *Paecilomyces lilacinus* could not be drawn due to the small number of isolates. Additionally, no conclusions could be drawn regarding the efficacy of

voriconazole in the treatment of a number of other fungal pathogens that did not have an adequate sample size to allow for conclusions.

The total sample size of 98 subjects was too small to draw valid conclusions regarding the efficacy of voriconazole depending on the underlying disease process. It appeared as if subjects with underlying hematologic malignancies had a lower success rate that those with a history of trauma or other underlying diseases.

80/98 (82%) of the FDA subjects were classified as requiring salvage treatment for a variety or reasons and had received varying amounts of previous antifungal treatment. 14 of these subjects were classified as complete successes (18%) and 25 (25%) were classified as partial successes as compared to 1/18 (6%) and 4/18 (22%) respectively of subjects who received voriconazole as primary treatment. 43% of salvage subjects as compared to 28% of primary therapy subjects were successes. As noted in other analyses, the sample size was too small to draw valid conclusions.

28/98 (29%) subjects had a documented risk factor. This number was too small to allow for valid conclusions. As expected, it appeared as if those subjects with profound neutropenia had the worst outcomes.

Special Populations:

Efficacy:

The sample size was too small to allow for the observation of differences in the efficacy rates with respect to race, gender, age, or ethnic group.

Recommendations:

The MO recommends approval for use of voriconazole in the treatment of serious fungal infections caused by *Scedosporium apiospermum* and *Fusarium* spp. in subjects intolerant of or refractory to other therapy. The MO does NOT recommend approval for a first-line indication as requested by the applicant as the sample size studied was small and the studies were non-comparative.

It is recommended that the applicant's proposed labeling be revised from:

[redacted]

as follows:

"VFEND™ is indicated for use in the treatment of serious fungal infections caused by *Scedosporium apiospermum (Pseudallescheria boydii)* and *Fusarium* spp including *Fusarium solani,* in patients intolerant of, or refractory to, other therapy".

The MO does NOT recommend approval for the following requested indication:

[redacted]

This non-approval is recommended because of the non-comparative nature of the studies, the small sample size not only of the total population but of each specific pathogen. The issuance of such a generalized approval is not feasible given the vastly different clinical responses (depending upon underlying disease and presence or absence of risk factors) that can be seen as well as the varying mycological efficacy rates not only of different pathogens but also within the same species.

Medical Officer's Clinical Review of NDAs 21-266 and 21-267

Indication: Voriconazole in the treatment of serious fungal infections caused by *Scedosporium* or *Fusarium* spp. and of other serious fungal infections in patients intolerant of, or refractory to, other therapy.

I. Introduction and Background

A. Applicant, Drug Established and Proposed Trade Names, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

Applicant: Pfizer Global Research and Development
Eastern Point Road
Groton, CT 06340

Date of Submission: November 17, 2000
CDER Stamp Date: November 22, 2000
Date Assigned to MO: April 19, 2001
Date Review completed: July 30, 2001

Drug Name: Voriconazole

Proprietary Name:
VFENDTM (voriconazole) Film-Coated Tablets
VFENDTM I.V. (voriconazole) for Infusion

Pharmacologic Category: Triazole antifungal

Chemical Name: (2R, 3S)-2-(2,4-difluorophenyl)-3-(5-fluoro-4-pyrimidinyl)- 1-(1H - 1,2,4-triazol-1-yl)-2-butanol with an empirical formula of C, H, F, N, O and a molecular weight of 349.3.

Dosage Form: Film-coated tablets for oral administration, and a lyophilized powder for solution for intravenous infusion.

Route of Administration: Intravenous and oral

Strengths: 50 or 200 mg tablets and 200 mg voriconazole in a 30 ml Type I clear glass vial.

Proposed Indications and Usage: VFEND™ is indicated for use in the treatment of serious fungal infections caused by *Scedosporium* spp. and *Fusarium* spp.

VFEND™ is indicated for use in the treatment of other serious fungal infections in patients intolerant of, or refractory to, other therapy.

Materials Reviewed:

NDA volumes 1.1, 1.3 120, 148, 149, 131- 134, 142, 138, 139
JMP datasets submitted 11/17/2000
CDROM with CRFs submitted 5/2/2001
CDROM with CRFs submitted 5/15/2001
CDROM with mycology reports submitted 6/4/2001
CDROM with JMP datasets submitted 5/31/2001
CDROM with WORD version of ISE submitted 6/8/2001
Populated MO tables, response to query submitted 6/19/01,
Email with 11 additional patients submitted 6/22/01
Email revised JMP datasets submitted 6/25/01
Email with JMP datasets submitted 8/31/01

Abbreviations:

CRF = Case Report Form
AMPB = Amphotericin B
ITR = Itraconazole
FLU = Fluconazole
ABLC = Abelcet
BMT = Bone Marrow Transplants
CRF = Case Report Form
AE = Adverse Event
EOT = End of Therapy
MITT = Modified Intent to Treat
CGD = Chronic Granulomatous Disease
GVHD = Craft versus Host Disease

Note on fonts: This review is written in Times New Roman 12. Arial is used for direct quotes from the applicant's submission.

B. State of Armamentarium for Indication(s):

Invasive fungal infections continue to present a major problem particularly in immunocompromised subjects, especially in those with hematologic malignancies (during induction or at the peak of granulocytopenia), those with immunosuppression due to organ transplantation, and in those with AIDS. Many of these subjects die from these infections (mortality ranging from 50 – 80%, Mandell, Douglas, Bennett, "Principles and Practice of Infectious Diseases", Chapter 259, 2000) depending on the causative fungal pathogen. Most common are infections due to *Candida* spp., followed by *Aspergillus* spp. However, in recent years infections due to *Fusarium* spp., zygomycetes, *Scedosporium* spp., and other fungi have been increasingly recognized. Many of these pathogens exhibit resistance to the currently available antifungals including AMP B, the liposomal preparations, ITR, and FLU. There is limited information regarding the *in vitro* activity of the recently approved Cancidas® (caspofungin acetate) versus these pathogens.

At present, although AMP B is routinely used for the treatment of invasive fungal infections in immunocompromised hosts, only ABELCET® (AP 5/96) received an approval (second line) for the treatment of "invasive fungal infections in patients who are intolerant of or refractory to conventional antifungal therapy." This approval was based on the evaluation of 556 cases of serious invasive fungal infections treated through an open label, emergency use trial. 291 cases were mycologically confirmed and there was a complete or partial response to ABLC in 17/24 (71%) of cases of zygomycosis, and 9/11 (82%) of cases of fusariosis. Only 5 cases of phaeohyphomycosis and hyalohyphomycosis were evaluated and response was poor (20%). It was postulated by the authors of the study report and subsequent publication; that this rate was due to the relative resistance of these fungi to AMP B preparations as opposed to the azoles (ABLC for Invasive Fungal Infections: Analysis and Efficacy in 556 cases; Walsh t. J. et all, Clinical Infectious diseases 1998; 26:1383 – 96). The current ABELCET® label states that "For evaluable patients, the following fungal infections were treated (n=282): aspergillosis (n=111), candidiasis (n=87), zygomycosis (n=25), cryptococcosis (n=16), and fusariosis (n=11). There were fewer than 10 evaluable patients for each of several other fungal species treated. For each type of fungal infection listed above there were some patients successfully treated. However, in the absence of controlled studies it is unknown how response would have compared to either continuing conventional amphotericin B therapy or the use of alternative antifungal agents."

