Note: 7 subjects counted more than once due to multiple infections (606-60050041: *Cladosporium, Scedosporium apiospermum*, complete success; 604-10326050: *Fusarium solani* and *Trichosporon beigelii*, partial success; 309-04801009: *Fusarium solani* and *Acremonium* spp., failure; 301-20030001: *Scedosporium prolificans*, fungus unspecified, and *Fusarium* spp. failure/stable; 301-04790001: fungus unspecified and *Exserohilum rostratum*, partial; 301-04391015: fungus unspecified, *Madurella mycetomi*; 301-04391005: fungus unspecified, *Trichosporon cutanaeum*).

Table 8
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

Applicant's Conclusions for the Treatment of Rare and Refractory Fungal Infections with Voriconazole:

Voriconazole was shown to be effective in the treatment of fungal infections due to *Scedosporium* and *Fusarium* species. The outcome for subjects contracting these infections is normally dire, and no other antifungal agents are approved for their treatment. In the pooled efficacy population there were 84 subjects with rare fungal pathogens – i.e., non-*Candida* or non-*Aspergillus* species. Most of the subjects (70) were treated with voriconazole as salvage therapy. Of the 27 subjects with *S. apiospermum* 16 (59%) had a successful outcome. Of the 15 subjects with *Fusarium* infections six (40%) had a successful outcome. The success of voriconazole in treating these infections included subjects with mixed fungal infections (1/3 subjects (33%) with *Scedosporium* and 2/4 subjects (50%) with *Fusarium*). Additionally, cerebral mould infections in immunocompromised patients are associated with poor outcome and the data provide persuasive evidence for the efficacy of voriconazole in the treatment of these infections.

Other successfully treated fungal infections included isolated cases of *Alternaria* spp., *Blastomyces dermatitidis, Blastoschizomyces capitatus, Cladosporium* spp., *Coccidioides immitis, Conidiobolus coronatus, Cryptococcus neoformans, Exserohilum rostratum, Exophiala spinifera, Fonsecaea pedrosoi, Madurella mycetomi, Paecilomyces lilacinus, Phialophora richardsiae, Scopulariopsis brevicaulis, and Trichophyton cutanaeum* infections.

FDA Analysis:

As noted previously after a review of all CRFs, excluded from the FDA MITT population were those subjects without reviewable documentation of a fungal infection. This was a not infrequent occurrence in the compassionate use protocols where such documentation was not required. 13 of the applicant's subjects were excluded in this manner. Additionally, the FDA requested that the applicant submit any additional cases of *Scedosporium* spp. and *Fusarium* spp. infection collected from studies 309 and 604 after the original cutoff date. The MO accepted the

applicant's determinations of efficacy in all cases. In the final analyses the MO as opposed to the applicant calculated success rates including subjects who relapsed as failures.

The FDA population consisted of 98 subjects with 147 isolates. There were 7 subjects that had more than 1 isolate. Most subjects were white and there were more males than females. The mean age was 40.9 (standard deviation 19.8), the median age was 42 and the range was 1, 76. There were 10 subjects ≤ 15 (10%) and 10 subjects ≥ 65 (10%). 33 (33%) of the subjects were female and 83 subjects were white.

A large number of subjects had underlying hematologic diseases, however, the primary underlying disease differed with the fungal pathogen. As expected, most subjects with *Cryptococcus* spp. infections had underling HIV as compared to subjects with *Scedosporium* spp. or *Fusarium* spp. infections. Documentation of underlying neutropenia as a risk factor was poor. In most subjects this factor was "unknown". This is a significant issue as in many cases of fungal infection in neutropenia subjects, the fungal process resolves as the neutropenia resolves. Of note however, was that patients in studies 309 and 604 were not allowed to receive colony-stimulating factors.

Duration of treatment varied with the fungal pathogen and site of infection. Overall, those patients with partial responses had more prolonged courses than those that failed or had complete responses. Follow-up was prolonged and extended up to at least 4 weeks post treatment. Mean duration of treatment was 100.3 days (standard deviation 103.2), the median was 83 days and the range was 1, 419. The mean duration of IV voriconazole was 22 days (standard deviation 30.3) and the median was 12 days (1, 210). The mean duration of PO voriconazole was 113.4 days (standard deviation 99.5) and the median was 99.5 days (2, 413).

82 of 98 subjects received voriconazole as salvage therapy 70 due to efficacy failure, 6 due to efficacy failure and intolerance, 3 due to intolerance, and 3 due to unknown reasons. Mean duration of previous antifungal therapy was 24.4 days (standard deviation 9.9), the median was 31 days and the range was 0, 52.

The MO elected to analyze each pathogen separately as an analysis of all rare pathogens is inappropriate given the differences in patients and the fungi themselves. Following the by pathogen analyses are efficacy analyses by underlying disease and risk factor. Additionally an analysis of efficacy by salvage or primary therapy is also provided.

Demographics:

Table 9
Demographics of FDA MITT Population

Demographic factor	*Sc. apiosp. Ps. boydii* N = 25	*Sc. prol. Sc. infl.* N = 8	*Paec. lilac.* N = 5	*Fusarium* spp. N = 21	*Crypto* spp. N = 13	All Others N = 33
Sex						
Male	13	4	4	16	11	21
Female	12	4	1	5	2	12
Age						
0 – 15	4	1	-	2	-	5
16 – 65	21	7	5	16	12	25
> 65	0	0	-	3	1	3
Mean (sd)	40.2 (19.8)	32.6 (19.0)	53.6 (9.3)	47.9 (21.8)	41.8 (9.6)	34.1 (19.9)
Median	46	28	58	56	40	31
Min., max.	1, 62	13, 62	40, 61	6, 76	30, 66	1, 70
Race						
White	24	6	5	12	11	21
Other	1	1	0	1	-	2
Black	-	-	-	1	1	4
Hispanic	-	-	-	1	1	3
Asian						2
Unknown		1				1
Underlying disease						
Hematologic Malignancy	8	5	1	10	-	14
Other malignancy	2	1	1	1	1	2
Transplant	6	-	2	-	2	-
Immunosuppression	4	-	-	3	-	5
Trauma	2	-	-	2	-	-
Surgery	1	1	-	3	-	-
CGD	1	1	-	-	-	3
Parenteral Drug Abuse	1	-	-	-	-	-
AIDS	-	-	1	-	10	3
Aplastic Anemia	-	-	-	1	-	1
Chronic Hepatitis B	-	-	-	1	-	1
GVHD						-
Unknown	-	-	-	-	-	4
Neutropenia						
Unknown	16	6	2	11	5	12
Yes	4	2	2	2	-	5
NO	5	-	1	8	8	16
EOT Duration						

Mean (sd)	163.7 (136.8)	68 (107.9)	59.6 (54.9)	84.1 (94.1)	89.3 (49.5)	84.3 (89.9)
Median	123	12	25	56	98	41
Min., Max.						
Other Documented Risk Factors						
Prolonged Neutropenia	2	2	-	5	2	9
Autologous BMT	1	1	-	-	-	-
Allogeneic BMT	1	-	-	1	-	1
GVHD	-	1	1	-	-	2
None Known	21	4	4	15	11	20
Malignancy Relapse	_	-	-	-	-	1

Scedosporium apiospermum and Pseudallescheria boydii:
(N = 33 isolates from 25 patients):

As expected, most subjects with *Scedosporium apiospermum* or *Pseudallescheria boydii* had underlying hematologic malignancies. Additionally, histologic or microbiologic documentation of the infection was uniformly high with 18/25 (72%) of subjects having a definite infection and 6/25 (24%) a probable infection and 1 (4%) a possible infection. 24 (96%) of subjects had received previous treatment with approved antifungal regimens (including AMP B, Ambisome, ITR, and FLU) and had failed treatment. 1 subject with cerebral disease received voriconazole as primary treatment.

Mean age of the subjects was 40.3 (median 46, range 1 – 62) and there were approximately equal numbers of males (13) and females (12).

4 subjects had 2 isolates each and 2 subjects had 3 each. The remaining 19 subjects had 1 isolate each. The brain (cerebral and/or CSF) was the most common site of infection (12 isolates, 10 patients), followed by the lung (7 patients) and skin (5 patients).

10 subjects had cerebral isolates (brain abscesses), followed by 7 subjects with pulmonary disease. As expected, the skin was also a frequent site of infection.

Mean duration of previous antifungal treatment was 24.0 days (median 31, range from -1 - 52). Mean duration of voriconazole treatment was 163.7 days (median 123 days).

Overall success rate was 15/25 or 64% at the EOT. However there were 3 relapses, for a true complete and partial success rate of 12/25 (48%).

The most common cause of failure was insufficient response (4), followed by death due to the underlying disease (2), intolerance in 1, and 3 subjects were failure/stable, i.e., did not deteriorate while on voriconazole.

More patients with pulmonary and skin disease were complete successes as compared to only 1 subject with cerebral disease.

Global response was assessed as complete in 7/25 (32%) and partial in 5/25 (20%). Global response was assessed as failure in 9 subjects (36%) and not assigned in 4 (16%). Overall satisfactory response rate was 12/25 (48%). The data was not collected in 2 of the unknowns and was listed as "unknown" for the other 2.

Mycological response was unknown in 18 subjects, indeterminate in 3, presumed eradication in 2 and persistence in 2. The collection of this information was not a protocol requirement in 16 subjects and was not collected for unknown reasons in 2.

Of the 10 subjects with cerebral infections, 3 were immunosuppressed due to drug or disease, 3 had a history of transplant, 1 was post-abdominal surgery, 1 was post-trauma, 1 had another malignancy, and 1 was an IVDA. None of these subjects had a specifically identified risk factor and all had a definite diagnosis except 1 that was probable. In 1 subject, voriconazole was used a primary treatment, in all others it was salvage. Outcome was 1 complete success, 5 partial successes and 4 failures. Relapse occurred in 1 subject with partial success. Of note, the subjects with complete successes had a history of renal transplant. Partial success was seen in post-injury, post-surgical subjects (1 each, as well as in the IVDA (1), and in 2 immunosuppressed subjects, 1 of whom relapsed.

