CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-266

21-267

STATISTICAL REVIEW(S)

Statistical Review and Evaluation

NDA #:	21-266 and 21-267
Applicant:	Pfizer Inc.
Name of Drug:	VFEND™ (voriconazole) Tablets and I.V. for Infusion
Documents Reviewed:	NDA Index and Summary sections (Vols. 1.1-1.3), Statistical sections (Vols. 1.120-1.155) dated November 17, 2000, and SAS datasets of the clinical efficacy and safety data. Major clinical amendment dated June 21, 2001 containing aspergillosis study 307/602 report and data.
Indications:	The treatment of invasive aspergillosis, serious *Candida* infections, infections caused by *Scedeosporium* spp. and *Fusarium* spp., rare and refractory infections, and empirical treatment.
Statistical Reviewer:	Cheryl Dixon, Ph.D. (HFD-725)
Medical Reviewers:	Dr. Rose Mary Tiernan (HFD-590)- aspergillosis, esophageal candidiasis, and safety Dr. Regina Alivisatos (HFD-590)- rare infections and refractory *Candida* infections Dr. John Powers (HFD-590)- empiric treatment of febrile neutropenic patients Dr. Rosemary Johann-Liang (HFD-590)- serious *Candida* infections

I. INTRODUCTION

Voriconazole is a new chemical entity of the azole class of antifungal agents developed by Pfizer Inc. It is available as an oral formulation and as an intravenous formulation. The clinical program was designed to support the following five indications:

- treatment of invasive aspergillosis,
- treatment of serious *Candida* infections (including *C. krusei*), including esophageal and systemic infections,
- treatment of serious fungal infections caused by *Scedosporium* spp and *Fusarium* spp,
- treatment of other serious fungal infections in patients intolerant of, or refractory to, other therapy, and
- empirical treatment of presumed fungal infections in febrile immunocompromised patients.

The data that are submitted to support these indications are a combination of completed studies and interim analyses of ongoing studies. These studies have been classified into four types of studies by the applicant – Phase 3 Comparative, Phase 2/3 Non-comparative, Compassionate Use, and Historical Control. This review will focus on the comparative studies, the non-comparative aspergillosis study, and the historical control study conducted for the purpose of comparison to the non-comparative aspergillosis study.

II. INVASIVE ASPERGILLOSIS

Non-Comparative Aspergillosis Study 304

Study 304 was conducted to support the indication for the treatment of invasive aspergillosis. The study was a multi-center uncontrolled study of voriconazole. It was conducted in the following European countries: Belgium, France, Germany, Italy, the Netherlands, Spain, and the United Kingdom. Patients were initially treated with intravenous voriconazole for a maximum of 28 days followed by oral voriconazole.

Patients aged 14-75 with a diagnosis of definite or probable acute invasive aspergillosis (primary therapy) or with a diagnosis of definite acute invasive aspergillosis and who had not responded to an adequate course of other antifungal therapy or were unable to tolerate IV amphotericin B therapy (salvage therapy) were enrolled into the study. Efficacy assessments were made at Week 1, 2, 3, 4, 8, 12, 16, 20, 24, and end of therapy (EOT). EOT was planned to be at Week 24, however some patients ended therapy before or after this point. Follow-up visits occurred at 4 weeks and 12 weeks after EOT.

At each visit, clinical response during treatment was assessed as complete response (complete resolution of symptoms and signs of invasive *Aspergillus* infection), partial response (major improvement short of resolution and not requiring other systemic antifungal treatment), stable (survived but overall condition unchanged or only minimally improved), or failure (deterioration of patient including subject death or drug withdrawal with evidence of fungal infection still present). At the follow-up visits, a patient was assessed as improvement, no change, or relapse.

Due to the open nature of the study, an expert from the United Kingdom carried out an independent assessment of efficacy. The expert determined the certainty of diagnosis of aspergillosis (definite, probable, possible, not aspergillosis), site of infection, primary underlying disease, therapeutic status (primary, salvage) and global response (complete, partial, stable, failure). The Expert defined a primary therapy subject as one who received less than ten days of previous systemic antifungals. All remaining subjects were considered to be receiving salvage therapy. Global response at EOT, as assessed by the Expert, incorporated clinical, radiological, and where appropriate, mycological data. At the request of the Division, two experts from the United States were asked to reassess the data in addition to the expert from the United Kingdom.

Reviewer's Comment: *For the purpose of this review, only the experts assessments will be presented and are considered primary.*

Three populations were defined: Intent to Treat (ITT), Per Protocol (PP), and Expert Evaluable. The ITT population included all subjects who received at least one dose of study treatment. The PP population included subjects who had no significant deviations from the inclusion/exclusion criteria and planned study conduct. The Expert Evaluable population included all subjects who satisfied the ITT criterion as well as a definite or probable diagnosis of aspergillosis as assessed by the Expert and did not take any prohibited concomitant antifungals from baseline until the EOT assessment or any other medications which may affect efficacy.

Reviewer's Comment: *The Expert Evaluable population is the primary analysis population considered for this review. The ITT analyses will be presented to test the robustness of the expert evaluable results.*

The primary objective of this study was to assess the efficacy of voriconazole in the treatment of invasive aspergillosis. A target of 120 patients represented the maximum number that were expected to enroll in the study during a period of 15-18 months and was thought to be sufficient to enable the efficacy of voriconazole to be assessed. Since this was a non-comparative study, no formal hypothesis tests were carried out. Satisfactory response rates (complete or partial response) are reported and survival at day 90 is also assessed.

Results: Efficacy

Study 304 was conducted at 34 centers in 7 countries. There were 1 to 12 centers participating from each country. France, which had 6 participating centers, enrolled the largest number of patients overall. A total of 137 patients received study treatment and all are included in the ITT population. As classified by the Expert, 72 patients received primary voriconazole therapy and 65 were on salvage therapy. The Expert Evaluable population consisted of 112 patients, 58 primary and 54 salvage. Of the 25 patients excluded from the Expert Evaluable population, 20 did not have a satisfactory diagnosis of aspergillosis at baseline, 2 took a concomitant antifungal medication, and 3 took a concomitant non-antifungal during the study.

Table 304-1 summarizes the demographic and baseline characteristics as assessed by the Expert of the ITT population by therapeutic status. Slightly more than half of the patients were male. The study was almost entirely white in race. The majority of the patients had a hematologic malignancy as their underlying disease and had a diagnosis of pulmonary aspergillosis.