This brief review of the current status of available antifungal agents approved for the treatment of rare and/or refractory fungal infections revealed that there is a need to increase the therapeutic options available to physicians in the treatment of severely ill immunocompromised subjects who develop such fungal infections. This need can only increase as the number of subjects with these rare pathogens increases.

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

A. Microbiology

Voriconazole like other azole antifungal agents acts by inhibiting fungal cytochrome P450-dependent 1a-sterol demethylase (P450 DM), an essential enzyme in ergosterol biosynthesis. It is more selective than other azoles for fungal sterol and steroid biosynthesis and has fungicidal as opposed to fungistatic activity. The overall profile of voriconazole indicates that its potent, broad-spectrum antifungal activity *in vitro* translates to excellent efficacy *in vivo* against aspergillosis, candidiasis, cryptococcosis, and scedosporiosis, irrespective of the immune status of the animal.

In vitro, voriconazole demonstrates potent activity against fluconazole-resistant strains of *Candida albicans*, as well as other *Candida* spp. including *Candida krusei* and *Candida glabrata*). Voriconazole is also active against a wide range of less common pathogens, including organisms that are resistant to fluconazole, itraconazole. and amphotericin B including *Fusarium* spp., *Scedosporium inflatum*, *Trichosporon* spp.. and *Pseudallescheria boydii*.

Using the NCCLS macrodilution method, adapted for moulds, Clancy (1) tested the activity of voriconazole and amphotericin B against 25 clinical isolates of *Fusarium*. Voriconazole MICs ranged from 0.25 to 2 mcg/ml, with a GM MIC of 1.2 mcg/ml and a MIC90 of 2 mcg/ml. By contrast, 82% of *Fusarium* isolates were associated with amphotericin B MICs of ³1 mcg/ml, a level that cannot be achieved reliably in serum. In a comparison of the susceptibility of various pathogenic moulds to voriconazole and itraconazole, voriconazole was more active in vitro than itraconazole against the six *Fusarium* isolates tested (2).

Voriconazole has been shown to be highly effective in vivo against systemic and pulmonary aspergillosis, systemic candidosis, scedosporiosis, and pulmonary and intracranial cryptococcosis, in both immune normal and immunocompromised guinea pigs.

1) Clancy, C. J., Y. C. Yu, and M. H. Nguyen. 1997. Comparison of in vitro activity of voriconazole and amphotericin B against filamentous fungi, abstr. E-89, p. 129. In Program and Abstracts of the 37thInterscience Conference on Antimicrobial Agents and Chemotherapy. American Society for Microbiology, Washington, D.C.III.

2) Radford, S. A., E. M. Johnson, and D. W. Warnock. 1997. In vitro studies of activity of voriconazole (UK-109,496), a new triazole antifungal agent, against emerging and less-common mould pathogens. Antimicrob. Agents Chemother. 41:841-843.

B. Pharmacokinetics and Pharmacodynamics

The following were copied from the applicant's PK/PD summary:

- The bioavailability of voriconazole was estimated from the population analysis to be 96% and the estimate of inter subject variability (CV) was 13%.

- Voriconazole is rapidly and almost completely absorbed following oral administration, with maximum plasma concentrations (C_{max}) achieved 1 to 2 hours after dosing.

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

III. Description of Clinical Data and Sources

A. Overall Data

Subjects assessed for the indication of rare fungal infections were obtained from Phase 2/3 non-comparative studies: 150-303, 150-304, 150-309, and 150-604

- **Study 150-303**: Open, non-comparative, multicenter study assessing the efficacy of orally administered voriconazole in the treatment of chronic invasive infections caused by *Aspergillus* spp. or *Candida* spp.

- **Study 150-304:** Open, uncontrolled, non-comparative, multicenter study of the efficacy of voriconazole in the treatment of acute invasive aspergillosis in immunocompromised subjects

- **Studies 150-309 and 150-604:** Open, non-comparative trials in subjects intolerant have or failing other therapies or with infections for which there is no approved therapy (interim analyses).

- Additionally patients were obtained from the following compassionate use studies: 150-301, 150-303a, 150-304a, and 150-606

B. Table Listing the Clinical Trials

Table 3
List of Clinical Trials

Study Number	Indication	Main Region	Study Status	Design
150 – 304	Acute Aspergillosis	Europe	Complete	Non-comparative
150 - 303	Chronic Aspergillosis and Candidiasis	Europe	Complete	Non-comparative
150 - 309	Rare and Refractory Fungal Infections	Europe	Interim Analysis	Non-comparative
150 - 604	Rare and Refractory Fungal Infections	US	Interim Analysis	Non-comparative
150 – 301	Compassionate Use	Europe	Complete	Non-comparative
150 – 303A	Compassionate Use	Europe	Complete	Non-comparative
150 – 304A	Compassionate Use	Europe	Interim Analysis	Non-comparative
150 - 606	Compassionate Use	US	Interim Analysis	Non-comparative

C. Postmarketing Experience

This drug is not marketed at present.

D. Literature Review

1) Medical Mycology 2000; 38 Suppl. 1:225 – 36, Emerging pathogens, Ponton J et al. An assessment of 2 yeast species (*Saccharomyces cerevisiae* and *Candida dubliniensis*) and 2 moulds (*Fusarium* spp. and *Scedosporium prolificans*) as emerging human pathogens.

Specifically regarding *Fusarium*, the authors make the point that it is destined to be one of the "star fungi" of the 21st century because members of this species are ubiquitous, can easily disseminate in immunocompromised hosts, and are resistant to conventional antifungal agents. Over 100 cases have been reported since 1973 and 90 occurred in subjects with acute leukemia. The rate in BMT recipients was 0 – 2% depending on transplant type. Blood, skin, and lung are the most common sites of human infection. These infections are refractory to standard antifungals such as AMP B and systemic triazoles with mortality rates ranging from 50 – 70%. As per the authors, " on the basis of the NCCLS microdilution method adapted for moulds, *Fusarium* isolates (n = 22) showed a limited susceptibility to voriconazole (1 – 16 mcg ml^{-1})."

Regarding *Scedosporium prolificans*, the asexual state of this fungus, is also emerging as a cause of severe and increasingly frequent infections in patients with hematological malignancies. Approximately 100 cases have been published and were often fatal. Most common sites of infections include skin, blood, and lung. Most isolates are resistant to all available antifungals. As per the authors testing of 10 antifungals versus 11 isolates of *Scedosporium apiospermum* and 33 isolates of *Scedosporium prolificans*, revealed excellent activity of voriconazole versus *Scedosporium apiospermum* (MIC 0 – 1 mcg.ml^{-1}) and also performed well versus *Scedosporium prolificans*.

2) Fungal Infections in Patients with Neutropenia; Herbrecht et al, Drugs and Aging 2000 Nov 17 (5): 339 – 351.

Pertinent to this review, the authors' comments regarding a) Fusariosis: Often fatal outcome despite antifungal therapy. High dose intravenous AMP B and lipid formulations are the current mainstay of treatment but newer azoles may be of more benefit; b) Trichosporonosis: Mortality rate in disseminated disease is > 70%. These fungi are resistant to AMP B. Azoles appear more appropriate in the treatment of these infections; c) Cryptococcosis: First line treatment remains IV AMP B with 5FC for 2 weeks followed by FLU; d) Mucormycosis: Despite treatment, mortality ranges in the 80% range. Treatment remains IV AMP B with debridement; e) AMP B remains the standard of treatment of other fungal infections with the exception of those due to *Scedosporium apiospermum* and deep-seated dermatophytes where the use of azoles may be more appropriate.