Of 4 subjects with a documented risk factor (BMT, profound neutropenia), the 2 with hematologic malignancies and profound neutropenia had bone and lung scedosporiosis. 1 subject (bone) was a complete success, the other with lung disease was a stable failure. Both subjects with a history of BMT were complete successes and had one each bone and pulmonary scedosporiosis.

A total of 8 subjects died during the study period or follow-up, in 4 cases death was due to underlying disease and in an additional 2 to underlying disease and infection. Only 2 cases had a follow-up assessment (#304 00630521and 309 01441181). These subjects were followed for 84 and 29 days post treatment respectively. The first subject had probable pulmonary scedosporiosis and was a partial success and the second has involvement of the skin and was a complete success. The latter had a relapse after 4 weeks, whereas the former continued to do well.

Mean calculated survival day from the start of treatment was 174.3 days (sd 134.2), median 161, range 5, 419.

In conclusion, voriconazole appeared effective in the management of fungal infections due to *Scedosporium apiospermum* and *Pseudallescheria boydii*. Given the resistance that this isolate exhibits versus AMP B and the very high mortality associated with it (> 75%) for cerebral disease), 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.

Table 10
Description of Scedosporium isolates

	Scedosporium apiospermum/ Pseudallescheria boydii N = 33	*Scedosporium prolificans/ Scedosporium inflatum* N = 12
Definite	24 (73%)	9 (75%)
Probable	8 (24%)	2 (17%)
Possible	1 (3%)	1 (8%)
Salvage	32 (97%)	9 (75%)
Primary	1(3%)	3 (25%)
Cerebral	10 (30%)	2 (17%)
Pulmonary	7 (21%)	2 (17%)
Skin	5 (15%)	3 (17%)
Bone (spine)	4 (12%)	1 (8%)
Sinus	2 (6%)	1 (8%)
CSF	2 (6%)	-
Blood	-	3 (25%)
Spleen	1 (3%)	-
Eye	1 (3%)	-
Synovial	1 (3%)	-

Table 11
Outcome by patient
FDA Population

	Scedosporium apiospermum/ Pseudallescheria boydii N = 25	*Scedosporium prolificans/ Scedosporium inflatum* N = 8
Complete success	8 (32%)*	-
Partial success	7 (28%)*	2 (25%)
Failure ALL	10 (40%)	6 (75%)
Death	3 (12%)	3 (29%)
Intolerance	1 (4%)	-
Insufficient response	4 (16%)	2 (29%)
Stable	2 (18%)	1(14%)

*** = Relapse: N = 3 , 2 complete, 1 partial.** In 2 cases (1 complete and 1 partial), relapse was related to cerebral isolates and was associated with the development of bran abscesses.

Table 12
Outcome by site/isolate
Scedosporium apiospermum

	Cereb N = 10	Pul N = 7	Skin N = 5	Bone N = 4	Sinus N = 2	CSF N = 2	Spleen N = 1	Eye N = 1	Syn. N = 1
Complete success	1	3*	3*	3	-	-	1	1*	1
Partial success	5*	2	-	-	1	1	-	-	-
Failure ALL	4	2	2	1	1	1	-	-	-
Death	2	1	-	-	-	-	-	-	-
Intolerance	-	-	1	-	-	-	-	-	-
Insufficient response	2	-	-	1	1	1	-	-	-
Stable	-	1	1	-	-	-	-	-	-

*** = Relapse, (1 cerebral partial, and 1 skin complete)**

Table 13
Outcome by site/isolate
Scedosporium prolificans/ Scedosporium inflatum

	Cerebral N = 2	Pulmonary N = 2	Skin N = 3	Bone N = 1	Blood N = 3	Sinus N = 1
Complete success	-	-	-	-	-	-
Partial success	-	1	1	1	1	-
Failure ALL	2	1	2	-	2	1
Death	1	1	1	-	1	-
Intolerance	-	-	-	-	-	-
Insufficient response	1	-	1	-	1	-
Stable	-	-	-	-	-	1

Scedosporium inflatum/prolificans:

The dataset included 8 subjects with 12 isolates including 1 subject with 3, 1 with 2, and remainder with one isolate each. 4 subjects were male and 4 female with a mean age of 32.6 and median 28 (range 13, 62).

Mean duration of previous antifungal treatment in 6 subjects (6 salvage vs. 2 primary) was 26.6 days (S.D. 7.4), and median was 31 days, (range 13, 31).

The mean duration of treatment was 68 days (S.D. 107.9), median 12, (range 1, 292). Follow-up beyond the EOT was not obtained because of death in 5 subjects and for unknown reasons in 3.

Underlying diseases included hematological malignancy in 5, other malignancy in 1, trauma in 1, and post surgery in 1. 2 of the hematological malignancy subjects had profound neutropenia, 1 had GVHD, and 1 had an autologous BMT. There were no documented risk factors for the remaining subjects. All had definite infections except 1 subject who had probable disease. There were 2 partial successes in subjects with blood and bone infections. The former had a hematologic malignancy and autologous BMT and the latter was post surgery.

Overall success rate was 29%. 6 subjects were failures, 3 due to death from the underlying disease, 2 due to insufficient response and 1 was stable.

Global response was failure in 5, complete success in 1(blood), partial in 1 (bone) and unknown in 1 subject because the CRF was lost.

Mycological response was not collected in any subject.

Mean calculated survival day from the start of treatment was 77.2 days (SD 113.2), median 14 (range 2, 292).

In conclusion, a decision could not be made regarding the effectiveness of voriconazole in the management of fungal infections due to *Scedosporium prolificans/inflatum* because of the small number of patients and isolates collected. The 12 isolates represented 8% of the total isolates and the 8 subjects represented 8% of the total population. Both are lower than the 10 required in FDA guidance documents as an amount necessary for approval in association with adequate efficacy. The MO recommends a non-approval for this isolate.

***Fusarium* spp.:**

There were 21 subjects with 32 isolates in the final FDA database. 5 subjects (7 isolates) had *Fusarium solani*, 1 subject (2 isolates) had *Fusarium oxysporum*, and the remaining isolates were unspeciated. 17 subjects received voriconazole as salvage therapy, in 2 due to intolerance and in 15 due to efficacy failure. The mean duration of previous antifungal treatment was 26 days, (SD 10.2), and the median was 31 days, (range 9, 48).

4 subjects received voriconazole as the primary treatment of their infection (4 isolates). Of those 4, 2 had eye infections and both failed voriconazole. Of the remaining 2 subjects one had a blood infection (underlying hematologic malignancy) and was a complete success and the other had a skin infection (underlying immunosuppression), and was a partial success.

The mean age of the subjects was 47.9 (SD 21.3), with a median of 56 (range 6, 76). 3 subjects had probable disease and 18 had definite infections. The mean duration of treatment was 84.1 days (SD 94.1), and the median was 56 days, (range 5, 401).

10 subjects had underlying hematologic malignancies, 3 were immunosuppressed, 3 had had surgery 2 had trauma, 1 subject had another malignancy, 1 was aplastic, and 1 had chronic hepatitis B. 5 subjects had documented profound neutropenia and 1 had allogeneic BMT.

Of the 21, 3 subjects had complete successes (14%) and 6 (29%) were partial successes. The remaining 12 were failures. 2 of the subjects with partial success relapsed after 4 weeks with a final success rate of 34%. One subject who relapsed had blood and eye infections with *Fusarium oxysporum*, s/p surgery with an initial partial response, after 56 days of treatment. This subject received voriconazole due to intolerance to previous treatments. 29 days post EOT the patient was recategorized as a relapse. The second subject had a sinus infection with *Fusarium* spp. with a history of prolonged neutropenia on the basis of an underlying "other malignancy". This

patient had received 9 days of previous antifungal treatment and received voriconazole due to insufficient response. Duration of treatment was 83 days and of follow-up 39 days.

Of the 3 subjects with complete responses, 1 had 3 isolates of *Fusarium solani* (synovial fluid, pulmonary and skin), and the other 2 had 1 each *Fusarium solani* isolates of the blood and eye. The first 2 subjects had underlying hematologic malignancies and the latter had sustained trauma. Long-term follow up was provided for only the last subject with the eye infection who continued to be a cure after 29 days.

Of the 12 subjects who failed, 4 (6 isolates) were designated as failure/stable. 1 subject had 3 isolates (triceps muscle, sinus, and liver), and there was 1 each from the eye, sinus, and skin. None of these subjects had follow-up beyond the EOT.

A breakdown of efficacy by isolate revealed that the most predominant infection was that of the skin followed by the eye. There was no specific site where efficacy was markedly better than others.

Follow-up (30 days) was obtained in 8 subjects including 2 who were relapses and 1 who was a cure. Mean calculated survival day from the start of treatment was 85.4 days (SD 93.3), median 49 (range 6, 401).

In conclusion, the 32 *Fusarium* spp. isolates represented 22% of the total isolates and the 21 subjects represented 21% of the total population. Thus there was adequate data available to make a regulatory decision in accordance with the "rule of 10" required in FDA guidance documents as an amount necessary for approval in association with adequate efficacy.

Voriconazole appeared somewhat effective in the management of fungal infections due to *Fusarium* spp. Given the resistance that this isolate exhibits versus AMP B and currently available antifungal agents, and the very high mortality associated with it (> 80%) the MO recommends approval as salvage treatment.

Although there were only 7 isolates of *Fusarium solani* from 5 patients, 3 subjects (1 with 3 isolates), were complete successes. The remaining 2 were failures, both with eye infection of whom one was stable. 2 of the 7 cases received voriconazole as primary therapy (1 blood infection in a patient with hematologic malignancy who was a complete success and 1 post-traumatic eye infection assesses as a failure.

Thus although the applicant did NOT collect an adequate sample size of speciated *Fusarium solani*, the MO recommends that the approval be extended to *Fusarium solani* as well as *Fusarium* spp.

Table 14
Descriptive of FDA Fusarium isolates

	Fusarium spp. N = 32
Definite	24 (75%)
Probable	7 (22%)
Possible	1 (3%)
Salvage	28 (88%)
Primary	4 (13%)
Eye	7 (22%)
Pulmonary	4 (13%)
Skin	9 (31%)
Hepatosplenic	1 (3%)
Sinus	4 (13%)
Muscle	1 (3%)
Synovial fluid	1 (3%)
Blood	5 (16%)

Table 15
Outcome by patient
Fusarium spp.