Table 304-1
Demographic and Baseline Characteristics (ITT)

Characteristic	Primary (n=72)	Salvage (n=65)	Total (n=137)
Gender			
Female	30 (41.7)	30 (46.2)	60 (43.8)
Male	42 (58.3)	35 (53.8)	77 (56.2)
Race			
White	70 (97.2)	64 (98.5)	134 (97.8)
Black	0	1 (1.5)	1 (0.7)
Other	2 (2.8)	0	2 (1.5)
Age			
Mean (sd)	48.8 (16.4)	41.4 (14.8)	45.3 (16.0)
Min, max	15, 74	13, 75	13, 75
Underlying Disease			
AIDs	2 (2.8)	3 (4.6)	5 (3.7)
BMT	15 (20.8)	13 (20.0)	28 (20.4)
Cancer	10 (13.9)	2 (3.1)	12 (8.8)
Hematologic Malig.	31 (43.1)	34 (52.3)	65 (47.4)
Organ Transplant	1 (1.4)	6 (9.2)	7 (5.1)
Other	13 (18.1)	7 (10.8)	20 (14.6)
Site of Infection			
Cerebral	5 (6.9)	14 (21.5)	19 (13.9)
Disseminated	3 (4.2)	3 (4.6)	6 (4.4)
Hepatosplenic	-	1 (1.5)	1 (0.7)
Osteomyelitis	1 (1.4)	-	1 (0.7)
Other	5 (6.9)	5 (7.7)	10 (7.3)
Pulmonary	56 (77.8)	36 (55.4)	92 (67.2)
Sinus	1 (1.4)	4 (6.2)	5 (3.7)
Tracheobronchial	1 (1.4)	2 (3.1)	3 (2.2)
Certainty of Diagnosis			
Definite	19 (26.4)	30 (46.2)	49 (35.8)
Probable	41 (56.9)	28 (43.1)	69 (50.4)
Possible	5 (6.9)	1 (1.5)	6 (4.4)
Indeterminate	2 (2.8)	1 (1.5)	3 (2.2)
Other	5 (6.9)	5 (7.7)	10 (7.3)

Expert assessment of therapeutic status, underlying disease, site of infection, and certainty of diagnosis.

The Expert's satisfactory global response rate at EOT was 49.1% overall as shown in Table 304-2. For primary therapy patients, the satisfactory response rate was 60.3% and for salvage therapy patients it was 37.0%. Table 304-2 also summarizes the global response at EOT by underlying disease, site of infection, and certainty of diagnosis. The results for the ITT population are similar with a satisfactory global response rate of 45.3% overall and 54.2% for primary therapy and 35.4% for salvage therapy. In the ITT population, 55.5% of the patients were alive at 90 days.

Table 304-2
Global Response at EOT (Expert Evaluable Population)

	Primary (n=58)	Salvage (n=54)	Total (n=112)
Overall	35 (60.3)	20 (37.0)	55 (49.1)
Underlying Disease			
AIDs	0/1	0/1	0/2
BMT	4/12	4/12	8/24
Cancer	7/7	0/1	7/8
Hematologic Malig.	18/28 (64.3)	12/30 (40.0)	30/58 (51.7)
Organ Transplant	-	3/6	3/6
Other	6/10	1/4	7/14
Site of Infection			
Cerebral	2/5	2/13	4/18 (22.2)
Disseminated	1/3	2/3	3/6
Hepatosplenic	-	0/1	0/1
Osteomyelitis	0/1	-	0/1
Pulmonary	31/47 (66.0)	16/32 (50.0)	47/79 (59.5)
Sinus	0/1	0/4	0/5
Tracheobronchial	1/1	0/1	1/2
Certainty of Diagnosis			
Definite	10/18 (55.6)	7/27 (25.9)	17/45 (37.8)
Probable	25/40 (62.5)	13/27 (48.1)	38/67 (56.7)

Results: Safety

A total of 128 patients (93.4%) had at least one adverse event. The most common adverse events were rash (19.7%) and fever (17.5%). Abnormal vision was reported in 16 patients (11.7%). Treatment related adverse events occurred in 47 (34.3%) patients. The most commonly occurring treatment related adverse event was abnormal vision (9.5%). Most of the adverse events were mild to moderate in severity. Treatment related adverse events were classified as severe in 13 patients. There were 92 (67.2%) patients with serious adverse events. Sixty-two subjects died during therapy or within 30 days of EOT. There were 18 additional that occurred more than 30 days after EOT. None of the deaths were reported as related to study treatment. Five patients had a serious adverse event reported as related to study treatment.

For a more detailed review of the safety data, please see the Medical Officer Safety review written by Dr. Rose Mary Tiernan.

Study 1003-Historical Control to Study 304

The historical control study was designed to retrospectively collect global response and 90 day survival data of patients who received standard therapy for definite or probable invasive aspergillosis between 1993 and 1995. These patients were obtained from a search of hospital records in Europe and the United States and from an EORTC database. This population was to act as the comparison group for the primary voriconazole treated patients of Study 304. There were 257 evaluable subjects in the

historical control and 72 primary (as assessed by the sponsor) evaluable subjects in the Study 304 voriconazole population. In order to provide the most comparable population, primary patients who received 5 days or less prior antifungal therapy were case matched on a 2:1 basis by the prognostic factors of certainty of diagnosis, underlying disease, and site of infection. The best matched ≤5 day population consisted of 50 voriconazole Study 304 subjects and 92 historical control patients.

Table 1003/304-1 summarizes the results for both the evaluable population and the ≤5 day population. Depending on population, overall satisfactory global response rates at end of therapy ranged from 52.0% to 55.6% for voriconazole patients and from 25.0% to 29.2% for the historical controls. European historical control subjects had slightly better satisfactory response rates than the US historical control subjects did. When only the European historical control subjects are compared to voriconazole Study 304 patients, the difference in satisfactory global response still favors voriconazole. The probability of survival at Day 90 was higher for voriconazole patients than for the historical controls. When considering survival, US historical control subjects had a significantly lower chance of survival than the European historical control subjects and the survival benefit seen with voriconazole when compared to only the European historical control patients is reduced (see Figure 1003/304-1). One explanation for this difference in survival could be that the majority of the US historical control subjects had bone marrow transplant or other as their underlying disease whereas the majority of the European historical control subjects and the voriconazole Study 304 subjects had hematologic malignancy as their underlying disease.

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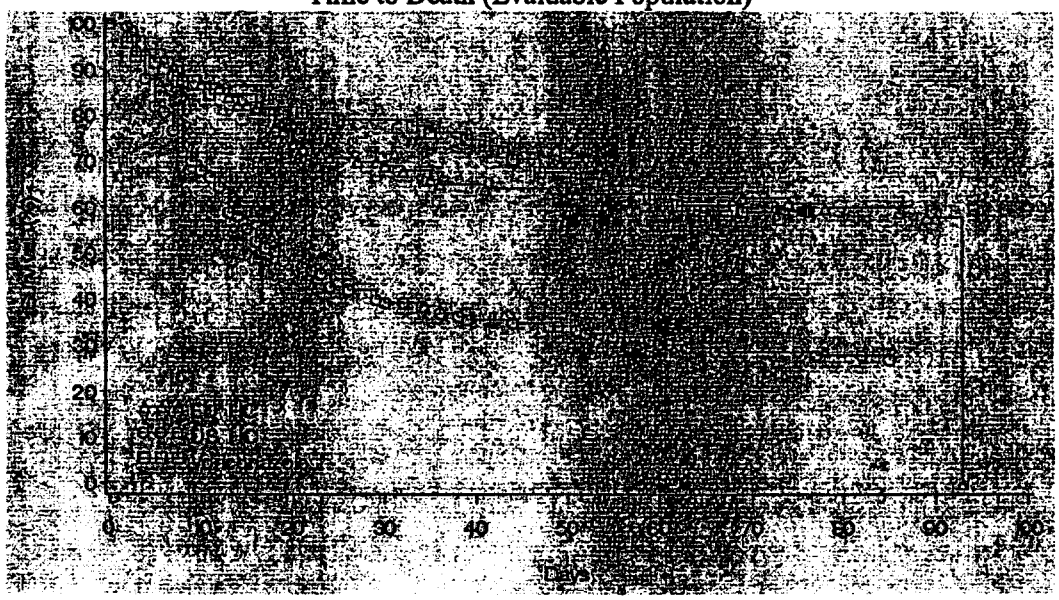
Table 1003/304-1
Efficacy Evaluation