3) The Epidemiology of fusariosis in patients with hematological diseases; Girmenia et al, British Journal of Hematology 2000. 111; 272 – 276

Fusariosis is increasing in frequency throughout the world although in a non-homogenous manner. Clusters should be considered. At MD Anderson, the rate increased from 5 to 38 cases between 1975 – 85 and 1986 – 95 respectively.

4) Current and future antifungal therapy: new targets for antifungal agents, Andriole, V. T., Journal of Antimicrobial Chemotherapy (1999) 44, 151 – 162

The incidence of invasive fungal infections in immunosuppressed patients continues to increase and they are significant causes of morbidity and mortality. Fungi such as *Fusarium*

spp. are increasing in frequency. *Fusarium* spp, *Trichosporon* spp. and *Pseudoallescheria boydii* are often resistant to AMP B. There is reasonable efficacy of ABLC in these infections but overall there remains a need for well-tolerated and more effective therapies.

5) Disseminated Infection and Colonization by *Scedosporium prolificans:* a review 1990 – 1999, Idigora P. et al, CID 2001:32 (1 June).

Infections can be localized or disseminated and is are usually associated with 3 different human conditions; a) colonization especially respiratory in subjects with cystic fibrosis; b) superficial or deep localized infections in immunocompetent or immunosuppressed subjects including cutaneous, ocular, pulmonary, and osteoarticular infections; and c) disseminated infections in immunosuppressed patients. Species inflatum and prolificans are the same and the names are used interchangeably. Susceptibility testing of 15 isolates revealed resistance to all drugs tested with the azoles having the lower MICs. Voriconazole was used in one of their patients without success.

6) *Fusarium,* a significant emerging pathogen in patients with hematologic malignancy, Boutati EI and Anaissie EJ; Blood, Vol. 90, No 3 (August 1), 1997: pp 999 – 1008
A retrospective analysis of 40 patients with disseminated fusariosis and 3 with invasive lung infections were included. All patients were immunosuppressed. Response was associated with granulocyte transfusions, AMP B lipid formulations (4 each), and voriconazole (2). These infections are associated with a very high mortality and are refractory to currently available antifungals.

7) Mandell, Douglas, Bennett, "Principles and Practice of Infectious Diseases", Chapter 259, 2000: Miscellaneous Fungi and *Prototheca.*

Pseudallescheria boydii (anamorph *Scedosporium apiospermum*): can cause mycetoma or pseudallescheriasis. Most common sites of the latter are lung, bone, joints, and CNS. Other sites have also been described. Portal of entry is via inhalation or trauma. Usually pseudallescheriasis occurs in immunosuppressed subjects and localized disease such as that of the eye can occur in the setting of a non-affected immune system. Effective antifungal therapy has NOT been established. Mortality is subjects with brain abscess is > 75%. Some successes have been reported with miconazole and ketoconazole.

Scedosporium prolificans (inflatum): Subjects with intact immune systems develop localized disease and those who are immunosuppressed develop disseminated disease. Localized disease has been described in the bone, joints, nail and eye. Skin and pulmonary disease are usually found in the setting of dissemination. As above, the treatment of choice is not known as the fungus is inherently resistant to most available antifungals.

Fusarium spp.: disease usually occurs after trauma in healthy and immunocompromised hosts. *Fusarium solani* is one of the most common causes of fungal keratitis. Disseminated disease occurs mostly in subjects with acute leukemia (70 – 80% of cases) and prolonged neutropenia (> 90% of cases). Again optimal treatment has not been established.

IV. Clinical Review Methods

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

CRFs of all cases identified by the applicant as having an infection with a rare fungal isolate were reviewed. This included all fungi excluding *Aspergillus* spp. or yeast such as *Candida* spp. Subjects included in the applicant's database from studies other than 309 and 604, frequently did not have baseline culture or histopathological information to document the presence of an infection and were included in the database based only on investigators comments made when requesting voriconazole for compassionate use. A review of these protocols (301, 303A, 603, 606) revealed that the submission of culture (or other) evidence was not an inclusion criterion, that these studies were not monitored, and that the verification of cases was difficult in the absence of culture (or other) information. Therefore, the MO determined to exclude any case from these protocols where culture or histopathological evidence of a deep fungal infection was not provided. For studies 309 and 604, where the submission of cultures was an inclusion criterion and where the subjects were monitored, the MO accepted all cases.

The MO requested that the applicant submit any cases of *Fusarium* or *Scedosporium* spp. infection not submitted in the 11/2000 submission, but collected since the original cutoff date. This request was made in order to increase the size of the database for each fungal pathogen and thus to allow for a larger sample size on which to base a regulatory decision.

Multiple JUMP datasets were merged and a final FDA population dataset was constructed. Demographics and basic descriptive statistics were performed on this dataset.

The applicant's analyses are presented in brief as the MO accepted the applicant's definitions of response as well as the individual patient responses. This information was in the original 11/2000 submission and included in the 309 and 604 interim study reports as well as in the ISE.

The MO performed a literature search utilizing MEDLINE and EMBASE of all articles within the last 5 years pertinent to the indications. The references generated provided a baseline "success" rate for the infections under review.

B. Were Trials Conducted in Accordance with Accepted Ethical Standards

It appeared as if all trials were conducted ethically and after IRB approval. In all CRFs reviewed, the consent forms were signed.

C. Evaluation of Financial Disclosure

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

V. Integrated Review of Efficacy

A. Brief Statement of Conclusions

Voriconazole appeared relatively effective as salvage therapy in the treatment of fungal infections due to *Scedosporium apiospermum/Pseudallescheria boydii* and in those due to *Fusarium solani/Fusarium* spp. in subjects refractory to or intolerant of conventional antifungal treatments. Although the success rates are not high especially for *Fusarium* spp. infections (33%), the mortality associated with these infections can be > 80%, thus the success rates obtained with voriconazole are clearly an improvement and provide an obvious benefit to patients.

Voriconazole was ineffective in the treatment of infections due to *Cryptococcus neoformans/Cryptococcus* spp. including CNS infections and is not recommended for such processes. Additionally voriconazole was ineffective in the treatment of zygomycosis (success 0/4).

Conclusions regarding the efficacy of voriconazole in the treatment of infections due to *Scedosporium prolificans/inflatum* and *Paecilomyces lilacinus* could not be drawn due to the small number of isolates. Additionally, no conclusions could be drawn regarding the efficacy of voriconazole in the treatment of a number of other fungal pathogens that did not have an adequate sample size to allow for conclusions.

The total sample size of 98 subjects was too small to draw valid conclusions regarding the efficacy of voriconazole depending on the underlying disease process. . It appeared as if subjects with underlying hematologic malignancies had a lower success rate that those with a history of trauma or other underlying diseases.

80/98 (82%) of the FDA subjects were classified as requiring salvage treatment for a variety or reasons and had received varying amounts of previous antifungal treatment. 14 of these subjects were classified as complete successes (18%) and 25 (25%) were classified as partial successes as compared to 1/18 (6%) and 4/18(22%) respectively of subjects who received voriconazole as primary treatment. 49% of salvage subjects as compared to 28% of primary therapy subjects were successes. As noted in other analyses, the sample size was too small to draw valid conclusions.