	Fusarium spp. N = 21
Complete success	3 (14%)
Partial success	6 (29%)*
Failure ALL	12 (57%)
Death	1 (5%)
Intolerance	1 (5%)
Insufficient response	4 (19%)
Stable	6 (29%)*

*** 2 relapses after 4 weeks**

Table 16
Outcome by site
***Fusarium* spp.**

	Eye N = 7	Pulmonary N = 4	Skin N = 9	Synovial N = 1	Sinus N = 4	Muscle N = 1	Blood N = 5	Hep/spl N = 1
Complete success	1	1	1	1	-	-	1	-
Partial success	3*	-	1	-	2*	-	1*	-
Failure ALL	3	3	7	-	2	1	3	1
Death	-	-	-	-	-	-	-	-
Intolerance	-	1	1	-	-	-	-	-
Insufficient response	2	1	4	-	-	-	2	-
Stable	1	1	2	-	2	1	1	1

***relapse of 1 eye at 4 weeks 1 sinus at 4 weeks, 1 blood after 4 weeks**

Paecilomyces lilacinus:

There were 8 isolates from 5 subjects in the database including 1 subject with 3 isolates (skin, lung, sinus) and 1 with 2 (eye and skin). 1 subject (2 isolates) received voriconazole as primary therapy. In the remaining 4 subjects voriconazole was used as salvage therapy due to previous failure. The mean duration of previous antifungal therapy was 27 days (SD 8) with a median of 31 (range 15, 31).

One subject was female and all subjects were between 18 and 65 with a mean age of 53.6 (SD 9.2 and a median of 58 (range 40 –61). Underlying diseases included heart transplant, lung transplant, AIDS, other malignancy, and hematologic malignancy. 1 subject with underlying hematologic malignancy had GVHD as a risk factor. Risk factors were not identified in the other subjects. 5 subjects had skin infections, 1 had an eye infection, 1 had a lung infection, and 1 had a sinus infection.

Mean duration of treatment was 59.6 days (SD 54.8) and the median was 25 (range 13, 135).

By patient outcomes revealed a partial success in 1 subject (20%) and failure in 4 (80%). Only 1 subject with a skin isolate had a satisfactory response. All other subjects and isolates were classified as failures. However, in 3 cases the patients were stable and in 1 case the subject died. There were 2 deaths overall, the second after the EOT and in both cases death was due to the underlying disease process. In only 1 case of failure was there follow-up beyond the EOT. In that case in a patient with an eye infection the assessment at follow-up was stable.

Mean calculated survival day from the start of treatment was 91.2 days (SD 113.0), median 32 (range 14, 284).

In conclusion, a decision could not be made regarding the effectiveness of voriconazole in the management of fungal infections due to *Paecilomyces lilacinus* because of the small number of patients and isolates collected. The 8 isolates represented 5% of the total isolates and the 5 subjects represented 5% of the total population. Both are lower than the 10 required in FDA guidance documents as an amount necessary for approval in association with adequate efficacy. In addition only 20% efficacy was shown. The MO recommends a non-approval for this isolate

Table 17
***Descriptive of FDA Paecilomyces lilacinus:* 8 isolates from 5 patients**

	Paecilomyces lilacinus N = 8
Definite	5 (63%)
Probable	1 (13%)
Possible	2 (25%)
Salvage	6 (75%)
Primary	2 (25%)
Eye	1 (13%)
Pulmonary	1 (13%)
Skin	5 (63%)
Sinus	1 (13%)

Table 18
Outcome by patient
Paecilomyces lilacinus

	Paecilomyces lilacinus N = 5
Complete success	-
Partial success	1 (20%)
Failure ALL	4 (80%)
Death	1 (20%)
Intolerance	-
Insufficient response	-
Stable	3 (60%)

Table 19
Outcome by site
Paecilomyces lilacinus

	Eye N = 1	Pulmonary N = 1	Skin N = 5	Sinus N = 1
Complete success	-	-	-	-
Partial success	-	-	1	-
Failure ALL	1	1	4	1
Death	-	-	1	-
Intolerance	-	-	-	-
Insufficient response	-	-	-	-
Stable	1	1	3	1

Cryptococcus spp.:

There were 13 patients with 21 isolates in the database. 1 subject had 4 isolates (blood, eye, pulmonary, skin), 1 subject had 3 isolates (CSF, cerebral, skin), 3 subjects had 2 isolates each and the remaining 8 had 1 isolate each.

All subjects except 1 with pleural infection received voriconazole as salvage treatment with a mean duration of previous antifungal treatment of 22.9 days (SD 11.2) and a median of 28.5 (range 1, 31).

As expected the CNS was the most common site of infection with 4 subjects with documented cerebral isolates and an additional 7 subjects with meningeal or CSF isolates. 4 subjects had bloodstream infections and in 2 the fungemia was concurrent with meningeal disease.

10 subjects had AIDS, 1 each had a heart and renal transplant, and 1 had another malignancy. There were 2 women and 11 men and 12 were between 18 and 65 with a mean age of 41.7 (SD 9.6) and a median age of 40 (range 30, 66). 1 subject was > 65. 11 were white, 1 was black and 1 was Hispanic.

Mean duration of treatment was 89.3 days (SD 49.4) with a median of 98 (range 27, 148).

16 of 21 isolates were identified as *Cryptococcus neoformans* and 5 isolates were not speciated. All subjects had at least 1 speciated isolate except 1, the subject with heart transplant and 4 isolates.

Complete success was obtained in only 1 subject with meningeal disease. An additional 3 had partial successes (1 subject with prostate disease and 2 with meningeal), however 9 subjects were classified as failures (69%). 7 subjects with meningeal/cerebral disease were failures.

Global response was assigned to12 of 13 subjects. 4 subjects were assigned a partial response, 1 a complete and 7 were failures. The 1 additional partial response was in the heart transplant patient who discontinued treatment for protocol violations. Mycological response was also assessed in 10 subjects. It was not a protocol requirement in 3. There was documented persistence in 3 subjects (4 isolates), eradication (documented) in 2 (3 isolates), presumed eradicated in 2 (2 isolates) and indeterminate in 2. 3 of the persistent isolates were from the CNS and 1 was from the blood. Follow-up was obtained in only the 1 subject with a complete response who continued to do well after 45 days.

4 subjects died subsequent to the study of their disease process.

Mean calculated survival day from the start of treatment was 110.9 days (SD 78.2), median 103 (range 27, 266).

In conclusion, the MO determined that voriconazole was NOT effective in the salvage therapy of fungal infections due to *Cryptococcus* spp. with a success rate of only 31% as compared to the

much higher rates that can be obtained with accepted antifungal regimens (IV AMP B, followed by FLU in meningitis).

Table 20
Descriptive of *Cryptococcus* spp. Isolates
21 isolates from 13 patients

	Cryptococcus spp. N = 21
Definite	17 (81%)
Probable	1 (5%)
Possible	3 (15%)
Salvage	20 (95%)
Primary	1 (5%)
Cerebral	5 (25%)
Pulmonary	1 (5%)
Pleural	1 (5%)
Skin	2 (10%)
Meninges	5 (25%)
CSF	1 (5%)
Prostate	1 (5%)
Eye	1 (5%)
Blood	4 (20%)

Table 21
Outcome by patient
***Cryptococcus* spp.**

	Cryptococcus spp. N = 13
Complete success	1 (8%)
Partial success	3 (23%)
Failure ALL	9 (69%)
Death	-
Intolerance	1
Insufficient response	4
Stable	4

Table 22
Outcome by site
***Cryptococcus* spp.**

	Cerebral N = 5	Pleural N = 1	Pulm. N = 1	Eye N = 1	Menin. N = 5	Prostate N = 1	Blood N = 4	Skin N = 1
Complete success	-	-	-	-	1	-	-	-
Partial success	1	-	-	-	1	1	2	-
Failure ALL	4	1	1	1	3	-	2	2
Death	-	-	-	-	-	-	-	-
Intolerance	-	-	1	1	-	-	1	1
Insufficient response	1	-	-	-	3	-	1	-
Stable	3	1	-	-	-	-	-	1

Other Fungal Pathogens:

There were an additional 33 subjects with 41 isolates included in the FDA dataset, Included in this category were 4 subjects with zygomycoses, 10 subjects with unspecified fungal pathogens, 1 with an unspecified yeast, 3 with *Trichosporon* spp., 2 with *Alternaria* spp., 2 with *Penicillium* spp., and 1 each of *Bipolaris* spp, *Blastomyces dermitidis, Coccidiodes immitis, Cladosporium* spp, *Exophiala spinifera, Exserohilum rostratum, Fonsecae pedrosoi. Geotrichium candidum, Histoplasma, capsulatum, Madurella mycetomi, Mycoleptodiscus indicus, Phialophora richardsiae,* and *Rhodotorula glutinis.* As noted previously some subjects had mixed infections.

In 23 subjects voriconazole was utilized as salvage treatment and as primary in 10 subjects. The mean duration of previous antifungal treatment was 25.1 days (SD 10.4) with a median of 31 (range –1, 31).

21 subjects were men, 12 were women, 25 were between 16 and 65, 5 were < 16 and 3 were > 65. Hematologic malignancies were the most common underlying disease process.

An outcome of note included the failure of all cases of zygomycosis (N = 4). For specific outcomes, Please see the MO table of outcomes. No general conclusions could be drawn from this category of patients. 10 subjects died during and post EOT, all deaths were due to the underlying disease processes.

Mean calculated survival day from the start of treatment was 102.2 days (SD 104.5), median 43 (range 2, 361).