	Evaluable Population		≤ 5 Day Matched Population	
	Vori 304 (n=72)	Historical Control (n=257)	Vori 304 (n=50)	Historical Control (n=92)
Overall Global Response	40 (55.6)	75 (29.2)	26 (52.0)	23 (25.0)
Underlying Disease				
BMT	8/16 (50.0)	8/62 (12.9)	6/12 (50.0)	3/16 (18.8)
Hematologic Malig.	26/ 41 (63.4)	46/112 (41.1)	14/26 (53.9)	16/52 (30.8)
Other	6/15 (40.0)	21/83 (25.3)	6/12 (50.0)	4/24 (16.7)
Site of Infection				
Pulmonary	39/60 (65.0)	57/202 (28.2)	25/41 (61.0)	22/82 (26.8)
Brain	0/7 (0.0)	1/10 (10.0)	0/6	1/6
Systemic (non-brain)	1/1 (100.0)	8/20 (40.0)	1/1	-
Other	0/4 (0.0)	9/25 (36.0)	0/2	0/4
Certainty of Diagnosis				
Definite	4/15 (26.7)	34/111 (30.6)	2/9 (22.2)	2/17 (11.8)
Probable	36/57 (63.2)	41/146 (28.1)	24/41 (58.5)	21/75 (28.0)
Study Site				
EU	40/72 (55.6)	42/107 (39.3)	26/50 (52.0)	12/41 (29.3)
US		33/150 (22.0)		11/51 (21.6)
Prob of Survival at Day 90	.574	.399	.554	.417
EU	.574	.577	.554	.573
US		.270		.290

Figure 1003/304-1
Time to Death (Evaluable Population)



Even though the applicant took substantial efforts in the design of the historical control, all of the potential biases inherent with the use of historical controls were not adequately controlled. Study 304 was conducted exclusively in Europe, whereas the historical control study included U.S. patients as well. These differences in the patient populations could impact the success rate of treatment if patient care and support differ across countries. As discussed above, when the U.S. patients are removed from the historical control group, a benefit of voriconazole with respect to global response remained but the survival benefit of voriconazole was less extreme. There were differences in the total days of treatment, with the voriconazole treatment group having longer duration of antifungal therapy. Differences in inclusion and exclusion criteria could possibly allow for sicker patients to be included in the historical control than in the voriconazole study. These differences between study populations could act to predispose the historical control group to have lower success rates and the voriconazole treated group to have a higher success rate, independent of treatment with voriconazole. For a complete discussion of the comparability of the historical control study with Study 304, please see the OPDRA consult written by Judy Staffa, Ph.D., R.Ph..

Global Comparative Aspergillosis Study 307/602

Study 307/602 consisted of two comparative, open-label, phase III studies of voriconazole vs. amphotericin B (followed by other licensed antifungal therapy, OLAT) in the primary treatment of invasive aspergillosis. The European Organization for Research and Treatment of Cancer (EORTC) led one study and U.S. investigators led the other. Both protocols were essentially identical with respect to entry criteria, treatment regimens, study procedures, and outcome assessments. Since it would take years for each of the studies to reach their required enrollment, the applicant proposed to combine interim data from both studies into an umbrella analysis for the purpose of submitting an NDA. In 1997, a statistical analysis plan was submitted to the Division for concurrence. The umbrella analysis was powered to meet specified objectives and contained measures to preserve the integrity of the individual studies. Therefore, the Division agreed to the combining of interim data from the two studies. Both studies databases were closed in the beginning of 2001 based on recommendations from the EORTC and the US investigators due to changes in medical practice and the choice of comparator agents. Since the combined enrollment was that which was agreed upon for the umbrella analysis, the Division shared the recommendation to close the studies. It was requested that the combined data of these studies be analyzed according to the umbrella analysis plan and submitted to the NDA for review. The results of the study were submitted as a major clinical amendment to the NDA on June 21, 2001.

Males and non-pregnant females at least 12 years of age with a diagnosis of definite or probable acute invasive aspergillosis were enrolled into the studies. Patients were randomized to receive initial study treatment (initial randomized therapy, IRT) with either voriconazole or amphotericin B. Voriconazole was administered as IV for at least 7 days and then could be switched to oral voriconazole for up to 12 weeks. Initial therapy with amphotericin B was to continue at least 12 days. In both arms, patients were allowed to

switch to OLAT if they failed to respond or were unable to tolerate IRT. Efficacy assessments (radiological, mycological, and global responses) were made at Weeks 6 and 12, end of randomized therapy (EORT), and Week 16. Due to the open label design of the trial, a Data Review Committee (DRC) was used to perform an independent review of the data. The DRC determined certainty of diagnosis of aspergillosis, assessed the global response to therapy at the EORT and Week 12, and the cause of death (where applicable) in a blinded fashion.

The primary objective of the umbrella protocol was to demonstrate non-inferiority in the rates of satisfactory global response in the modified intent to treat (MITT) population at Week 12. Assuming a rate of satisfactory global response at Week 12 of 50% for both groups, a sample size of 264 subjects would be adequate to demonstrate that the difference in satisfactory response rates were no less than –20% with more than 90% power. A secondary objective was to detect a difference of 20% in the rates of satisfactory global response at EORT. An expected satisfactory global response at EORT was expected to be 55% for voriconazole and 35% for amphotericin B. A sample size of 276 subjects was required to ensure that a difference of 20% between voriconazole and amphotericin B is detected at the 5% significance level with 90% power. Assuming 25% of randomized patients would be excluded from the MITT population, 368 patients were needed to provide the required 276 patients. Recruitment was stopped in October 20, 2000 when a total of 392 had been enrolled.

Reviewer's Comment: *The secondary endpoint of global response at EORT was included as an endpoint in the protocol primarily for purposes of European registration. Due to differences in the duration of IRT, this endpoint will not be discussed any further in this review.*

The primary efficacy analysis was based on the MITT population. The MITT population included all subjects who received at least 1 dose of their IRT and had confirmation of definite or probable primary diagnosis of invasive aspergillosis as assessed by the DRC. Two-sided 95% confidence intervals were used to estimate the difference in the proportion of global response between the treatment groups. The confidence intervals were calculated using a Mantel-Haenszel stratified approach adjusting for protocol. A conclusion of non-inferior efficacy of voriconazole was drawn if the lower limit of the confidence interval (voriconazole-amphotericin B) was greater than or equal to –20%. Time to death was summarized using Kaplan-Meier curves.

Interim assessments were performed by the respective Data Safety Monitoring Boards to oversee the progress of the study and to ensure that subjects were not exposed to unacceptable toxicity. As part of this assessment, interim analyses of mortality were performed. No interim analyses of efficacy were performed.

Results: Efficacy

Study 307 was conducted in Europe, Israel, and Australia. Study 607 was conducted in the United States, Canada, South America, and India. In total, the studies were

conducted at 199 centers. Three hundred ninety two patients were enrolled in Study 307/602: 199 in the voriconazole arm and 193 in the amphotericin B arm. One hundred forty-four voriconazole patients and 133 amphotericin B patients were included in the modified intent-to-treat (MITT) as assessed by the DRC.