28/98 (29%) subjects had a documented risk factor. This number was too small to allow for valid conclusions. As expected, it appeared as if those subjects with profound neutropenia had the worst outcomes.

Total by patient success rate was 43/98 (44%) or 36/98 (37%) excluding relapses. Total by pathogen rate was 68/147 (46%) or 60/147(41%) excluding relapses.

B. Detailed Review of Trials by Indication

Studies 150-309 and 150-604 are identical ongoing protocols conducted in Europe and the US respectively.

150-309: An open label, non-comparative, multicenter, phase III trial of the efficacy, safety, and toleration of voriconazole in the primary or secondary treatment of invasive fungal infections

Principal Investigators: Australia: Dr L Dalla Pozza, Dr S Chen. Belgium: Dr M Aoun, Dr F Jacobs, Dr H Spapen, Dr S de Wit. Denmark: Dr L R Mathiesen, Dr J Gerstoft. France: Prof B Dupont, Dr A Datry, Dr R Herbrecht, Prof N Milpied, Dr D Caillot, Dr P Germaud, Dr S Fournier, Dr H La Selve, Dr S Lariven, Dr F Varaigne, Dr C Faucher. Germany: Prof Dr H Lode, Prof Dr H Breithaupt, Prof Dr E Thiel, Dr H Wandt, Prof Dr A Zander, Dr W Langer, Dr R Schwerdtfeger, Prof Dr P Kujath, Prof Dr H Rueckle-Lanz, Dr H Bertz, Dr H Brodt. Italy: Prof C Viscoli. Spain: Dr K Aguirrebengoa, Dr M Rovira, Dr JM Cisneros, Dr J de la Torre Cisneros, Dr J Lahuerta Palacios. United Kingdom: Prof A Goldstone, Prof R Hay.

Interim Study Dates: 31 July 1998 – 20 September 1999 (interim cut-off date)

Study Objectives: The primary objective of this study was to investigate the efficacy, safety, and toleration of voriconazole in the treatment of systemic and invasive fungal infections for which there was no licensed therapy and in the treatment of systemic or invasive fungal infections in subjects failing or intolerant of other treatments. The secondary objective was to collect random plasma levels of voriconazole to assist population pharmacokinetic modeling in this diverse group of subjects.

Study Design: Open label, non-comparative study in which all subjects were allocated to receive voriconazole. The investigators used their clinical judgement as to whether initial therapy should be by the intravenous or oral route (oral and intravenous doses of 200mg and 4mg/kg twice daily, respectively). The maximum total duration of voriconazole treatment (intravenous and oral) for any subject was expected to be 12 weeks. The actual total duration of treatment in each subject was determined by the investigator depending on the subject's response. For subjects who continued voriconazole for more than 12 weeks, the end of therapy (EOT) assessments were carried out at week 16 or EOT whichever was sooner. With the agreement of the sponsor, any subject requiring more than 16 weeks of treatment received further voriconazole therapy in continuation protocol 150-311. Subjects who continued in this way had their final assessment recorded as a Week 16 assessment rather than an EOT assessment. The follow up visit took place 4 weeks after EOT for all subjects who completed voriconazole therapy in this study.

Most patients were expected to be hospitalized at the beginning of study treatment and, therefore, were under continuous medical surveillance during the early period of therapy. Those with more chronic disease and those who were discharged from hospital received therapy on an outpatient basis.

Summary of study activities

Study Week	S/BL	1	2	4	8	12	EOT	16	F/U
Informed consent	•								
Medical history	•								
Clinical signs and symptoms[a]	•	•	•	•	•	•	•	•	•
Clinical response		•	•	•	•	•	•	•	•
Imaging (*e.g.* X-ray, CT-scan)	•		•		•	•	•	•	•
Imaging response			•		•	•	•	•	
Mycology (*e.g.* histology and/or specimen culture)	•		•		•	•	•	•	
Mycological response			•		•	•	•	•	
Fungal serology[b]	•		•		•	•	•	•	•
Serological response[b]			•		•	•	•	•	
Global response						•[c]	•[c]	•[c]	•
Plasma/tissue for voriconazole pharmacokinetics		•	•	•	•	•	•	•	
Visual safety[d]	•	———	•		•	•	•	•	•
Laboratory safety tests[e]	•	•	•	•	•	•	•	•	•
Adverse events	•	•	•	•	•	•	•	•	•
Serious adverse events		Immediate reporting to the sponsor							

Source: Protocol (Section 11, Item 1) Appendix A
S/BL – screening/baseline F/U – follow up
[a] The investigator recorded clinical signs and symptoms of fungal infection defined by National Cancer Institute criteria [Protocol (Section11, Item 1) Appendix D].
[b] Where appropriate diagnostic tests were available (see below).
[c] The global response was performed at EOT or week 12 (whichever is the sooner) or up to week 16 for subjects that received extended voriconazole treatment.
[d] Visual function tests were carried out at baseline or within two weeks of baseline for those subjects too ill to have the tests done sooner (see Section 5.6.4).
[e] Laboratory safety tests are described in Section 5.6.3.

Global, clinical, mycological, serological, and radiological (imaging) evaluations were carried out at various points throughout the study (see above table). Sub-cultures of isolates of all fungal pathogen(s) cultured from subjects were sent to the Public Health Laboratory, Mycological Reference Laboratory, Bristol, UK for further investigation. This included confirmation of the identity of the fungal pathogen, speciation and drug sensitivity testing.

The minimum duration of initial intravenous dosing for each subject was three days. Subjects capable of receiving oral therapy at baseline started treatment with voriconazole tablets. Prior to protocol amendment II, no oral loading dose was administered. Subjects switching from intravenous to oral dosing did not receive a loading dose, but commenced directly with 200mg twice daily. Subjects could be restarted on intravenous voriconazole if they were unable to tolerate continued oral dosing (*e.g.* due to gastritis). Subjects switching from oral to intravenous dosing did not receive a second loading dose of intravenous voriconazole (see table above). In addition the maintenance dose of voriconazole was increased after three days of oral voriconazole treatment, if:

- There was a lack of clinical improvement; and
- there had been no treatment related serious adverse events; and
- clinical chemistry parameters were within the protocol specified limits for entry into the study. (Clinical chemistry results from the local hospital laboratory were used pending the results from a blood sample sent to the central laboratory at the time of voriconazole dose escalation. The central laboratory results were used to determine the final eligibility of the subject for dose escalation. If the central laboratory results were not within the range acceptable for entry into the study, voriconazole dose escalation was not permitted);
- the dose had not already been increased due to concomitant medications.

No dose escalation for inadequate clinical efficacy was permitted during intravenous dosing with voriconazole. Dose reduction took place if a subject was unable to tolerate a particular dose. If toleration or safety problems persisted despite dose reduction, it was recommended that treatment with voriconazole be discontinued. Prior to both dose escalation and reduction a plasma sample was taken for subsequent population pharmacokinetic studies.

This was an open, non-comparative study and therefore no randomization took place.

Diagnoses and Criteria for Inclusion of Subjects: Subjects had to be at least 12 years of age, with a diagnosis at baseline and documented within four weeks preceding study entry of a systemic or invasive fungal infection for which there was no licensed therapy or a systemic or invasive fungal infection with evidence of failure and/or intolerance to approved treatments.