General efficacy by underlying disease:

Table 23
Success rate by Underlying Disease by patient

Underlying Disease	Complete Success	Partial Success	All Success	Failure
Hematologic malignancy	5/35 (14%)	7/35 (20%)	12/35 (34%)	23/35 (66%)
Immunosuppression	-	5/10 (50%)	5/10 (50%)	5/10 (50%)
AIDS	-	4/14 (29%)	4/14 (29%)	10/14 (71%)
Transplant	4/10 (40%)	1/10 (10%)	5/10 (50%)	5/10 (50%)
CGD	2/3 (67%)	-	2/3 (67%)	1/3 (33%)
Malignancies (other)	1/8 (13%)	2/8 (25%)	3/8 (38%)	5/8 (62%)
Trauma/surgery	2/11 (18%)	5/11 (45%)	7/11 (64%)	4/11 (36%)
Aplastic Anemia	-	1/2 (50%)	1/2 (50%)	1/2 (50%)
IVDA	-	1/1 (100%)	1/1 (100%)	-
Chronic Hepatitis B	-	-	-	1/1 (100%)
Unspecified	1/3 (33%)	2/3(66%)	3/3 (100%)	-
ALL	**15/98 (15%)**	**28/98 (28%)**	**43/98 (44%)**	**55/98 (56%)**

NOTE: difference of 8 between organism and patient rate is due to more the presence of multiple isolates in 7 subjects

5 relapses = success rate of 38/98 (39%)

35/98 (36%) subjects with 57 isolates had underlying hematologic malignancies. 5 of these were classified as complete successes, 7 as partial successes, 16 as failures due to insufficient response, and 5 as failure/stable, 1 as a failure due to death, and 1 as a failure due to discontinuation. Thus the overall success rate in this population was 34%. Of note, 11 of these subjects had infections with *Fusarium* spp. including 2 subjects with *Fusarium solani* (19 isolates total, 4 solani). Of these 11, 2 were classified as complete responses including both patients with *Fusarium solani* (4 isolates) and 1 as a partial response (1 isolate).

9/98 (10%) subjects had infection with *Scedosporium apiospermum* (11 isolates). Of these 1 was classified as a complete response and 1 as a partial response.

11/98 (11%) subjects with 14 isolates had immunosuppression due to disease or drugs. Of these, 6 subjects (55%) were partial successes and the remainder were failures. Included in this group were 3 subjects with *Fusarium* spp. infections (1 *Fusarium solani* that was a failure/stable and 2 spp. that were partial successes). 1 subject with *Scedosporium apiospermum* was classified as a partial success, 1 as a failure due to discontinuation and 1 as a failure due to insufficient response.

14/98 (14%) subjects with 19 isolates had AIDS/HIV as the underlying disease process. 4 subjects (29%) were classified as partial successes. 10 of these subjects had *Cryptococcus neoformans* (2 successes).

10/98 (10%) subjects with 18 isolates had a history of transplant. Of these, 4 were classified as complete successes (40%) and 1 as a partial success for a total rate of 50%. 6 of these subjects has infections due to *Scedosporium apiospermum* and 3 were complete successes.

4/98 (4%) subjects had CGD, 2 of whom were complete successes including 1 subject with *Scedosporium apiospermum.*

8/98 (8%) subjects had other malignancies with a complete and partial success rate of 3 (38%) including 1 subject with *Fusarium* spp. and 1 with *Scedosporium apiospermum.*

11/98 (11%) subjects had a history of surgery or trauma. There were 2 complete successes including 1 in a subject with *Fusarium solani* and 1 in a subject with *Pseudallescheria boydii* and 5 partial successes for a total rate of 7/11 (64%).

2/98 (2%) subjects had aplastic anemia one of whom was a partial success; the other with an infection due to *Fusarium* spp. was a failure/stable.

1/98 (1%) subject was an IVDA and was classified as a partial success (*Pseudallescheria boydii* infection). 1/98 (1%) subject had chronic hepatitis B and was classified as a failure due to intolerance. (2 *Fusarium* spp. isolates and 1 *Acremonium* spp.)

4/98 (4%) subjects (6 isolates) had unspecified underlying diseases and all were classified as successes (1 complete, 3 partial). 2 of these had unspecified fungal infections, 1 had *Coccidioides immitis*, and 1 had *Fusarium oxysporum.*

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:

19/98 (19%) of subjects had documented profound neutropenia. 4 (21%) of these subjects were classified as partial successes after voriconazole treatment and 1 (5%) was classified as a complete success. The remaining 14 (73%) subjects were failures including failure due to insufficient response in 11, failure/stable in 2, and failure/unevaluable in 1.

2/98 (2%) subjects with autologous BMT were both successes (one partial, one complete) as compared to 1 (4%) patient with allogeneic BMT (counted twice) who was initially categorized as a complete success and then as a failure due to insufficient response after a relapse.

4 (4%) subjects had GVHD. 2 of these were classified as partial successes and 2 as failure, one due to death and one due to insufficient response.

1(2%) subject had a listed risk factor of relapsed hematologic malignancy. This subject was a failure due to insufficient response.

70/98 subjects (71%) had no known risk factor. 22 (31%) of these subjects had a partial response and 12 (17%) a complete response. The remaining 36 (51%) \subjects were failures due to insufficient response in 20, failure/stable in 11, intolerance in 4, and unevaluable in 1.

Conclusion: 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.

Efficacy by Savage vs. Primary Treatment:

68/98 (69%) of subjects were classified as in need of salvage treatment because of efficacy failure. 10 of these (15%) were classified as complete successes and 21(31%) were classified as partial successes. 35 (51%) were classified as failures including 2 due to death, 3 due to intolerances, 17 due to insufficient response and 13 failure/stable subjects.

3/98 (3%) of subjects including one subject counted twice (4%) underwent salvage treatment for unknown reasons. 2 were classified as complete successes and 2 were classified as failures due to insufficient response. One subject accounted for both a success initially and then a failure.

6/98 (6%) subjects were determined to need salvage therapy because of both efficacy failure and intolerance. 3 of these were classified as partial successes and 1 was classified as a complete success. There were 2 failures, one due to insufficient response and 1 failure/stable.

4/98 (4%) of subjects were deemed in need of salvage treatment because of intolerance. There was 1 each a partial and a complete success and 2 failures due to insufficient response.

18/98 (18%) of subjects in the FDA database received voriconazole as primary treatment. 4 of these were classified as partial successes and 1 was classified as a complete success. The remaining 13 were classified as failures due either to insufficient response in 12 or to intolerance in 1.

Conclusion: 80/98 (82%) of the FDA subjects were classified as requiring salvage treatment primarily due to efficacy failure of previous treatments 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.

D. Efficacy 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. 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. 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.

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 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.

APPEARS THIS WAY
ON ORIGINAL

B. Recommendations

The MO recommends approval for use of voriconazole in the treatment of serious fungal infections caused by *Scedosporium apiospermum* and *Fusarium solani*/spp. in subjects intolerant of or refractory to other therapy. The MO does NOT recommend approval for a fist 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:

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:

The clinical studies section should be modified as follows:

Other Serious Fungal Pathogens:

In pooled analyses of patients voriconazole was shown to be effective against the following additional fungal pathogens:

Scedosporium apiospermum -Successful response to voriconazole therapy was seen in 15 of 2 patients . 3 of these relapse within 4 weeks including 1 with pulmonary, skin and eye infections, 1 with cerebral disease, and 1 with skin infection. 10 had evidence of cerebral disease and 6 of these had a successful outcome (1 relapse). In addition, a successful response was seen in one of three patients with mixed organism infections

Fusarium spp.- 9 of 21 (43%) of patients were successfully treated with voriconazole. Of these nine patients, 3 had eye infections, 1 had an eye and blood infection 2 had sinus infections, and one had disseminated infection pulmonary, skin, hepatosplenic).

3 of these (one with disseminated disease, one with an eye infection and one with a blood infection) had *Fusarium solani* and were complete successes. 2 of these patients relapsed, one with a sinus infection and profound neutropenia and 1 post surgical patient with blood and eye infections.

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/
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SEP 22 1998

Medical Officer's Review of IND ———
Ophthalmology Consultation

IND ———
Ophthalmology Consultation

Submission dates: 5/8/98 & 7/28/98
Consult Request: 8/23/98
Review date: 9/22/98

Sponsor:

Pfizer
Central Research Division
Eastern Point Road
Groton, CT 06340
(860) 441-4100

Drug: Voriconazole

Pharmacologic Category: Triazole anti-fungal agent

Submitted:

"Enclosed is the Pfizer Position Paper on Voriconazole and Altered Vision. It consists of a review of the visual adverse events in clinical trials together with the results of exploratory work and analyses Pfizer has performed to help understand the visual phenomena. Appendices to the Position Paper include an Expert Report on Study 150-231, a double-blind clinical study to investigate electrophysiological changes in the retina and visual cortex of healthy male subjects; a discussion of the binding of drugs to eye melanin; and a summary of an Ophthalmology Expert Panel which met in October, 1995 to address the visual disturbances associated with voriconazole. It is our position that the events are transient, fully reversible and without consequence to the daily functioning of subjects. In addition, there is no evidence from animal data that voriconazole causes structural damage to the eye in the long term.

We seek the Agency's concurrence that:

- Additional mechanistic investigations would not likely further elucidate the mechanism of action of these visual events.
- The long term ocular safety of voriconazole is comprehensively addressed by the combination of visual function tests performed to date, the bedside monitoring of patients in forthcoming studies and detailed animal histopathology of the eye.
- With the completed investigations and the proposed monitoring programme, the visual disturbances will have been adequately addressed in our planned NDA.
- The completed investigations and the proposed monitoring programme will support the use of voriconazole in adult and pediatric patients as proposed in the End-of-Phase 2 meeting."

Applicant's EXECUTIVE SUMMARY

"Voriconazole administration has been associated with a mild alteration in vision, generally described as enhanced perception or brightness of light or blurred vision. The phenomenon has been described by both healthy volunteers and patients. The attached document summarises, in detail, the visual disturbance phenomenon with voriconazole and the results of exploratory work and analyses Pfizer has performed to help understand this event. The following summarises the principal conclusions and proposals found in the document:

- Altered vision has been **reported in around 20% of volunteers or patients** receiving voriconazole
- The event is transient, fully reversible and without consequence to the daily functioning of subjects
- Comprehensive testing has uncovered no changes in visual function of subjects during the clinical trials programme, with the exception of slightly impaired colour discrimination in one test
- The site of action is most likely to be the retina; neither other structures within the eye nor the central nervous system pathways appear to be affected
- There is no evidence from animal data that voriconazole causes damage to structures of the eye in the long term

Pfizer has performed a comprehensive series of tests early in the development programme in order to understand this phenomenon. Our assessment is that it is a minor side effect, of no clinical importance. We are seeking the Agency's views on the following proposals:

Pfizer suggests that further mechanistic investigations would not be useful in comprehending either the mechanism of action or any risk to patients. This is because the site of action is within a poorly understood part of the visual pathway and mechanistic data will be difficult to interpret.