Table 307/602-1 shows the demographic and baseline characteristics of the MITT population. Two thirds of the patients were males and most of the patients were white. The mean age was 48 years for the voriconazole group and 50 years for the amphotericin B group. The most common underlying disease in both treatment groups was hematologic malignancy, which consisted primarily of leukemia but also included autologous bone marrow transplants, autologous peripheral stem cell transplants, and other hematologic malignancies. As assessed by the DRC, most subjects had pulmonary aspergillosis. More cases were diagnosed as probable aspergillosis than definite. Within each treatment group, there were more definite infections in the primarily US based study 602 than the primarily European based study 307. The majority of the cases diagnosed as probable were pulmonary aspergillosis. Twice as many subjects in the amphotericin B group switched to OLAT compared to subjects in the voriconazole group.

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Table 307/602-1
Demographic and Baseline Characteristics (MITT)

Patient Characteristic	Amphotericin B N=133	Voriconazole N=144
Protocol		
307	84 (63.2)	86 (59.7)
602	49 (36.8)	58 (40.3)
Gender		
Female	44 (33.1)	46 (31.9)
Male	89 (66.9)	98 (68.1)
Race		
White	126 (94.7)	130 (90.3)
Black	1 (0.8)	7 (4.9)
Other	6 (4.5)	7 (4.9)
Age		
Mean (sd)	50.5 (14.8)	48.5 (15.8)
Min, max	12, 75	13, 79
Underlying Disease		
Allogenic BMT/ PSCT	30 (22.6)	37 (25.7)
Autologous BMT/ PSCT or other hematologic malig	84 (63.2)	81 (56.3)
Other underlying disease	19 (14.3)	26 (18.1)
Site of Infection		
Cerebral	1 (0.8)	2 (1.4)
Disseminated	10 (7.5)	12 (8.3)
Other single site	3 (2.3)	3 (2.1)
Pulmonary	112 (84.2)	119 (82.6)
Sinus	7 (5.3)	7 (4.9)
Skin	-	1 (0.7)
Certainty of Diagnosis		
Definite	41 (30.8)	67 (46.5)
Probable	92 (69.2)	77 (53.5)
Pulmonary	83	73
Non pulmonary	9	4
Neutropenic Status		
< 500	60 (45.1)	63 (43.8)
≥ 500	73 (54.9)	81 (56.3)
Switch to OLAT		
No	26 (19.5)	92 (63.9)
Yes	107 (80.5)	52 (36.1)

DRC assessment of underlying disease, site of infection, and certainty of diagnosis.

The reasons for discontinuing IRT are listed in Table 307/602-2. More patients on voriconazole completed treatment on their IRT. Similar numbers of patients discontinued IRT due to death. Discontinuation due to an adverse event or laboratory abnormality was primarily related to creatinine increases and renal insufficiency for the amphotericin B treatment group. For the amphotericin B group, discontinuation for other reasons included patient switching to oral therapy. For the voriconazole group, not being able to take oral therapy was included as a discontinuation for other reasons.

307/602-4 also summarizes the results according to underlying disease, site of infection, certainty of diagnosis, neutropenic status, and whether the patient switched to OLAT.

Table 307/602-4
Global Response at Week 12 (MITT)

	Amphotericin B N=133	Voriconazole N=144	Weighted diff and 95% CI
Overall	42 (31.6)	76 (52.8)	21.6 (9.6, 33.6)
307	31/84 (36.9)	49/86 (57.0)	
602	11/49 (22.5)	27/58 (46.6)	
Underlying Disease			22.4 (10.6, 34.2)
Allogenic BMT/ PSCT	4/30 (13.3)	12/37 (32.4)	
Autologous BMT/ PSCT or other hematologic malignancy	32/84 (38.1)	51/81 (63.0)	
Other underlying disease	6/19 (31.6)	13/26 (50.0)	
Site of Infection			21.9 (10.0, 33.8)
Disseminated	1/10 (10.0)	6/12 (50.0)	
Pulmonary	39/112 (34.8)	66/119 (55.5)	
Single Site (excluding pulmonary)	2/11 (18.2)	4/13 (30.8)	
Certainty of Diagnosis			23.1 (11.2, 35.0)
Definite	8/41 (19.5)	30/67 (44.8)	
Probable	34/92 (37.0)	46/77 (59.7)	
Pulmonary	33/83 (39.8)	44/73 (60.3)	
Non pulmonary	1/9 (11.1)	2/4 (50.0)	
Neutropenic Status			21.9 (10.0, 33.8)
< 500	19/60 (31.7)	32/63 (50.8)	
≥ 500	23/73 (31.5)	44/81 (54.3)	
Switch to OLAT			
No	1/26 (3.9)	51/92 (55.4)	
Yes	41/107 (38.3)	25/52 (48.1)	

DRC assessment of global response, underlying disease, site of infection, and certainty of diagnosis.
CI is weighted by protocol and given characteristic

Three additional analyses were performed to test the robustness of the previous results. Since the DRC was blinded to the investigator's assessment, an upgrading of the investigator's assessment by the DRC was possible. Therefore, the Division performed a conservative analysis that did not allow an upgraded response by the DRC. The second analysis performed is essentially a voriconazole IRT versus the amphotericin B regimen. In this analysis, voriconazole patients who switched to OLAT were considered failures with the exception of 13 patients. These patients completed voriconazole treatment with a satisfactory response and went on prophylaxis after at least 84 days of voriconazole or went on prophylaxis during chemotherapy. In the third analysis, response at Week 16 was assessed. From Week 12 to Week 16, 9 voriconazole patients and 6 amphotericin B patients achieved a satisfactory response. During this same period, 6 voriconazole and 1 amphotericin B patients relapsed. There were an additional 13 voriconazole and 3 amphotericin B patients who had an indeterminate or missing Week 16 assessment and were considered as failures in this analysis. Table 307/602-5 summarizes the results of these analyses. In all of these analyses, the satisfactory response of voriconazole was consistently greater than the satisfactory response of the amphotericin B regimen.

Table 307/602-5
Additional Analyses

	Amphotericin B N=133	Voriconaozle N=144	95% CI
Not allowing an upgrading by the DRC	39 (29.3)	67 (46.5)	(5.2, 29.2)
Voriconazole IRT vs. amphotericin B/OLAT	42 (31.6)	65 (45.1)	(1.4, 25.6)
Week 16 follow-up	44 (33.1)	66 (45.8)	(0.6, 24.8)

Survival through Day 84 was a secondary endpoint. Voriconazole was shown to have a significant survival advantage compared to the amphotericin B regimen. The probability of survival at Day 84 was 0.708 for the voriconazole arm compared to 0.579 for the amphotericin B regimen (log-rank p-value=0.015). Figure 307/602-1 presents the Kaplan-Meier plot of the time to death. Study 307 had better survival than Study 602 for both treatment groups. However, the survival benefit of voriconazole was not as great in Study 307 as it was in Study 602. This was consistent with the trends observed in the analysis of global response.