Diagnosis of failure was made according the following criteria:

- for invasive aspergillosis and other invasive fungal infections: lack of clinical response after at least 7 days of systemic antifungal treatment at an adequate dose

Diagnosis of intolerance/toxicity to other antifungal agents:

- intolerance to infusion related toxicities of amphotericin B preparations despite appropriate supportive measures
- nephrotoxicity defined as a serum creatinine increased by $\geq$1.5mg/dl while receiving conventional amphotericin B therapy
- pre-existing renal impairment defined as a serum creatinine that has increased to $\geq$2.0mg/dl due to reasons other than conventional amphotericin B therapy

Documentation of baseline fungal infection was determined as follows:

- positive histopathology with evidence of tissue invasion by fungal elements

or

- positive serology (where diagnostic *e.g.* for *Cryptococcus*, CSF antigen; *Coccidioides*, serum or CSF antibody; *Histoplasma*, CSF or urine antigen)

or

- positive mycology culture from a normally sterile site taken during the current episode of infection

Excluded were:

1. Subjects with superficial fungal diseases alone (*e.g.* oropharyngeal candidiasis or dermatophytosis) or allergic bronchopulmonary aspergillosis, pulmonary aspergilloma, zygomycoses, candiduria, catheter- and/or device-related candidemia.

2. Subjects who received or were likely to receive white blood cell transfusions, granulocyte-colony stimulating factor (G-CSF) or granulocyte/macrophage-colony stimulating factor (GM-CSF) for the infection under study (*i.e.* routine use of these growth factors in the treatment of neutropenia, aplastic anemia or other hematologic disease or coadministration with cytotoxic chemotherapy was allowed).

Removal of Subjects from Treatment or Assessment:

A discontinuation was defined as occurring when an enrolled subject ceased participation in the clinical trial, regardless of circumstances, prior to their completion of the protocol. The reason for a subject discontinuing was recorded on the CRF. The final evaluation required by the protocol was performed just prior to study drug discontinuation if medically acceptable. Otherwise, final evaluation was performed as soon as possible after study drug discontinuation.

Efficacy and Safety Evaluations: The primary efficacy variable in this study was the global response (complete, partial, stable, or failure) evaluated by the investigator at EOT/Week 16 (for subjects continuing with voriconazole therapy), based on their overall clinical, mycological, radiological, and serological responses. Global response was also assessed 4 weeks after EOT (and compared with EOT) in subjects who stopped voriconazole therapy at or before week 16 and whose global response at EOT was complete, partial or stable disease. Clinical, radiological, mycological, and serological responses were evaluated at weeks 2, 8, 12, or EOT/week 16 (for those subjects continuing therapy). Clinical response was also evaluated at weeks 1 and 4. If no response for any of the clinical, mycological, serological or radiological responses at EOT was recorded the assessment was set to 'missing' by the applicant and "unknown by the MO".

Table 4
Schedule of Assessments

Assessment	When Assessed	Grading
Clinical Response	Weeks 1, 2, 4, 8, 12, 16, and EOT	Complete, partial, stable, failure
Mycology	Weeks 2, 8, 12, 16, and EOT	Eradication, presumed eradication, persistence, indeterminate
Radiology	Weeks 2, 8, 12, 16, and EOT	Complete, partial, stable, failure
Serology	Weeks 2, 8, 12, 16, and EOT	Normalized, improved, unchanged, worsened, indeterminate
Global Response	EOT or Week 16	Complete, partial, stable, failure
Global Response follow-up	4 weeks after EOT	Cured, improved, stable, relapsed

Definitions:

- **Global response at EOT or week 16 for subjects continuing with voriconazole therapy (primary efficacy variable):** A subject's response was assessed by the investigator as complete, partial, stable, or failure, based on their overall clinical, mycological, radiological, and serological responses.

- **Complete response**
  Resolution of all clinical signs and symptoms, bronchoscopic and/or radiographic abnormalities attributable to fungal infection present at baseline
  AND
  Normal serological response (where appropriate)
  AND
  Mycological eradication (where obtainable)

- **Partial response**
  Major improvement in clinical signs, symptoms, bronchoscopic and/or radiographic abnormalities attributable to fungal infection present at baseline
  AND/OR
  Normal or improved serological response (where appropriate)

- **Stable disease**
  Minor or no improvement in clinical signs, symptoms, bronchoscopic and/or radiographic abnormalities attributable to fungal infection but subject continued on therapy without deterioration
  AND/OR
  Unchanged serological response (where appropriate)

MO Comment: *The category of stable was assessed as a category of failure by both the applicant and the MO.*

- **Failure**
  Deterioration in clinical signs, symptoms, bronchoscopic and/or radiographic abnormalities attributable to fungal infection necessitating alternative antifungal therapy or resulting in death
  AND/OR
  Worsened serological response (where appropriate)
  AND/OR
  Persistence of fungal infection (based on culture, microscopy or histopathology)

In the applicant's analysis, global response was measured with a four point ordered categorical scale. Satisfactory global response was derived in the following way:
Satisfactory Response = Complete or Partial global response
Unsatisfactory Response = Stable or Failure global response
Missing = Missing global response assessment
Subjects who had no EOT global response assessment, or an EOT assessment which fell outside the EOT window had their EOT assessment set to 'missing'.

Medical Officer's Comment: *Global assessments were provided only for those subjects from studies 309 and 604. Global assessments were NOT performed for patients from all other compassionate use studies. Therefore the MO used clinical response as the main determinant of efficacy.*

- **Global Response at Follow up:** 4 weeks after EOT (and compared with EOT) in subjects who stopped voriconazole therapy at or before week 16 and whose global response at EOT was complete, partial or stable disease. Global response was categorized as one of the following:

- **Cured**
  Continued resolution in clinical signs, symptoms, radiographic and/or bronchoscopic findings attributable to the fungal infection compared to EOT and normalized serological response (if applicable).

- **Improved**
  Further improvement in clinical signs, symptoms, radiographic and/or bronchoscopic findings attributable to the fungal infection compared to EOT and improved serological response (if applicable).

- **Stable**
  No improvement in clinical signs, symptoms, radiographic and/or bronchoscopic findings attributable to the fungal infection compared to EOT or unchanged serological response (if applicable).

- **Relapsed**
  Deterioration in clinical signs, symptoms, radiographic and/or bronchoscopic findings attributable to the fungal infection compared to EOT or worsened serological response (if applicable).

♦ **Clinical Response:** Clinical response was evaluated at weeks 1, 2, 4, 8, 12, or EOT/week 16. Clinical response was categorized as one of the following four possible outcomes:

- **Complete**: Resolution of all signs, symptoms and/or bronchoscopic abnormalities attributable to fungal infection present at baseline.

- **Partial**: Major improvement (usually nearly complete) in the signs, symptoms and/or bronchoscopic abnormalities attributable to fungal infection present at baseline.

- **Stable Disease**: Minor or no improvement in the signs, symptoms and/or bronchoscopic abnormalities attributable to fungal infection present at baseline but continued therapy with study drug.

- **Failure**: Deterioration of any signs, symptoms and/or bronchoscopic abnormalities attributable to fungal infection resulting in the use of alternative antifungal therapy or death.