The long term ocular safety of voriconazole is comprehensively addressed by the combination of visual function tests performed to date, the bedside monitoring of patients in forthcoming studies and detailed animal histopathology of the eye.

With the proposed monitoring programme, Pfizer believes visual disturbances will have been suitably addressed and will have no impact on marketing approval."

Reviewer's Comments:

Strongly disagree. The effects observed to date appear to be clinically significant. The ocular testing performed to date has had numerous problems and additional testing is highly recommended. The visual affects are potentially sight threatening and consequently will have to be weighed in individual decisions concerning benefit to risk ratios.

Voriconazole and Altered Vision

"The adverse event described with the highest frequency in patients and volunteers receiving voriconazole is "abnormal vision." The phenomenon was first reported in an early Phase I oral dose escalation Study (150-204) in which the planned doses were 4, 5 and 6mg/kg. After visual disturbance was reported by 7/7 volunteers at 5mg/kg, the study was stopped; follow-up showed that one volunteer at 4mg/kg had also reported visual disturbance. Since this early study, visual disturbances have regularly been reported throughout the clinical development programme.

Adverse events related to vision have now been reported in most Phase I studies and all Phase II studies. The 1997 APR database (cut-off June 29, 1997) of a total of 876 patients and volunteers exposed to voriconazole. The data in Table 1 summarise events that may be related to vision or visual function. In addition, retinal haemorrhage (2), retinal detachment (1) and retinitis (2) were reported as treatment emergent adverse events. None of the latter 3 were considered treatment-related.

Event	Treatment-emergent (%)	Treatment-related (%)
Abnormal vision	162 (18.5)	140 (16.0)
Abnormality of accommodation	1 (0.1)	1 (0.1)
Colour blindness	1 (0.1)	1 (0.1)
Diplopia	2 (0.2)	1 (0.1)
Eye disorder	3 (0.3)	1 (0.1)
Hallucinations	1 (0.1)	1 (0.1)
Oculogyric crisis	2 (0.2)	2 (0.2)
Photophobia	37 (4.2)	35 (4.0)
Visual field defect	1 (0.1)	1 (0.1)

Total (active)	73/499 (14.5%)
Phase I	40/238 (16.8%)
Single dose ORAL	8/89 (9.0%)
Multiple dose ORAL	27/83 (32.5%)
Single dose IV	5/45 (11.1%)
Multiple dose IM	0/21(0%)
Placebo	8/98 (8.2%)
Phase II 33/261 (12.6%)	
Study 302 (oropharyngeal candidiasis)	17/165 (10.3%)
Study 303 (chronic aspergillosis)	10/25 (40.0%)
Study 304 (acute aspergillosis)	6/71(8.5%)"

"Descriptions vary from a general blurring of vision to the more specific reports of 'brighter objects' or 'brighter lights.' Investigators have sometimes used the term "photophobia" when describing these events. Reports that have been offered less commonly by subjects, include glare, flashes, flickering, colour change, halos and dots.

To help simplify presentation of the events in study reports and summary documentation, 5 different categories are to be used. This report will continue to use the preferred terms of abnormal vision or photophobia.

1. Altered visual perception. This is felt to be the true visual phenomenon induced by voriconazole. It encompasses "enhanced perception," "brighter lights and objects," "dazzle and glare" and "flashes and flickering." This term will also be used where the investigator has simply entered "visual disturbance" or "abnormal vision" on the CRF.

2. Blurred vision. This is a non-specific description that is reported with numerous drugs. Expert consultation has suggested that the majority of visual disturbances reported with drugs listed in data sheet compendia, are this type of non-specific report.

3. Altered colour vision. Although reported only rarely, a mechanistic clinical study suggests voriconazole has potential to cause an alteration in colour perception.

4. Photophobia. Only when written by the Investigator on the CRF

5. Other. This encompasses either events that cannot easily be categorised as above (e.g., dots, scotoma or visual field defect), or events not related to the principal effect on vision (e.g. lacrimation or oculogyric disorder).

In the early single dose volunteer studies, the visual disturbances occurred with an approximate relationship to dose. In Study 204, the event occurred at an oral dose of 5mg/kg in all 7 subjects, in only one subject at 4mg/kg and had not been reported at all in previous studies up to 2mg/kg.

The 1996 APR database confirmed a dose response in both the Phase I and Phase II programmes. The data indicate that the threshold oral dose, at which an increase in incidence of visual events is more likely to occur is around 4 and 5 mg/kg, for volunteers and patients, respectively. The planned oral dose of voriconazole is 200-300 mg bd.

Onset and duration of visual events in healthy volunteers receiving single or multiple dose oral voriconazole.

Route	Description	N	Onset range (mins)	Median onset (mins)	Duration range (mins)	Median duration (mins)
oral	Abnormal	83	—	25	—	20
oral	Photophobia	7	—	20	—	15

the event after an oral dose also has a broad range, however the median duration is 15-20 minutes. Similar data on duration were obtained with i.v. Phase I studies."

Study 231

"This was a randomised, double blind, placebo-crossover study to investigate electrophysiological changes in the retina and visual cortex of healthy male subjects administered single dose intravenous voriconazole in two sets of 2-way crossovers. Eight volunteers received voriconazole (8mg/kg) or placebo (saline) by intravenous infusion over 1 hour in each of 4 periods. The intravenous route was chosen to reduce variability in kinetics parameters. The dose of 8mg/kg was chosen as it had been associated with a high incidence of visual events; this dose is not normally used therapeutically. Electrophysiological parameters were measured during Periods 1 and 2 (see below) and pharmacokinetics, symptomatology and colour vision testing were performed during Period 3 and 4.

Symptomatology results

During Periods 1 and 2, 3/8 subjects receiving voriconazole and 0/8 receiving saline reported visual AEs (blue fog/blurred). During Periods 3 and 4, 7/8 subjects on voriconazole and 0/8 subjects on placebo reported visual AEs (dazzle/brightness). The onset was <30 minutes and the typical duration of the adverse event was 1 hour.

EOG results:

The mean Arden ratio after voriconazole treatment was significantly less than after placebo (190.0±56.9 versus 244.3±40.9, p=0.024). However, the mean value for voriconazole was similar to that obtained at baseline (186.1±25.7) and above the lower limit of normal (150). Two subjects receiving voriconazole presented abnormal Arden ratios below 150.

These results were discussed with external consultants. All agreed that the EOG data generated in Study 231 are difficult to interpret because of the variation between baseline and treatment periods noted above. Also, the baseline Arden ratios appeared to these experts to be lower than normal, leading to a suspicion that there may have been methodological problems with the test. However, since changes to another electrophysiology test were seen within this study, Pfizer considers the overall conclusion of this study to be sustainable and plans no further work of this type."

Reviewer's Comments:

The study shows a difference between groups with patients treated with voriconazole performing inferiorly to patients on placebo.

VEP results:

"Checkerboards of four different sizes were used (15x15, 30x30, 50x50 and 70x70). The electrical signal after stimulation with the smallest (70x70) and the largest (15x15) checkerboard sizes was analysed.

The only statistically significant change in the pattern VEP was a small increase in P100 latent time for the 15x15 checkerboard with voriconazole compared to placebo (89.6±3.3 ms vs. 86.4±6.5 ms; p=0.044). Considering the very small difference (-3.5%), this change is not considered to have any clinical significance. There were no differences in amplitude of N75, PI 00 and N1 40 waves, regardless of stimulation, and overall the results are considered to show no effect of voriconazole on visual evoked potential."

Reviewer's Comments:

This summary is very misleading. One of the patients could not complete the test because he experienced "dazzles during voriconazole and had difficulty in fixing the checkerboard."

Flash ERG results:
"The key result from the ERG evaluations was that voriconazole produced a notable decrease in b-wave amplitude under both photopic and scotopic conditions.

Under photopic conditions, the decrease was around 30%, depending on the nature of the stimulus. Different coloured stimuli were used to determine whether the effect was due to rod or cone systems. The data suggest that both rod and cone systems are affected, since the same response was seen, regardless of stimulus.

In addition, a decrease in a-wave amplitude of around 15%, and a very small increase (-2%) in implicit time of the b-wave, were also observed with voriconazole. It is believed that these observations are secondary to the modification of the b-wave waveform, induced by voriconazole.

Volunteers with abnormal ERGs, after receiving voriconazole during Period 1, presented normal ERGs during Period 2. Volunteers, receiving voriconazole, with abnormal ERG results during Period 2, presented normal ERGs at follow up (2 weeks after the study). Thus, the voriconazole-induced effects to the ERG were fully reversible.

The data were discussed with independent experts. The interpretation of the ERG results is that they indicate an effect of voriconazole on the post photoreceptor system in the retina, and that both cone and rod systems are affected."

Reviewer's Comments:

Although the primary results have not been submitted. It seems reasonable to conclude based on the data submitted that both the cone and rod systems are affected.

Farnsworth Munsell 100 Hue test
"This assesses the subjects' ability to arrange 85 coloured discs in order of gradually changing hue under standard simulated daylight conditions. Results show that there was a statistically significant difference between voriconazole and placebo in the subject's total error scores. The difference of voriconazole over placebo was 53 with a 95% confidence interval of (17.8, 88.2). This may be explained by a higher error score in the yellow/green region."

Reviewer's Comments:

This supports the conclusion that there are affects on the cone system and it may be a useful way to follow patients.

Conclusions

The results of Study 231 suggest the following:

1. The site of action of voriconazole-induced visual effects is the retina; ERG data suggest the inner nuclear layer is principally affected.
2. Central pathways from the optic nerve to the visual cortex are not affected.
3. Changes to the ERG are fully reversible.
4. Voriconazole has the potential to affect colour discrimination

Reviewer's Comments:

It is not possible to conclude that the visual cortex is not affected. It is also not possible to conclude that the ERG changes are fully reversible.

Study 673

"This comparative study in the USA is to investigate the safety, toleration and pharmacokinetics; of voriconazole in subjects at risk for aspergillosis. A total of 36 subjects are to be enrolled into this study (12 patients/leg), which is ongoing. Subjects are randomised to either voriconazole or fluconazole, in a 3:1 distribution. The first leg (200mg bid for 14 days) was successfully completed and subjects have now started the second leg, receiving 300mg bid.