Table 307/602-6
Probability of Survival at Day 84 (MITT)

	Amphotericin B N=133	Voriconazole N=144
Overall	.579	.708
Study 307	.643	.744
Study 602	.469	.655

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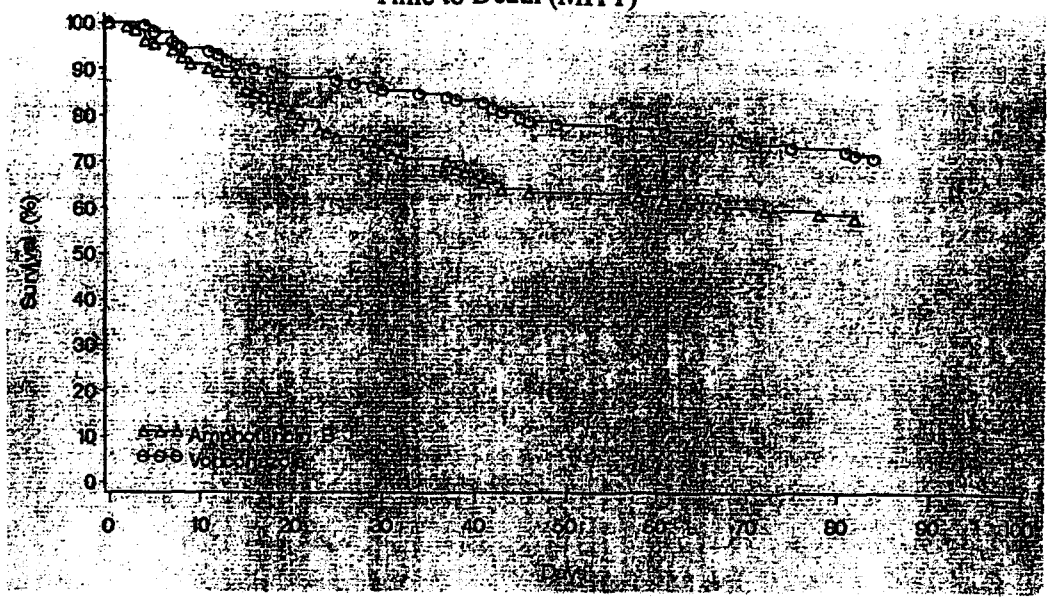
Figure 307/602-1
Time to Death (MITT)



Results: Safety

A total of 194 patients (99.0%) in the voriconazole IRT group and 184 patients (99.5%) in the amphotericin B regimen group had at least one adverse event. The most common adverse event in the voriconazole group was abnormal vision. The incidence of abnormal vision was statistically significantly higher in the voriconazole group (33.2%) than in the amphotericin B regimen (4.3%) ($p<0.0001$). Severe adverse events occurred in 62.8% of patients in the voriconazole group and 73.0% in the amphotericin B regimen.

There were 135 (68.9%) voriconazole patients and 139 (75.1%) amphotericin B regimen patients with serious adverse events. Fifty-nine voriconazole subjects and 61 amphotericin B regimen subjects died during therapy or within 30 days of EOT. There were 18 additional deaths in the voriconazole and 27 additional deaths in the amphotericin B regimen that occurred more than 30 days after EOT. Eight of the deaths within 30 days of EOT were reported as related to study treatment. One of the eight patients received voriconazole and the remaining 7 were in the amphotericin B regimen.

For a more detailed review of the safety data, please see the Medical Officer Safety review written by Dr. Rose Mary Tiernan.

III. SERIOUS CANDIDA INFECTION

Esophageal Candidiasis- Study 305

Study 305 was conducted to support the indication for the primary treatment of esophageal candidiasis. The study was a randomized, double blind, double dummy,

parallel group, active comparator study. It was conducted in the United Kingdom, Ireland, Poland, Thailand, Singapore, Russia, Australia, Austria, France, Germany, Italy, South Africa, and Spain. In this study, oral voriconazole 200 mg bid was compared to oral fluconazole 200 mg od following a loading dose of 400 mg on Day 1.

Patients aged over 18 years who were immunocompromized and had endoscopically-proven *Candida* esophagitis were enrolled into the study. Efficacy assessments were made on Days 8, 15, 29, and 43. The end of treatment (EOT) assessment could occur any time from Day 15 to Day 43. On Day 43 or EOT, a repeat endoscopy was also performed in addition to the assessment of the symptoms of esophageal candidiasis. A follow-up visit occurred four weeks after EOT.

At baseline and EOT, the degree of esophagitis was graded from 0 (no evidence of candidiasis) to 4. The EOT assessment was compared to the baseline visit and subjects were assessed as cured (normal endoscopy at EOT), improved (abnormal endoscopy at EOT but at least 1 grade improvement over baseline), or failed (no change or at least 1 grade deterioration over baseline). All of the symptoms of esophageal candidiasis (dysphagia, odynophagia, retrosternal/oropharyngeal discomfort, and nausea/vomiting) were assessed at each visit as none, mild, moderate, or severe. For each visit compared to baseline, the subjects were categorized as symptomatically cured (resolution of all symptoms of infection), improved (improvement in one or more variables but not complete resolution in all symptoms and no worsening in any symptom), or failed (worsening in any symptom or no change in all symptoms). Symptoms were also categorized at follow-up compared with Day 43 or EOT as improvement, no change, relapse, or not evaluable. At baseline, all patients had to have microscopic evidence of *Candida* isolated from an esophageal lesion and a positive culture from a specimen obtained by brush biopsy or tissue biopsy. A repeat microscopy, histopathology, and culture was to be performed at Day 43/EOT. Mycology compared to baseline was assessed as eradicated (no lesions present or if lesions were present, no growth of *Candida* on culture and no microscopic evidence of *Candida* present in the brushing or biopsy specimen) or persisted (lesions present with positive culture for *Candida* and/or microscopic evidence of *Candida* present in brushing or biopsy specimen).

Intent to Treat (ITT) and Per Protocol (PP) analysis populations were defined. The ITT population included all subjects who received at least one dose of their randomized study treatment. To be evaluable for the PP population, the subjects had to have in addition to no significant deviations from the inclusion /exclusion criteria and planned study conduct: 1) confirmation of *Candida* esophagitis by endoscopy, including presence of hyphae on biopsy or brushing and a positive culture, 2) received at least 12 days of treatment, 3) an EOT evaluation including a repeat endoscopy, 4) evidence of adequate compliance, 5) visits at each assessment time within the ± five day window, and 6) not received a forbidden study medication.

***Reviewer's Comment:** The PP population is the primary analysis population but the ITT analyses will be used to test the robustness of the per protocol results.*

The primary efficacy parameter was endoscopy result at Day 43/ EOT compared to baseline. A success was defined as cured or improved. For the ITT population, if a second endoscopy was not performed, the symptomatic assessment at EOT compared to baseline was used to define a success or failure. If the symptomatic assessment was also missing, the response was considered a failure. Assessment of symptoms of esophageal candidiasis was a secondary endpoint.

The primary objective of the study was to show that voriconazole was non-inferior to fluconazole. Sample sizes were based on 80% power to show that the lower bound of the two-sided 95% confidence interval for the differences in success rates (voriconazole-fluconazole) was no less than –15%. Three hundred twenty (320) patients were to be enrolled in order to provide 112 evaluable subjects per treatment group assuming a success rate of 80%. It was assumed that 30% of the population would be ineligible for the per protocol analysis. In July 1998, a decision was made that recruitment into the study would continue to the limit of drug supplies at that time because of a lower than expected evaluability rate that was discovered during a blinded assessment of evaluability. In total, 391 patients were randomized and 256 were analyzed in the PP population.