♦ **Mycological Response:** Mycological response was evaluated at weeks 2, 8, 12, or EOT/week 16. It was categorized as one of the following:

- **Eradication**: Absence of original fungal pathogen in a relevant clinical specimen (culture negative and absence of fungal elements by microscopy or histopathology, as appropriate).

- **Presumed eradication**: Inferred in patients with complete clinical and radiological response for whom an invasive procedure for obtaining the relevant clinical specimen was not performed.

- **Persistence**: Any evidence based on culture, microscopy or histopathology for the presence of the original fungal pathogen.

- **Indeterminate**: Inadequate data available for categorization as eradication, presumed eradication or persistence.

Medical Officer's Comment: *In very few subjects evaluated for the rare infections indication were mycological response collected. Therefore the MO made a presumptive assignment of mycological success or failure based on the subjects' clinical response.*

♦ **Radiological Response**
Radiological (imaging) response was evaluated at weeks 2, 8, 12 or EOT/week 16. Radiological response was categorized as one of the following:

- **Complete response**: Resolution (normalization of X-ray, CT-scan *etc*) of all radiological abnormalities attributed to fungal infection compared to baseline.

- **Partial response**: Major improvement of radiological abnormalities attributed to fungal infection compared to baseline.

- **Stable disease**: Minor or no improvement of radiological abnormalities attributed to fungal infection compared to baseline.

- **Failure**: Worsening of radiological abnormalities attributed to fungal infection compared to baseline.

♦ **Serological response**

Serological response was evaluated at weeks 2, 8, 12 or EOT/Week 16. For infections where serological tests were available and recognised as diagnostic for the type of specimen provided (*e.g.* cryptococcosis in CSF, coccidioidomycosis in serum or CSF, histoplasmosis in CSR or urine) response was categorised as one of the following:

- **Normal**: Test result returns to normal value (as for uninfected or cured individuals).

- **Improved**: Test result remains positive but clinically significantly decreased compared with baseline.

- **Unchanged**: No clinically significant change from baseline.

- **Worsened**: Clinically significant increase compared with baseline.

- **Indeterminate**: Sample not available or no result from the sample.

Safety:

Adverse events were recorded throughout the study. Blood and urine for laboratory tests were collected at screening/baseline and weeks 1, 2, 4, 8, 12, EOT/week 16 (in subjects continuing therapy) and at any dose level escalation or reduction. In females of childbearing potential, a pregnancy test was obtained at weeks 4, 8, 12, EOT and 16. Ophthalmologic safety tests were done at any time up to week 2 (baseline) and at weeks 8 and 12 or EOT/week 16 and at the follow up visit.

Statistical Methods: This was a non-comparative study and no formal hypothesis testing was done. Efficacy data were presented using a modified intention to treat (MITT) population that included subjects who received at least one dose of study medication and had a definite or probable fungal infection at baseline as determined by the sponsor. Global response was measured with a four point ordered categorical scale (complete, partial, stable, failure) and satisfactory global response, the primary efficacy endpoint, included 'complete' and 'partial' global responses.

Survival: The applicant provided survival analyses at 30, 60, and 90 days post treatment. These results are not reported here because as noted previously, very few subjects from this study had rare infections.

Protocol amendments:
There were four amendments to this study before the interim cut off date:

Amendment I (11 March 1998)

- To ensure the protocol was conducted in accordance with FDA requirements for adverse event reporting, resulting from their adoption of ICH E2A (Definitions and Standards for Expedited Reporting)

Amendment II (23 April 1998)

- To change the dosing section of the protocol in order to allow the use of an oral loading dose in patients initially treated with oral voriconazole.
- To change the requirement for dose escalation due to inadequate clinical efficacy
- To clarify the dose reduction for intravenous formulation
- To correct a typographical error in the table describing dosing regimens
- To replace clinical response, radiological response and serological response by clinical signs and symptoms, radiological and fungal serology assessments at the follow up visit
- To clarify that only patients with complete response, partial response, or stable response at EOT were to have the follow up assessments
- To update the drug presentation and storage conditions and dosing instructions required for intravenous voriconazole
- To clarify the shipment of plasma and tissue sample and the laboratory that was to perform the voriconazole assay

Amendment III (10 May 1999)

- To ensure optimal monitoring of patient safety by adding screening for risk of occurrence of cardiac arrhythmia and cardiac monitoring during intravenous administration of voriconazole for subjects with history of risk for cardiac arrhythmia. In addition, the fact that simultaneous infusion of voriconazole and blood products or electrolyte supplementation was not allowed was added to the protocol.

Amendment IV (08 June 1999)

- To allow inclusion of subjects with greater degrees of renal insufficiency.
- To allow entry of subjects with *probable* pulmonary aspergillosis in cases where a definitive diagnostic procedure is not usually performed. In allogeneic BMT or neutropenic patients with autologous BMT, hematological malignancy (including lymphoma), aplastic anemia or myelodysplastic syndrome, the following findings supported a diagnosis of *probable* pulmonary aspergillosis: infiltrates, nodules or cavities on chest radiography and/or CT scan that were not attributable to other infection, lymphoma or postoperative changes and a specimen (bronchoalveolar

lavage (BAL) or transbronchial biopsy) collected by bronchoscopy that was positive for *Aspergillus* by culture, histopathology or cytology
- To allow patients to enter the study without having to be extubated.

MO NOTE: *Although the applicant indicated that global response at follow-up was collected on all subjects excluding 1, this information was NOT provided for this interim report.*

The study report submitted by the applicant described an interim analysis including all data collected from clinic visits that took place on or before 20 September 1999. The recruitment cut off date was 31 May 1999. Subjects who were recruited into the study after 31 May 1999 were not considered for the modified intent to treat (MITT) population and their efficacy data were not listed. However, all safety data collected for these subjects on or before 20 September 1999 were listed and summarized.

Study 150-604: An Open Label, Non-comparative, Multicenter, Phase III Trial of the Efficacy, Safety and Toleration of Voriconazole in the Primary or Secondary Treatment of Invasive Fungal Infections.

Principal Investigators: ***USA*****:** Richard Greenberg MD, Pablo Tebas MD, John R. Graybill MD, Janice (Wes) Brown MD, P.H. Chandrasekar MD, Bryan Simmons MD, Lawrence Corey MD, Peter Phillips MD, Issam Raad MD, Elias Anaissie MD, John F. Reinhardt MD, John Segreti MD, Patricia L. Hibberd MD, Robert Rubin MD, Adolph Karchmer MD, Jo-Anne van Burik MD, John Perfect MD, Phyllis Flomenberg MD, Stephen Dummer MD, W. Michael Scheld MD, Stephen Shafran MD, Roblee Allen MD, Kerry Blanchard, PhD MD, Jennifer Daly MD, Dave Mushatt MD, Dennis Maki MD, Arnold Louie MD, Bruce Ribner MD, Marcia Sokol-Anderson MD, Princy Kumar MD, Kamar Godder MD, Leland Rickman MD, John Powers MD, Saul Yanovich MD, John Pullman MD, Kristin Razecca MD, Don Murphey MD, Karin Byers MD, Wheaton Williams MD, ,Rodney D. Adam MD, LCDR Ken Earhart,Donald Graham MD, George A. Pankey MD, Thomas J. Walsh MD, Susan Jacobson MD, John Jernigan MD, Christos ***Canada*****:** Tsoukas MD, Eric Bow MD, ***Thailand*** Khuanchai Supparatpinyo

Study Dates: 8 December 1997 - 20 September 1999 (Interim cut-off date)

MO Comment: *Study 604 (primarily US) was identical in design to study 309). Study details can be found above. As in study 309, the submitted study report described an interim analysis of all efficacy data for all subjects who were eligible for inclusion in the MITT analysis and were entered in the study as of 26 May 1999. The nominal cut-off date for efficacy was 31 May 1999 (derived from 20 September 1999 minus the maximum time to final outcome assessment [16 weeks]). However, the actual recruitment cut-off date for efficacy was taken as 26 May 1999 since there was one subject recruited on 27 May who had not had a final outcome assessment by 20 September 1999.*

Applicant's Pooled Analyses – Rare and Refractory Fungal Infections:

The applicant provided 2 types of efficacy analyses. One set of analyses was based on the results of each clinical study conducted and analyzed in accordance with the protocol for that study.