The dose of 200mg PO BID is considered safe and well tolerated. A total of 3 subjects (two randomised to voriconazole and one to fluconazole) reported visual disturbances during the study.

In addition, 2 subjects receiving voriconazole had abnormalities on visual safety testing but did not concomitantly report any associated visual disturbances. One subject had a reduction in visual field testing on Day 15, compared to baseline, but did not report any associated visual symptoms. The subject also had punctate keratopathy probably related to dry eyes, first noted on the same day. A second subject presented a small nerve fibre haemorrhage on funduscopy at Day 15; this had resolved by Day 21. Neither of these abnormalities were considered to be clinically significant by the Investigator and have not been reported as adverse events.

There were no other findings from the extensive battery of visual function testing, in the first leg of this study."

Reviewer's Comments:

No explanations have been provided for the abnormalities identified above. The failure to list these events as adverse events calls into question the overall incidence of adverse events and suggests that the reported percentages are under reported.

Study 305

"This is a comparative Phase III study of voriconazole and fluconazole in the treatment of oesophageal candidiasis. Drug is administered for up to 6 weeks. The study remains blinded, however an interim analysis was performed on the first 100 patients. No significant changes from baseline were seen in any of the functional visual tests (visual acuity, contrast sensitivity, colour vision, funduscopy) in either study group."

Reviewer's Comments: *There is insufficient information in this summary to comment.*

Study [redacted]

"In this Japanese Phase I study, there were 9 reports of visual disturbances. At the highest dose tested (400mg), 4/6 volunteers reported abnormal vision. The study has not been formally analysed.

This study incorporated a number of visual tests; all except pupilloscopy were without drug-induced findings. In the automated test for pupillary reaction, pupil diameter after the voriconazole dose was apparently smaller than pre-dose measurement. When examined over the dose range, this apparent effect showed a dose-dependency. This was considered by the Investigator to be a reflex response to glare. It is noteworthy that miosis has been observed in dogs treated with voriconazole, although ft is impossible to conclude that the same mechanism is involved."

Reviewer's Comments: *There is insufficient information in this summary to comment.*

Study 207

"Contrast sensitivity _____ was performed on volunteers after the highest voriconazole dose tested (4mg/kg/d) in this 10-day, multiple dose i.v. study. There was no apparent effect of voriconazole on contrast sensitivity in either eye as judged from a comparison of pre-dose to post dose values, however, formal statistics have not yet been performed on these data."

Reviewer's Comments: *There is insufficient information in this summary to comment.*

Daily functioning

"A questionnaire was devised with the purpose of trying to assess how visual disturbances affect routine activities of subjects, whether there was any association with other symptoms and the degree of concern. This is a non-validated questionnaire that was intended to be used, in specific Phase I studies, to improve the Pfizer's understanding of the phenomenon; it is not being routinely used in the voriconazole programme.

The questionnaire was employed in three Phase I studies. From a preliminary review of the responses, the visual disturbance experienced by these volunteers appears to be one associated with brightness or flashing of lights. Colour perception and visual acuity were generally unaffected and volunteers could maintain their normal daily activities (reading, watching television, moving about).

The event, once perceived, does not worsen and improves with time. Headache, nausea and loss of appetite are not generally associated with the visual disturbance. In one study (Study 231), dizziness was associated with the visual disturbance in 50% of subjects, however this was not the case in the 2 other studies.

Also, in Study 230, 5/21 subjects who received only placebo reported similar visual disturbances to those reported by subjects receiving voriconazole. When their responses to the visual disturbance questionnaire were examined, these were found to be broadly comparable to those provided by subjects receiving voriconazole.

Considering the lack of impact on the daily functioning of the volunteers, there is no contraindication on driving or operating heavy machinery while taking voriconazole in the current voriconazole Investigator Brochure. The IB states, however, that patients should be cautioned against performing these tasks *during* a disturbance."

Reviewer's Comments:

Disagree. The testing was insufficient to form these conclusions.

MONITORING DURING PHASE III

"The sponsor intends to monitor patients for visual safety during the Phase III programme. However, assessing visual function in the target population is not without complications:

1. Severely ill patients will be unable to co-operate with rigorous ophthalmological procedures.

2. The patients may have underlying diseases (e.g. leukaemia, AIDS) or be receiving concomitant medications (e.g. cytotoxic drugs) with ophthalmological manifestations.

3. Most of the studies will be unblinded, leading to possible bias.

Nevertheless, the sponsor considers tests of function that can be performed at the bedside by the attending physician to be appropriate. Phase III protocols will therefore contain the following tests:

1. Visual acuity, using a reduced Snellen chart
2. Visual fields, by confrontation perimetry
3. Funduscopy

Patients with an abnormal finding will have a fuller examination performed by an ophthalmologist."

Reviewer's Comments:

The proposed testing is not expected to be useful. If adequate testing is not available during hospitalization, there should be full ophthalmologic examinations including best corrected visual acuity, direct and indirect funduscopy and Farnsworth-Munsell 100 hue (24 or 40 hue may also be acceptable) testing on all patients. In addition, patients who are treated for an extended period of time (>28 days) should have automated visual field testing.

PLANS FOR OTHER ADDITIONAL WORK

Pfizer intends to perform a morphometric analysis of the retina in sections through the eye of rats from the 6-month oral toxicology study. This will confirm the absence of retinal thinning after chronic dosing with voriconazole.

In addition, Pfizer will perform periodic reviews of the database, using logistic regression techniques, in an attempt to better understand this adverse event.

There are no further plans for additional mechanistic work.

Reviewer's Comments:

If additional work is not carried out, the product should carry a WARNING (possibly boxed) of potential visual loss.

Sponsor's DISCUSSION AND CONCLUSION

After thorough investigation, and in agreement with expert consultation, Pfizer considers the visual disturbances to be minor side effects of voriconazole, albeit occurring at a high incidence. The effect is transient, fully reversible and does not appear to affect the daily functioning of subjects.

Reviewer's Comments: *Disagree.*

The majority of reported events can generally be classified into four descriptions (altered visual perception, blurred vision, colour vision change, photophobia). The events are dose-related with an increased likelihood of occurring, between 4 and 5mg/kg. The relationship to plasma levels is less clear, however, and there is an apparent difference in incidence between oral and iv routes.

Reviewer's Comments:

The proposed dosing is in the range where adverse effects have been observed. It appears that no all adverse experiences have been classified as adverse events.

Reviewer's Comments

If additional work is not carried out, the product should carry a WARNING (possibly boxed) of potential visual loss.

The long-term risks to patients have been and will be assessed by incorporating functional tests in protocols, appropriate for the subject population involved. Thus, more rigorous visual function testing has been performed in volunteer and selected patient trials (for example Study 305). In contrast, the poor general condition of the patients to be treated in the Phase III studies will allow less rigorous testing, and a basic bedside screen is to be used. In all, Pfizer considers the data will adequately address long term safety issues pertaining to visual disturbances.

Reviewer's Comments:

The proposed testing is not expected to be useful. If adequate testing is not available during hospitalization, there should be full ophthalmologic examinations including best corrected visual acuity, direct and indirect funduscopy and Farnsworth-Munsell 100 hue (24 or 40 hue may also be acceptable) testing on all patients. In addition, patients who are treated for an extended period of time (>28 days) should have automated visual field testing.

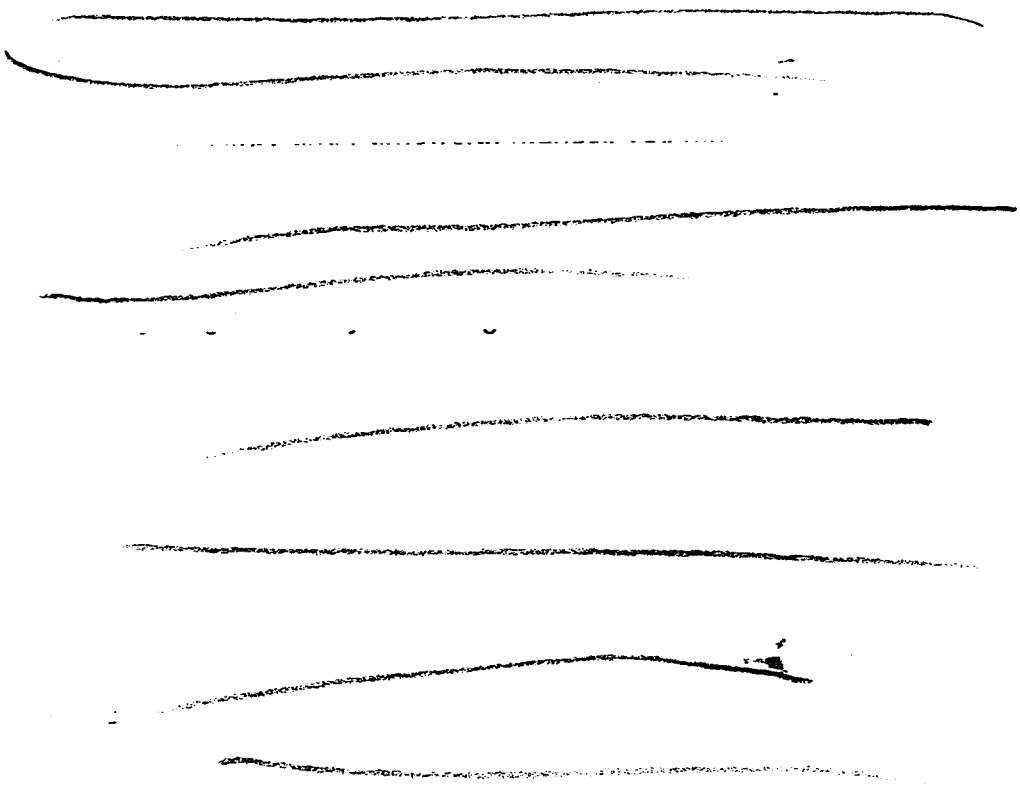
___/___ page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

Summary Requests from Sponsor:

- Additional mechanistic investigations would not likely further elucidate the mechanism of action of these visual events.