The primary efficacy analysis was based on the PP population. Two-sided 95% confidence intervals, calculated using the normal approximation to the binomial distribution with continuity correction, were used to estimate the difference in the proportion of success between the treatment groups. A conclusion of non-inferior efficacy of voriconazole was drawn if the lower limit of the confidence interval (voriconazole- fluconazole) was greater than or equal to –15%. In addition, a 95% confidence interval was also calculated using a Mantel-Haenszel stratified approach adjusting for country. Due to the small number of subjects in some countries, the data from the United Kingdom and Ireland and the data from Poland, Thailand, Singapore, and Russia were pooled. The data from the remaining countries were not pooled. Due to the high success rates, exact 95% confidence intervals will also be presented.

Two interim analyses were performed during this study. The first interim analysis was performed as planned on 100 subjects. The data was kept blinded. No formal hypothesis testing was done and no decisions based on the analyses were made that affected the course of the study. Therefore, no adjustments were made to the final analysis at the end of the study. The second interim analysis was done in order to answer FDA questions concerning the incidence of visual disturbance. This analysis occurred after the last randomized subject had completed treatment. Summary tables were presented by treatment code and no formal statistical tests were performed.

Results: Efficacy

Reviewer's Comment: *A 20% random sample of the patients enrolled in this study was generated by the statistical reviewer and reviewed by the medical officer. No changes were made to either evaluability or outcome. Therefore, the sponsor's data was accepted and all analyses are based on the data as submitted by the sponsor.*

Study 305 was conducted at 53 centers in 13 countries. There were 1 to 8 centers participating from each country. South Africa, which had 6 participating centers, enrolled the largest number of patients overall. A total of 391 patients were randomized to receive study treatment, 200 were randomized to receive voriconazole and 191 to receive fluconazole. All 391 patients were included in the ITT population. A total of 85 (42.5%) voriconazole and 50 (26.3%) fluconazole patients were excluded from the PP population. Most subjects were excluded from the PP population for more than one reason. The most common reason for exclusion for both treatment groups was the patient only had one endoscopy (23.0% voriconazole and 14.7% fluconazole). Other common reasons for exclusion are the patient received less than 12 days of therapy, the patient received systemic antifungals less than 3 days prior to baseline, and there was no mycological evidence of esophageal candidiasis at baseline.

Reviewer's Comment: *Since more voriconazole than fluconazole patients were excluded from the PP population, there was concern that the reason behind the exclusion was due to more adverse events or lack of efficacy in these patients. This could then affect the interpretation of the results of the PP efficacy analyses. For each patient excluded from the PP population, a primary reason for exclusion was selected. The majority of the voriconazole patients (34/85, 40%) were primarily excluded because only one endoscopy was performed. Of these 34 patients, 7 patients discontinued due to lack of efficacy or drug related adverse events, 4 patients died, and 7 patients had non-related adverse events. The remaining voriconazole patients excluded did not have an exclusion reason that could be attributed to the effect of the drug. Fifteen of the 50 (30%) fluconazole patients excluded were excluded primarily because only one endoscopy was performed. Two of these 15 patients had insufficient clinical response, 2 subjects died, and 1 patient had a non-related adverse event. Therefore, it could not be discerned that more patients were excluded from the PP population for reasons that could be explained by lack of efficacy or other drug related reasons.*

Table 305-1 shows the demographic and baseline characteristics of the ITT population. There were no significant differences across treatment groups. More than three-quarters of the patients were male and the majority of the patients were white. The mean age was 36 years in the voriconazole group and 37 years in the fluconazole group. The majority of the patients had severe AIDS.

Table 305-1
Demographic and Baseline Characteristics (ITT)

	Treatment Group	
	Voriconazole	Fluconazole
# Patients	200	191
Gender		
Female	47 (23.5)	47 (24.6)
Male	153 (76.5)	144 (75.4)
Age mean (SD)	36.4 (9.6)	37.4 (9.8)
Min, max	19, 75	19, 71
Race		
White	135 (67.5)	125 (65.5)
Black	48 (24.0)	50 (26.2)
Asian	13 (6.5)	13 (6.8)
Other	4 (2.0)	3 (1.6)
AIDS Category		
Non-AIDS	23 (11.5)	25 (13.1)
Non-severe AIDS	43 (21.5)	43 (22.5)
Severe AIDS	117 (58.5)	114 (59.7)
Indeterminate	17 (8.5)	9 (4.7)

There were 201 isolates in the voriconazole group and 193 isolates in the fluconazole group detected at baseline. Some patients had more than one pathogen detected at baseline. *Candida albicans*, the most common pathogen detected at baseline for both groups, was found in 179 (89.5%) voriconazole patients and 175 (91.6%) fluconazole patients. *Candida glabrata* was found in 6 subjects from each treatment group and *Candida krusei* was found in 2 subjects from each treatment group. Unknown *Candida* spp. were found in 14 voriconazole patients and 6 fluconazole patients.

Table 305-2 summarizes the results of the endoscopy assessment at EOT for the PP population. The esophageal candidiasis success (cured + improved) rate was 98.3% for voriconazole and 95.0% for fluconazole. The difference in success rates (voriconazole-fluconazole) was 3.3%. As noted in Table 305-3, regardless of the method used to calculate the 95% confidence interval about the difference in success rates, the lower limit of the 95% confidence interval is greater than the non-inferiority margin of –15%.

Table 305-2
Endoscopy Assessment at EOT (PP Population)

	Treatment Group	
Endoscopy Assessment, n (%)	**Voriconazole (N=115)**	**Fluconazole (N=141)**
Cured	109 (94.8)	127 (90.0)
Improved	4 (3.5)	7 (5.0)
Failed	2 (1.7)	7 (5.0)

Table 305-3
Analysis of Endoscopy Assessment at EOT (PP Population)

Method	Difference in success rates (voriconazole-fluconazole)	95% CI
Unadjusted	3.3	(-1.8, 8.4)
Exact	3.3	(-3.6, 10.7)
Adjusted by Country	3.1	(-3.5, 9.7)

Reviewer's Comment: *The results stated in the above table are slightly different than those stated by the sponsor in the study report. A continuity correction was applied to the above non-exact confidence intervals and will be applied in all non-exact confidence intervals presented in this review.*

Tables 305-4 and 305-5 present the results for the ITT population. For the ITT population, the esophageal candidiasis success (cured + improved) rate was 87.5% for voriconazole and 89.5% for fluconazole. The difference in success rates was –2.0%. These results support the claim of non-inferiority of voriconazole compared to fluconazole.

Table 305-4
Endoscopy* Assessment at EOT (ITT Population)

Endoscopy Assessment, n (%)	Treatment Group: Voriconazole (N=200)	Fluconazole (N=191)
Cured	157 (78.5)	156 (81.7)
Improved	18 (9.0)	15 (7.9)
Failed	14 (7.0)	15 (7.9)
Not assessable	11 (5.5)	5 (2.6)

* EOT Clinical assessment was used for patients with only one endoscopy. If there was no EOT assessment, then the patient was non assessable.

Table 305-5
Analysis of Esophageal Success at EOT (ITT Population)

Method	Difference in success rates (voriconazole-fluconazole)	95% CI
Unadjusted	-2.0	(-8.9, 4.8)
Exact	-2.0	(-10.0, 5.4)
Adjusted by Country	-2.1	(-9.2, 5.0)

Results: Safety

A total of 159 patients (79.5%) in the voriconazole group and 141 patients (73.8%) in the fluconazole group had at least one adverse event. The most common adverse event in the voriconazole group was abnormal vision. The incidence of abnormal vision was statistically significantly higher in the voriconazole group (22.5%) than in the fluconazole group (7.9%) ($p<0.0001$). Twenty-three patients (11.5%) in the voriconazole group and 8 patients (4.2%) in the fluconazole group discontinued study drug due to adverse events.