The second set of analyses was based on a pooled database containing subjects with documented fungal infections from the 13 Phase 2/3 studies using standardized criteria. For the indication of rare fungal infections, the MO determined that because patients were collected from a number of studies, the presentation of efficacy results from each study was not useful. Therefore, only the applicant's pooled results are presented. As per the applicant, "Individual subject data were evaluated for key parameters under proscribed criteria and enabled the correct allocation of fungal infections (species, site, and certainty of diagnosis) across protocols. The pooled analysis incorporated the assessments made by independent external experts or Data Review Committees (DRCs) where these were used for individual studies (150-304, 150-603 and 150-608). The procedures used for assessment of subjects and formation of the pooled database are referred to as the Voriconazole Efficacy Response Assessment (VERA)."

Subjects were reviewed for key elements including (i) primary underlying condition, (ii) hematological risk factor, (iii) previous antifungal treatment, (iv) infection details with pathogen, site and certainty of infection, and (v) outcome. Where available, the DRC/expert assessments took precedence over any other assessment. For those studies where an expert or DRC was not employed, outcome at End of Therapy (EOT) used the investigator assessment, within the context of other available pertinent information. The sponsor was allowed only to downgrade and never upgrade an investigator outcome assessment.

NOTE: VERA was utilized in a portion but not all subjects with rare fungal infections. Those subjects who were in compassionate use protocols did not undergo VERA.

MO Comment: *The applicant's efficacy analyses were performed on a modified intent-to-treat (MITT) population defined as subjects that received at least one dose of voriconazole, had a definite or probable diagnosis of systemic or invasive fungal infection at baseline, and were recruited on or before 26 May, 1999 (Study 150-604) or May 31, 1999 (Study 150-309). The interim analysis includes all data collected from visits before September 20, 1999.*

The applicant also collected a number of cases of rare fungal infections from other studies 301, 303a, 304, 304a, 603, and 606a and included them in the ISE if they met the MITT population definition. 35 of the applicant's subjects were from studies 309 and 604, the remaining subjects included 49 who received voriconazole as salvage therapy in a variety of compassionate use protocols as well as subjects with mixed or multiple fungal infections (N = 17) for a total of 101 subjects not including subjects counted twice because of mixed infections or 111 including such patients.

There appeared to be more men than women in the applicant's population both overall and by pathogen. The patients were primarily between the ages of 16 – 65 with less than 10% of subjects < 16 or > 65. Subjects were primarily white and had a hematologic malignancy as the underlying disease process and/or risk factor for a fungal infection. The underlying disease however varied with the fungal infection. The presence or absence of neutropenia was unknown in the majority of the applicant's subjects. Median duration of treatment also varied depending on the fungus being treated from 20.5 days for subjects with Scedosporium prolificans infections to 140 days for those with Scedosporium apiospermum infections.

The sponsors overall success rate by pathogen was 64/136 (47%) and by patient was 45/101(45%) The by pathogen breakdown included a 59% success rate for Scedosporium apiospermum and a 40% success rate for Fusarium spp. These rates do not take relapses into account. Relapses were counted as failures by the MO but not by the applicant. Overall, it appeared as if voriconazole was moderately successful in the eradication and treatment of infections due to Scedosporium apiospermum and Pseudallescheria boydii (59%). 13 of the applicant's subjects with this pathogen had brain abscesses and 7 of these were determined to be a success (54%). Regarding Fusarium, voriconazole appeared more effective than currently available treatments (40%). However, it should be noted that at least 2 of the subjects with a complete or partial response, had ocular disease that has a different prognosis than disseminated infection in a subject with hematologic malignancy. As noted above, these rates did not take relapses into consideration. Voriconazole is relatively ineffective versus cryptococcus spp. infections including cerebral infections due to Cryptococcus neoformans. Finally, there were too few isolates from other species on which to base regulatory or scientific decisions.

In the ISE, the applicant separately addressed cerebral mold infections and stated "Patients with cerebral mould infections often fail available antifungal therapies. A mortality rate of nearly 100% has been reported in previous studies (Denning, 1996; Hooper *et al.*, 1982; Weiland, 1983; Burch *et al.*, 1987). There is a clear difference in outcome between immunocompromised and non-immunocompromised patients. Among 141 immunocompromised patients with cerebral aspergillosis, 140 died. In contrast, only two of the 15 non-immunocompromised patients died (Denning, 1996).
A total of 45 subjects with cerebral aspergillosis and 13 with cerebral scedosporiosis received voriconazole and were included in the pooled analysis. In all cases the diagnosis was based either on the positive brain/CSF histology/mycology (definite infection) or on the typical brain CT/MRI findings accompanying a definite fungal infection in another site. The majority of these subjects were immunocompromised and had failed previous antifungal therapies. A successful outcome was demonstrated in 11/45 (24.4%) and 7/13 subjects (53.8%) with aspergillosis and scedosporiosis, respectively. Since cerebral mould infections in immunocompromised patients are associated with poor outcome, these data provide persuasive evidence for the efficacy of voriconazole in the treatment of these infections.

The applicant's demographics and results can be found in the following tables generated by the MO and populated by the applicant:

Table 5
Demographics of Applicant's MITT Population

Demographic factor	*Sc. apiosp. Ps. boydii* N = 27	*Sc. prol. Sc. infl.* N = 8	*Paec .lil* N = 6	*Fusarium* spp. N = 15	*Cryptococcus* spp. N = 13	All Others N = 38
Sex						
Male	14	3	5	12	11	24
Female	13	5	1	3	2	14
Unknown	-	-	-	-	-	1
Age						
0 – 15	6	2	-	2	-	5
16 – 65	20	6	6	11	12	29
> 65	1	-	-	2	1	4
Unknown						1
Mean (sd)	38.9 (20.9)	29.4 (21.1)	54.7 (8.7)	43.2 (21.8)	41.8 (9.6)	35.2 (20.0)
Median	42	23.5	59	52	40	32
Min., max.	1, 75	7, 62	40, 61	6, 71	30, 66	1, 75
Race						
White	20	7	6	12	11	25
Other	1	1	-	1	-	2
Black	-	-	-	1	1	5
Hispanic	-	-	-	1	1	4
Asian	-	-	-	-	-	2
Unknown	-	-	-	-	-	1
Underlying disease						
Hematologic Malignancy	9	6	1	7	-	15
Other malignancy	2	1	1	1	1	2
Transplant	3	-	3	-	2	1
Immunosuppression	6	-	-	3	-	5
Trauma	1	-	-	2	-	-
Surgery	1	1	-	-	-	1
CGD	2	-	-	-	-	2
Parenteral Drug Abuse	-	-	-	-	-	-
AIDS	-	-	1	-	10	3
Aplastic Anemia	-	-	-	1	-	1
Chronic Hepatitis B	-	-	-	1	-	2
GVHD	-					-
Unknown	3	-	-	1	-	8
Neutropenia						
Unknown	22	6	3	10	5	17
Yes	1	2	2	1	-	4
NO	4	-	1	4	8	16
Duration of Treatment						