Reviewer's Comments: *Unknown.*

- The long term ocular safety of voriconazole is comprehensively addressed by the combination of visual function tests performed to date, the bedside monitoring of patients in forthcoming studies and detailed animal histopathology of the eye.



/S/
Wiley A. Chambers, M.D.

cc: Orig IND
HFD-590
HFD-590/Frank
HFD-590/Roca
HFD-550/Consult File
HFD-105
HFD-550/MO/Chambers

D.V

Medical Officer's Review of IND ——
Ophthalmology Consultation

OCT 6

Request From: Teresa Wu, M.D.
HFD-530 Division of Antiviral Drug Products

Subject: UK- 109,496

Review date: 10/1/95

Sponsor: Pfizer
Central Research
Sandwich, Kent

Drug: UK-109,496

Pharmacologic Category: Antifungal

Proposed Indication: For the treatment of Aspergillosis in immunocompromised patients.

Dosage Form and Route of Administration: Oral Tablets

Submitted: Protocol for use of UK-109,496 in patients with Acute Myelogenous Leukemia or Autologous Bone Marrow Transplantation at risk of Aspergillosis.

Background:

"UK-109,496 has been given to approximately 500 humans in volunteers and patients in Europe, at doses of 200 mg PO BID for up to 24 weeks. The most common treatment-related adverse effect reported to this date is a dose related **visual disturbance**, reported in 14.5% of the participants enrolled in phase I and II trials. These events were usually described as "blurred vision", "altered perception of light" or that objects appear to be brighter." These events have occurred after a median period of 25 minutes and have been transient, resolving after a median period of 20 minutes. In multiple dosing trials, visual disturbances developed after 4-7 days of treatment, and often decreased over time with continued dosing."

Requested: Are these ADR's being investigated adequately?

Protocol # 95CK39-0673

Title:

A Multicenter Randomized, Double Blind, Placebo-Control Phase I Study to Investigate the Safety, Tolerance and Pharmacokinetics of Three Increasing Oral Doses of UK 109,496 in Patients with Acute Myelogenous Leukemia or Autologous Bone Marrow Transplantation at Risk for Aspergillosis.

Design:

This Phase I, multicenter, randomized, double blind, placebo-controlled, study is designed to evaluate the safety, tolerance and pharmacokinetics of three increasing doses of UK-109,496. The study will be conducted in up to three sequential phases at three sites. In each phase of the study, a sufficient number of patients will be recruited to produce 12 evaluable patients. In the first phase of the study, patients will be randomized to received either 200 mg BID of oral UK 109,496 or placebo administered for a period of 14 days. When a total of 12 patients have been accrued, the blind will be broken and an analysis to assess the safety and tolerance of that dose will be performed by the sponsor. If the 200 mg dose is judge as well tolerated the dose of 300 mg BID will be tested 12 additional patients for 14 days and if well tolerated the dose of 400 mg BID will be tested in a final group of 12 patients for 14 days.

Reviewer's Comments: *Only ophthalmologic evaluations will be addressed*

Study Flow Chart

Visit #	1	2	3	4	5	6	7	8
Study Phase	Screening	Treatment						Follow-up
Study Day	0	1	4	7	10	14	15	21
Informed Consent	x							
Entry Criteria	x							
Medical History	x							
Vital signs	x	x	x	x	x	x	x	x
Physical Exam	x						x	
Ophthalmology	x						x	
EKG	x						x	
Chest X-Ray	x							
Adverse events assessment		x	x	x	x	x	x	x
Hematology	x	x	x	x	x		x	x
Chemistry	x	x	x	x	x		x	x
Urinalysis	x	x	x	x	x		x	x
Hepatitis Screen	x							
Retinol, RBP		x	x	x	x	x		
Pregnancy Test	x							
Full Pharmacokinetics		x				x		
Drug levels			x	x	x			

Reviewer's Comments: *Any abnormal ophthalmic finding should be repeated at Visit 8.*

Within 7 days prior to randomization, and on day 15 (End of Therapy) each patient will undergo an assessment of visual function. It includes the following:

1. Visual Acuity: snellen chart test letters at 20 feet with and without correction.

Reviewer's Comments: *Visual acuity without correction is not needed. Visual acuity testing should be best corrected using a "ETDRS" type chart (i.e., equal number of letters per line).*

2. Color Vision: City University Color Test

Reviewer's Comments: *Assuming that each eye is performed separately, this is acceptable, however, it would be preferable to perform a ——— ? or Farnsworth Munsell 100 test.*

3. Contrast Sensitivity: ———

Reviewer's Comments: *Acceptable.*

4. Photostress Recovery Time (PSRT): One eye is illuminated for 30 seconds with a penlight held 2 to 3 cm from the eye. The PSRT is measured in seconds as the time required to read the Snellen letters on the line above that of the best corrected repeated testing. Each eye is tested separately.

   A significant change in photostress recovery time is one which is maintained on repeated testing.

Reviewer's Comments: *The number of "repeat tests" should be clarified.*

5. Visual Fields (optional): Utilizing quantitative Humphrey Perimeter test with small red test object in center.

Reviewer's Comments: *The specific program to be used should be specified and the conditions when the "option" will be used to test patients should be specified.*

6. External Eye Exam (eye alignment, eyelids, ——— conjunctiva) pupillary reflexes (direct and consensual) to light and accommodation.

Reviewer's Comments: *Specific measurements of pupillary diameter should be made and recorded.*

7. ———

Reviewer's Comments: *Acceptable.*

8. Slit Lamp Exam

Reviewer's Comments: *Acceptable.*

9. Funduscopy: Dilated Fundus Examination

Reviewer's Comments: *Acceptable. The duration of the exam should be kept to a minimum.*

10. [redacted]

Reviewer's Comments: [redacted]

Adverse Events (Visual Disturbances)

Patients reporting visual disturbances at any time during the study will be evaluated within 2 hour of onset of symptoms. The ophthalmologic examination conducted at baseline will be repeated. Any abnormal ophthalmologic finding detected at this time will be assessed by the investigator for clinical significance and the decision to stop medication will be made on a case-by-case basis.

Reviewer's Comments: *Acceptable.*

Additional Comments:

There have been a number of skin reactions (erythema/rash) recorded, principally in study 303, but also sporadically in volunteers and patients in study 302 and 304. ... In Studies 303 and 304, the reactions were largely localized to areas of the skin exposed to light and may, therefore, indicated photosensitizing potential.

Reviewer's Comments: *If the drug product has a photosensitizing potential, it may also enhance light toxicity to the retina. This may explain the observed ocular adverse experiences.*

Recommendations:

From the ophthalmologic point of view the study may proceed however the issues listed below should be addressed:

1. Any abnormal ophthalmic finding should be repeated at Visit 8.

2. Visual acuity without correction is not needed. Visual acuity testing should be best corrected using a "ETDRS" type chart (i.e., equal number of letters per line).

3. Assuming that each eye is performed separately, the proposed color vision testing is acceptable, however, it would be preferable to perform a ——— or Farnsworth Munsell 100 test.

4. The number of "repeat tests" in the Photostress recovery test should be clarified.

5. The specific program to be used in the visual field test should be specified and the conditions when the "option" will be used to test patients should be specified.

6. The duration of the fundus exam should be kept to a minimum.

7. Specific measurements of pupillary diameter should be made and recorded.

8. The fundus photography section should be clarified since it does not appear that fluorescein angiography is being performed. In addition, the conditions when the "option" will be used to test patients should be specified.

9. If the drug product has a photosensitizing potential, it may also enhance light toxicity to the retina. This may explain the observed ocular adverse experiences. Additional investigations should be directed at attempting to characterize the photosensitizing potential.

/S/

/ Jose A. Carreras, M.D.

cc: Orig IND ———
HFD-530
HFD-530/Wu
HFD-540/MO/JCarreras
HFD-540/MO/Chambers

/S/ 10/10/95

Medical Officer Review
of new IND——— UK 109,496
and
Protocol: A multicenter, randomized, double-blind placebo-controlled phase 1 study to investigate the safety, tolerance and pharmacokinetics of three increasing oral doses of UK 109,496 in patients with acute myelogenous leukemia or autologous bone marrow transplantation at risk for aspergillosis

Date submitted:	8/28/95
Date received:	8/29/95
Date assigned:	9/1/95
Ophthalmology consultation:	10/6/95
Date reviewed:	10/18/95

Sponsor: Pfizer Inc.
235 East 42nd Street
New York, N.Y. 10017
Contact person: Margaret A. Longshore, Ph.D.
Tel. (212) 573-2556

Drug: UK-109,496, triazole antifungal agent

Form/Route of Administration: 50-mg and 200-mg tablets, oral

Proposed Indications:
1. Invasive aspergillosis and invasive candidiasis
2. Empiric therapy of systemic mycoses

Resume: UK-109,496 is a novel triazole compound with antifungal activity against aspergillus, fusarium, candida, and cryptococcus. Similar to other triazole antifungal drugs, UK 109,496 inhibits the fungal cytochrome P-450 dependent 14 α-sterol demethylase of ergosterol biosynthesis.

In this IND, the sponsor proposed a phase 1 protocol designed to evaluate the safety, tolerability and pharmacokinetics of three increasing doses of UK 109,496. For each dose cohort, patients will be assigned to receive active drug or placebo in a 3:1 ratio. The study will begin with a dose of 200 mg BID in a group of 12 patients. If this dose is well tolerated, the dose of 300 mg BID will be tested in a second group of 12 patients. Similarly, the dose of 400 mg BID will be tested in the final

group of 12 patients. Duration of treatment for each of three doses is 14 days.

Patients with a diagnosis of acute myelogenous leukemia, or lymphoma who are within 2 months of chemotherapy or an autologous bone marrow transplant, who have received at least 5 days of intravenous amphotericin B empiric therapy, are eligible to be randomized. Justification for including a placebo arm in the design is based on that current standard of care does not mandate continued antifungal therapy for these patients without highly suspected fungal infection.

Prior to randomization, each patient will undergo a screening evaluation including a comprehensive ophthalmologic evaluation. During the study, patients will be followed closely with frequent safety monitoring visits and liver function testing. Pre-defined stopping rules and safety endpoints were also provided.

During each dosing phase, blood samples will be drawn at pre-scheduled time points as specified in Appendix B on days 1, 4, 7, 10, and 14.