Treatment related adverse events occurred in 60 patients (30.0%) in the voriconazole group and 27 patients (14.1%) in the fluconazole group. The most commonly occurring treatment related adverse event was abnormal vision in both treatment groups (15.5% voriconazole and 4.2% fluconazole). As with adverse events overall, abnormal vision related to study treatment was statistically significantly higher in the voriconazole group than in the fluconazole group (p=0.0002).

Most of the adverse events were mild to moderate in severity. Treatment related adverse events were classified as severe in 3.5% of voriconazole treated patients and 2.1% of fluconazole treated patients. There were 61 (30.5%) voriconazole patients and 52 (27.2%) fluconazole patients with serious adverse events. Fifteen voriconazole subjects and 18 fluconazole subjects died during therapy or within 30 days of EOT. There were 6 additional deaths in the voriconazole and 10 additional deaths in the fluconazole group that occurred more than 30 days after EOT. All of the deaths were reported as unrelated to study treatment. Three patients in the voriconazole group had a serious adverse event reported as related to study treatment.

For a more detailed review of the safety data, please see the Medical Officer Safety review written by Dr. Rose Mary Tiernan.

Systemic Candidiasis- Study 608

Study 608 is a randomized, open label, comparative study of voriconazole versus conventional amphotericin B followed by fluconazole in the treatment of candidemia in non-neutropenic patients. Only an administrative interim analysis of approximately 10% of the total number of subjects to be enrolled in the study has been provided for the NDA submission. The data was submitted at the request of the Division to provide as much information on the efficacy of voriconazole in the treatment of serious *Candida* infections. No formal statistical analyses were performed. Therefore, Study 608 will not be presented in this review. For a discussion of this study, refer to the Medical Officer review written by Dr. Rosemary Johann-Liang.

IV. TREATMENT OF RARE AND REFRACTORY INFECTIONS

Studies 604 and 309 are open label, non-comparative studies in which all subjects receive voriconazole to treat systemic, invasive fungal infections for which there is no licensed therapy or where subjects were failing or intolerant of other treatment. Both studies were ongoing at the time of the NDA submission. Pooling information across the entire clinical program provided additional information on rare infections. Due to the non-comparative nature of the aforementioned studies and the small numbers of rare infections pooled across studies, no formal statistical analyses were performed on this data. Information regarding rare and refractory infections will not be presented in this review. The only exception is the salvage aspergillosis patients in Study 304 that were previously discussed. For a discussion of the treatment of rare fungal infections and

refractory *Candida* infections, refer to the Medical Officer review written by Dr. Regina Alivisatos.

V. EMPIRICAL THERAPY

Study 603

Study 603 was conducted to support the indication of empiric antifungal treatment of febrile neutropenic patients. The study was a randomized, open label, comparative, and multicenter study of voriconazole versus liposomal amphotericin B (L-AMB). It was conducted at centers in the United States, Canada, France, India, Italy, and the United Kingdom.

Patients 12 years and older with neutropenia induced by cytotoxic chemotherapy or bone marrow/peripheral stem cell transplant for treatment of cancer were enrolled into the study. Prior to randomization, eligible subjects were to have had at least 96 hours of neutropenia, and oral temperature of at least 38°C, and at least 96 hours of systemic antibacterial therapy. Subjects were randomized to treatment in a 1:1 ratio and stratified according to risk of fungal infection and previous systemic antifungal prophylaxis. Patients were defined to be at higher risk of fungal infection if they had an allogeneic bone marrow/peripheral stem cell transplant or had relapsed leukemia. Voriconazole was administered as IV for at least 3 days and could then be given as oral voriconazole. Treatment with voriconazole was to last up to 3 days after recovery from neutropenia. Subjects with a baseline or breakthrough fungal infection could receive a maximum of 12 weeks of therapy. L-AMB was administered until up to 3 days after recovery from neutropenia, or resolution of baseline or breakthrough fungal infection for a maximum of 12 weeks of therapy, whichever came first.

During empirical treatment, study assessments were performed twice weekly until recovery from neutropenia. The single assessment of efficacy, overall response to empirical treatment, was made at least 7 days after the last day of study medication. Subjects diagnosed with a baseline or breakthrough fungal infection had study assessments made every 4 weeks while on study medication, at EOT, and 4 weeks after EOT. The overall response was assessed at least 7 days after the last dose. Due to the open label design of the study, a blinded DRC was used for the evaluation of the baseline and/or breakthrough fungal infections.

The primary objective of the study was to show that voriconazole was non-inferior to L-AMB. Voriconazole was to be considered non-inferior to L-AMB if the lower limit of the approximate two-sided 95% confidence interval for the difference in success rates at least 7 days after EOT between the two treatment groups did not fall below –10%. Assuming a success rate of 50% for both treatment groups, a sample size of 393 evaluable subjects per treatment group would be sufficient to demonstrate non-inferiority with 80% power. It was estimated that 10% of the subjects enrolled would be excluded

from the MITT group. Therefore, a total of 866 (433 per treatment group) were to be enrolled.

The primary efficacy analysis was based on the MITT population. This population included all subjects who had received at least one dose of randomized study medication and who had sufficient information to confirm the investigator's assessment of overall response. The primary endpoint was the composite variable denoted as overall response. The overall response was considered a success if all of the following criteria were met:

1. Survival for at least 7 days after discontinuation of study medication
2. Absence of breakthrough fungal infection during the period of neutropenia and for at least 7 days after discontinuation of study medication
3. Defervescence during the period of neutropenia or prior to EOT, which ever occurred first
4. No discontinuation from randomized study medication due to toxicity or lack of efficacy prior to recovery from neutropenia
5. For subjects with baseline fungal infections only: global response assessed as complete or partial at EOT

Otherwise, the response was considered a failure. The components of the composite endpoint were secondary endpoints. Two-sided 95% confidence intervals were used to estimate the difference in the proportion of success of overall response between the treatment groups (voriconazole- L-AMB). The confidence intervals were calculated using a Mantel-Haenszel stratified approach adjusting for risk of infection, previous systemic prophylaxis, and duration of baseline neutropenia (<7.7 days, ≥ 7.7 days).

There was a protocol specified interim analysis of efficacy when 50% of the subjects had completed the study. The purpose of the interim analysis was to ensure that neither of the two treatments was significantly inferior. The Lan and DeMets alpha spending function in the form of an [redacted] stopping boundary was used. A p-value less than 0.0034 was to be considered significant at the interim analysis. The interim analysis included the data of 552 enrolled subjects, 348 of whom had completed treatment. The results presented at the closed DSMB were not provided to the sponsor. No changes to the study design or conduct were recommended and the study continued to completion as originally planned. Since the interim analysis tested a hypothesis of inferiority and the final analysis tests a hypothesis of non-inferiority, no adjustments were made to the final analysis. The sponsor has conducted analytical and simulation investigations that confirm that the final type I error rate for non-inferiority is minimally affected and actually minimally reduced in this situation.