Mean (sd)	192.9 (151.4)	70.1 (106.9)	59.8 (49.1)	92.5 (106.7)	89.3 (49.5)	86.8 (98.1)
Median	140	20.5	43	49	98	46.5
Min., Max.						
Other Documented Risk Factors						
Prolonged Neutropenia	2	2	-	4	2	10
Autologous BMT	1	1	-	-	-	-
Allogeneic BMT	1	-	-	-	-	1
GVHD	-	1	1	-	-	2
None Known	23	4	5	11	11	24
Malignancy Relapse	_	-	-	-	-	1

Table 6
Applicant and FDA MITT Populations and Isolates

Pathogenic Organism	Applicant Isolates	FDA Isolates	Applicant Subjects	FDA Subjects
Scedosporium apiospermum and Pseudallescheria boydii	36	33	19	25
Fusarium spp.	23	32	15	21
Scedosporium inflatum and Scedosporium prolificans	10	12	8	8
Paecilomyces lilacinus	7	8	6	5
Cryptococcus spp.	18	21	14	13
Mucor spp. (*Rhizopus*)	5	4	5	4
Trichosporon spp.	5	3	5	3
Alternaria spp.	1	3	1	2
Histoplasma capsulatum	2	1	1	1
Mycoleptodiscus indicus	1	2	1	1
Penicillium spp.	2	2	2	2
Phialophora richardsiae	1	1	1	1
Madurella mycetomi	1	1	1	1
Coccidioides immitis	2	2	1	1
Geotrichum candidum	1	1	1	1
Rhodotorula glutinis	1	1	1	1
Exophiala spinifera	1	1	1	1
Cladosporium spp.	1	1	1	1
Blastomyces dermitidis	1	1	1	1
Fonsecae pedrosoi	1	1	1	1
Exserohilum rostratum	1	1	1	1
Acremonium spp.	1	1	1	1
Unspecified Fungi	12	14	12	12
Scopulariopsis brevicaulis	1	-	1	-
Conidiobolus coronatus	1	-	1	-
Blastoschizomyces capitatus	1	-	1	-
Total	**137**	**147**	**111***	**108***

Explanatory Note 1: The column "Sponsor Evaluable Isolates" includes all individual pathogens isolated: a subject may have had (i) more than one site of infection caused by a single organism (disseminated infection), (ii) more than a single organism at one site of infection (mixed infection), or (iii) more than one fungal pathogen causing fungal infection at more than one site (multiple infections). In this listing, a specific pathogen may be included more than once per subject.

Explanatory Note 2: The column "Sponsor Evaluable Subjects" reflects the number of subjects associated with the specific pathogen. Therefore, a disseminated infection with one organism is reported only once. However, where more than one pathogen was isolated (mixed or multiple infections), the subject is counted more than once.

*FDA: True subject N = 98 with 147 isolates. Table N of 108 includes 7 subjects with more than 1 isolate that were identified to species level. Similarly, the applicant's true N = 101.

**NOTE: FDA and applicant differ in calculation of FDA subjects by 1 patient and 2 isolates. This difference is due to the omission by the applicant from the FDA population of subjects # 309-02201701. This 27 YO female with a

history of cystic fibrosis and lung transplant, was originally enrolled as 301-02200004 and treated for skin, eye, and pulmonary *Scedosporium apiospermum* infections. Outcome was complete response followed by relapse a number of months later. The subjects was then enrolled in study 309 and treated for cerebral disease with ultimate outcome of failure and death due to the fungal disease process.

Additionally, the applicant omitted 1 cerebral isolate of *Scedosporium prolificans* from subjects 309-02251481. The reason for this omission was not clear.

Table 7

Complete and Partial Success Rates for Applicant and FDA Populations by Organism

Complete and Partial Success Rate by Pathogenic Organism	Applicant Isolates	FDA Isolates	Applicant Subjects	FDA Subjects by Organism
Scedosporium apiospermum and *Pseudoallescheria boydii*	24/36 (67%)	22/33 (67%) *5 relapses 17/33 (52%)	16/27 (59%)	15/25 (60%) * 3 relapses 12/25 (48%)
Fusarium spp.	7/23 (30.4%)	12/32 (38%) * 3 relapses 9/32 (28%)	6/15 (40%)	9/21 (43%) * 2 relapses 7/21 (33%)
Scedosporium inflatum and *Scedosporium prolificans*	3/10 (30%)	4/12 (33%)	2/8 (25%)	2/8 (25%)
Paecilomyces lilacinus	1/7 (14%)	2/8 (25%)	1/6 (17%)	2/5 (40%)
Cryptococcus spp.	6/18 (33%)	6/21 (29%)	5/14 (36%)	4/13 (31%)
Mucor/Rhizopus spp.	0/5	0/4	0/5	0/4
Trichosporon spp.	2/5 (40%)	2/3 (67%)	2/5 (40%)	2/3 (67%)
Alternaria spp.	1/1 (100%)	2/3 (67%)	1/1 (100%)	1/2 (50%)
Histoplasma capsulatum	0/2	0/1	0/1	0/1
Mycoleptodiscus indicus	0/1	0/2	0/1	0/1
Penicillium spp.	0/2	0/2	0/2	0/2
Phialophora richardsiae	1/1 (100%)	1/1 (100%)	1/1 (100%)	1/1 (100%)
Madurella mycetomi	1/1 (100%)	1/1 (100%)	1/1 (100%)	1/1 (100%)
Coccidioides immitis	2/2	2/2 (100%)	1/1 (100%)	1/1 (100%)
Geotrichum candidum	0/1	0/1	0/1	0/1
Rhodotorula glutinis	0/1	0/1	0/1	0/1
Exophiala spinifera	1/1 (100%)	1/1 (100%)	1/1 (100%)	1/1 (100%)
Cladosporium spp.	1/1 (100%)	1/1 (100%)	1/1 (100%)	1/1
Blastomyces dermitidis	1/1 (100%)	1/1 (100%)	1/1 (100%)	1/1 (100%)
Fonsecae pedrosoi	1/1 (100%)	1/1 (100%)	1/1 (100%)	1/1 (100%)
Exserohilum rostratum	1/1 (100%)	1/1 (100%)	1/1 (100%)	1/1 (100%)
Acremonium spp.	0/1	0/1	0/1	0/1
Scopulariopsis brevicaulis	1/1 (100%)	N/A	1/1 (100%)	N/A
Conidiobolus coronatus	1/1 (100%)	N/A	1/1 (100%)	N/A
Blastoschizomyces capitatus	1/1 (100%)	N/A	1/1 (100%)	N/A
Unspecified Fungi	8/12 (67%)	9/14 (64%)	8/12 (67%)	8/12 (67%)

***Rates are NOT per patient but per patient/isolate**