Patients reporting visual disturbances at any time during the study will have blood samples drawn for drug level, retinol, and retino-binding protein. A comprehensive ophthalmologic evaluation similar to that given at screen will be repeated. Whether the patient should be stopped therapy will be determined on a case-by-case basis.

BACKGROUND

I. Previous human experience

A total of 238 healthy male volunteers have received UK-109,496 via the oral (n=172) or intravenous (n=66) routes of administration in 17 phase 1 pharmacokinetics single and multiple dose studies. Four dosage forms were employed, they are: oral solution, capsule, tablet, and IV solution. For oral formulations, doses ranged from 0.06 mg/kg to 200 mg bid; for the IV formulation, 0.2 mg/kg/day to 8 mg/kg/day.

A. Pharmacokinetics

The pharmacokinetics of the oral administration is summarized as the following:

- T_{max} = 1 to 2 hrs.
- C_{max}, AUC over time increased disproportionally over the range of 0.06 mg/kg to 5 mg/kg.

- Steady state was achieved by the 5th or 6th day of dosing.
- The inter-subject pk variation was wide.
- A high fat meal was found to reduce the rate of absorption and the steady state AUC.
- The mean bioavailability of the tablet formulation relative to the capsule formulation was 106.7%.

The pharmacokinetics of the IV administration is summarized as the following:

- The pk of IV solution was proportional to dose up to 4 mg/kg. On higher doses, disproportional increases in AUC were evident.
- The steady state was achieved by the 6th day of dosing.
- The inter-subject pk variation was wide.
- The protein binding was about 58%.

B. Efficacy

Over 250 patients with fungal infection have received UK-109,496 in 3 clinical trials. The key design features of these studies are summarized in the table below:

Protocol	Design*	N	Patient	Disease	Doses	Duration
150-302	DB, DR	165	HIV+	Oral candidiasis	50mg od 200mg qd 200mg bid	7 days
150-303	OE,NC	24	non-neutropenic	Aspergillosis Candidiasis	200mg bid	4-24 weeks
150-304	OL,NC	71	Immunocompromised	Aspergillosis	IV 6mg/kg bid x1day followed by 3mg/kg bid for 6-27 days followed by 200 mg bid oral to a total 24 weeks.	Total up to 24 weeks

*DB=double blind; DR=dose ranging; NC=non-comparative

Preliminary results of the above studies showed that the 200 mg bid dosing regimen yielded better response rates(clinical response 100%, mycological response 74%) than the 200mg qd and 50 mg dose in the treatment of oral candidiasis, and that the IV dosing followed by oral dosing regimen (protocol 304) yielded a better clinical response rate (75%) than the oral dosing alone (69%, protocol 303) in the treatment of aspergillosis.

C. Safety

1. Visual disturbance

Adverse events of visual disturbance have reported at 14.5% of all study subjects (volunteers and patients), regardless of route of administration. Visual disturbance was described as altered perception of light, such as glare and object brightness, or blurred vision. Symptoms usually occurred between 30 and 60 minutes post-dose and lasted less than 1 hour. Results of ophthalomological tests performed so far in selected volunteers have provided no clues for a potential mechanism.

Comment: The sponsor concurred with this reviewer that potential CNS involvement can not be ruled out despite the lack of CNS symptomatology.

2. Elevation of LFTs

There was an incidence of >10% (the sponsor did not provide a precise figure) of elevated LFTs in Studies 303 and 304. Enzyme elevations appeared to be temporally related to onset of UK 109,496 therapy. No such finding reported among volunteers.

3. Skin rash

Skin reactions occurred in 2.8% of study subjects (1.7% in volunteers: 3.8% in patients.) In Studies 303 and 304, the reaction were largely localized to areas of the skin exposed to light, suggesting a photosensitizing potential with UK 109,496.

Ophthalmologist comment (Dr. Jose Carreras, HFD-540): "If the drug product has a photosensitizing potential, it may also enhance light toxicity to the retina. This may explain the observed ocular adverse experiences. Additional investigations should be directed at attempting to characterize the photosensitizing potential."

4. Teratogenicity

In the rat fetotoxicity study, UK-109,496 was shown to be teratogenic at the high dose of 60 mg/kg/day. This dose level is well below the starting human dose proposed in the protocol.

SAFETY MEETING (9/26/95)

Preclinical reviewers for this IND are:

Linda Gosey (Microbiology)
Owen McMaster, Ph.D. (Pharmacology)
Albinus D'sa, Ph.D. (Chemistry)

At the safety meeting, there were no safety concerns expressed by the above reviewers about the proposed clinical study design. The issues of teratogenicity and visual disturbances were discussed at length. The discussions have resulted in sponsor's revision on the contraceptive issue and the initiation of an ophthalmological consultation within the Agency. Please refer to comments under PROTOCOL.

(Recommendations from the ophthalmologic consultation revealed no safety concerns. Please refer to the attached consultation review.)

PROTOCOL

I. Principal Investigator

Name(s) and Cvs are to be provided.

II. Study objective

To evaluate the safety, tolerability and pk of 3 doses (200 mg bid, 300 mg bid, and 400 mg bid) of oral UK 109,496, compared to placebo, in patients with acute myelogenous leukemia or patients with autologous bone marrow transplants at risk for development of aspergillosis

Comment The dose range selection was based on a preliminary inspection of random plasma concentrations generated from a subset of patients participating in Studies 303 and 304. Due to wide inter-patient variations, some patients receiving a 200 mg dose of UK 109,496 had levels below 1 mcg/ml which is considered a threshold drug concentration for achieving a clinical response in the treatment of aspergillosis. Therefore, the 200 mg bid dosing regimen was chosen as the starting dose with two higher doses to follow.

III. Inclusion criteria

- Male of female of ≥18 years of age
- Patients with a diagnosis of AML, within 2 months of completion of reduction, first consolidation, or reinduction chemotherapy,or patients with a diagnosis of leukemia or lymphoma after successful engrafment of

an autologous bone marrow transplant
- Patients who have completed, within 2 weeks of screening, at least 5 days of IV AmB for empiric antifungal therapy
- ANC ≥1000/mm3
  Hgb ≥ 7 g/dl
  Platelet ≥ 50,000/mm3

IV. Exclusion criteria

- Patients with evidence of fungal infection or any systemic infection at screening
- Patients with an anticipated need for the following medications during study period:

  . Immunosuppressive agents
  . Drugs that are primarily metabolized by hepatic cytochrome P450 enzymes. This drug list includes: rifampin, rifabutin, coumadin, sulfonylureas, erythromycin, phenytoin, barbiturates, cabamazepine, cisapride, cimetidine, ranitidine, non-sedating antihistamines.

  . Topical ophthalmologic medications
  Medications with known ophthalmologic side-effects. This drug list includes: ethambutol, chloroquine, digitalis, isoniazid, sulfonamides, and oral contraceptives.

- Women of childbearing potential, including women who are post-menopausal for less than 2 years

  Comment: The above criterion as written appears to be in contradiction with what has been stated under the inclusion criteria in which women above 18 years of age are qualified to enroll. What is needed to be provided in the protocol is an explicit statement about the types of contraceptive methods women of childbearing age should use while receiving UK 109, 496. In a discussion with FDA, the sponsor agreed to amend the protocol with "barrier type contraceptives to be used by women of childbearing age, including women within 2 years of post-menopause". Similar statement is to be reflected in the informed consent form.

- Patients with retinal or ocular disease except congenital strabismus, astigmatism or myopia.
- Serum creatinine ≥ 2 mg/dl
  AST,ALT ≥ 3x ULN
  Alkaline phosphatase, total bilirubin ≥ 2x ULN

V. Conduct of the study

The study will be conducted in 3 sequential phases. The total duration is expected to be 6 months. The number of patients will be recruited is targeted at 12 "evaluable" cases per each phase, giving a total of 36 evaluable patients. An evaluable case is defined as follows:

- A patient that has completed the full 14-day treatment.
- A patient that has discontinued treatment because of a treatment-related adverse event.

After 12 evaluable patients have been accrued, the blind will be broken and safety and tolerability for that dose will be assessed. Only when that dose is judged to be well-tolerated, will the next dosing phase begin enrolling patients.

VI. Stopping rules

The study will be terminated at the current phase if:

- A new, clinically significant abnormality on ophthalmologic examination is reported in a study subject randomized to UK 109.496
- Visual disturbance longer than 24 hours of duration occurring in ≥ 25% of study subjects randomized to UK 109,496.
- Marked LFTs elevation in 25% of study subjects randomized to UK 109,496 "Marked elevation" is defined as:

  ≥3X ULN for AST or ALT
  ≥1.5X ULN for alkaline phosphatase
  ≥2X ULN for total bilirubin

VII. Study visits and treatments

Patients will be expected to report to the study sites on scheduled dates (within 7 days prior to randomization, days 1,4, 7, 10, 14, 15, and 21). At each visit, the patient will remain on site for a period until all scheduled blood tests are taken. These blood samples will be sent to [redacted] for testings which include hematology, chemistry, urinalysis, serum gonadotropin and hepatitis screen. Drug levels, retinal, and retinal-binding protein will be performed by the sponsor.

In the first phase of the protocol, the patient will be instructed to take one 200 mg tablet or a matching placebo for each dose. In the second phase of the protocol, the patient will be instructed to take one 200 mg tablet and two 50 mg tablets of active drug or matching placebos for each dose. In the third phase of the protocol, the patient will be instructed to take two 200 mg tablets or identical placebos for each dose. All doses are to be taken twice daily, 8 am and 8pm, at least one hour before or two hours after a meal.

VIII. Regulatory Actions

The study was allowed to proceed as of 10/4/95. Dr.Carreras' recommendations on ophthalmologic evaluations were faxed to the sponsor on 10/10/95. To date, the sponsor has not submitted the revised protocol. A regulatory letter should be written to include comments from the preclinical reviewers, and the ophthalmology consultation.

Medical Officer

/S/

Teresa C. Wu, M.D.,Ph.D.

Concurrences:

Div. Dir.: Feigal /S/ 11.5.95
Team leader:Gitterman w/b.l.r

CC:
HFD-530 Div file
HFD-530 Orig IND
Chem/D'Sa
Micro/Gosey
Pharm/McMaster
MO/WuT
CSO/KinseyV