Results: Efficacy

Study 603 was conducted at 73 centers in 6 countries. The United States had 46 participating centers and enrolled the majority of the patients. A total of 871 patients were randomized to receive study treatment, 435 randomized to receive voriconazole and 436 to receive L-AMB. Fourteen patients in the voriconazole group and 8 patients in the L-AMB group did not receive study treatment and were excluded from the safety population leaving 421 voriconazole and 428 L-AMB patients. An additional 6 patients

from each group were excluded from the MITT population. Therefore, the MITT population consisted of 415 voriconazole patients and 422 L-AMB patients.

The demographic and baseline characteristics of the MITT population are shown in Table 603-1. There were no significant differences across treatment groups. Slightly more males than females were enrolled into both treatment groups. The majority of the patients were white. The mean age was 46 years in the voriconazole group and 44 years in the L-AMB group. The most common underlying disease in both treatment groups was newly diagnosed leukemia. One-third of the patients were categorized as being at higher risk of developing a fungal infection. More than half of the patients received prior antifungal prophylaxis.

Table 603-1
Demographic and Baseline Characteristics (MITT)

Patient Characteristic	L-AMB N=422	Voriconazole N=415
Gender		
Female	206 (48.8)	182 (43.9)
Male	216 (51.2)	233 (56.1)
Race		
White	333 (78.9)	325 (78.3)
Black	32 (7.6)	35 (8.4)
Asian	23 (5.5)	29 (7.0)
Other	34 (8.1)	26 (6.3)
Age		
Mean (sd)	44.9 (15.6)	46.3 (15.1)
Min, max	12, 80	12, 82
Underlying Disease		
Lymphoma	63 (14.9)	57 (13.7)
Multiple myeloma	24 (5.7)	22 (5.3)
Newly diagnosed leukemia	130 (30.7)	130 (31.3)
Other	63 (14.9)	62 (14.9)
Relapsed leukemia	84 (19.9)	92 (22.2)
Solid organ malignancy	59 (14.0)	52 (12.5)
Risk of Fungal Infection		
High	141 (33.4)	143 (34.5)
Moderate	281 (66.6)	272 (65.5)
Prior Prophylaxis		
Yes	250 (59.2)	222 (53.5)
No	172 (40.8)	193 (46.5)

The overall response rates and the results for each component of the composite endpoint are presented in Table 603-2. Treatment with voriconazole resulted in a 26.0% success rate compared to a success rate of 30.6% with L-AMB. The lower limit of the 95% stratified confidence interval, –11.6%, was below the –10% needed to demonstrate non-inferiority of voriconazole. For the individual components, 99% confidence intervals have been presented in Table 603-2. Even though this was not prespecified in the protocol, this was done to adjust for multiple endpoints of interest. Four of the five

components favor L-AMB. The only exception is with breakthrough fungal infections. In the treatment of febrile neutropenic patients, reducing the number of breakthrough fungal infections could be argued to be the main endpoint of interest. Due to the difficulty in designing a trial based on this endpoint alone, the composite endpoint has been used for assessing efficacy. If a study were to be designed with breakthrough infections as the primary endpoint, deaths would still be included in the endpoint. An analysis was performed based on no breakthrough infections and survival through 7 days of EOT. The response rate for both treatment groups is 90.8% (383/422- L-AMB and 377/415-voriconazole). The corresponding 95% confidence interval about no difference is (-4.2, 4.2).

Table 603-2
Overall Response and Response by Component (MITT)

	L-AMB N=422	Voriconazole N=415	Difference and CI*
Overall Response	129 (30.6)	108 (26.0)	-5.3 (-11.6, 1.0)
No breakthrough fungal infection within 7 days of EOT	401 (95.0)	407 (98.1)	3.1 (-0.4, 6.6)
Survival through 7 days of EOT	397 (94.1)	382 (92.0)	-2.1 (-6.9, 2.7)
No discontinuation due to toxicity or lack of efficacy before recovery from neutropenia	394 (93.4)	374 (90.1)	-3.3 (-8.4, 1.8)
Resolution of fever during neutropenia	154 (36.5)	135 (32.5)	-4.0 (-12.7, 4.7)
Global response of baseline fungal infections at EOT	4/6 (66.7)	6/13 (46.2)	-20.5 (-93.7, 52.7)

*A difference and 95% confidence interval stratified by risk of fungal infection, prior prophylaxis, and duration of baseline neutropenia is reported for the overall response success rate. Raw differences and 99% confidence intervals are reported for the 5 individual components.

As shown in Table 603-2, the assumed overall response rate of 50% was not achieved for either treatment group. The lower than expected success rate can be explained by the failure of many patients to defervesce before recovery from neutropenia. Further investigation led to the realization that the response rate seen is highly dependent on how defervescence is defined. In this study, defervescence was required to occur at least 48 hours prior to recovery of neutropenia. In the prior study that obtained a 50% response rate, a patient only needed not to have a fever at the time of recovery from neutropenia. Therefore, sensitivity analyses (Table 603-3) were performed with two alternative definitions of defervescence. The first definition required that defervescence occur at least 24 hours prior to recovery of neutropenia and the second allowed defervescence to occur at any time prior to recovery from neutropenia. Overall success rates increased with each definition in a similar fashion for each treatment group. The assumed success rate of 50% was reached when a similar definition of defervescence as that in the previous study was used. Even though the assumed rate of 50% was achieved, non-inferiority of voriconazole is still not demonstrated.

Table 603-3
Overall Response with Alternative Definitions of Defervescence (MITT)

Definition of Defervescence	L-AMB N=422	Voriconazole N=415	Difference and 95% CI

Defervescence within 24 hours of recovery of neutropenia	172 (40.8)	149 (35.9)	-4.9 (-11.7, 1.9)
Defervescence any time prior to recovery from neutropenia	237 (56.2)	208 (50.1)	-6.1 (-13.1, 0.9)

One additional explanation for the failure of many patients to defervesce is the length of neutropenia after randomization. In previous studies of febrile neutropenia, the median duration of neutropenia after randomization was 10 days. In this study, the median duration of neutropenia was about 5 days for both treatment groups. Therefore the combination of the 48 hours for the definition of defervescence and the shorter duration of neutropenia may further explain the lower numbers of patients who defervesced prior to recovery from neutropenia.

Reviewer's Comment: *As seen with this study, overall success rates are highly dependent on the definition of defervescence. For future studies, the importance of defervescence as part of the endpoint to determine efficacy needs to ascertained. If it is to remain a part of the composite endpoint, an appropriate definition of defervescence needs to be agreed upon in order to make sufficient claims regarding efficacy.*

One of the randomization factors was risk of fungal infection. Table 603-4 presents the results of overall response by the risk of fungal infection. The applicant is making the claim that the success of voriconazole is more pronounced in the high risk patients than in the moderate risk patients. The difference in overall response favors voriconazole for the high risk patients but favors L-AMB for the moderate risk patients. The test for treatment by risk of fungal infection interaction is not statistically significant (p=0.30). Since the interaction is not significant, there is no statistical evidence to suggest that the two risk groups should not be pooled. However, because of the applicant's claim regarding the high risk group, an adjustment is being made for looking at the two risk groups separately. The lower bound of the 97.5% confidence interval for the difference in success rates for the higher risk group is lower than the 10% non-inferiority margin.

Table 603-4
Overall Response by Risk of Fungal Infection (MITT)

Risk of Fungal Infection	L-AMB N=422	Voriconazole N=415	Difference 95% CI 97.5% CI
High	42/141 (29.8)	45/143 (31.5)	1.7 (-9.7, 13.1) (-11.3, 14.7)
Moderate	87/281 (31.0)	63 /272 (23.2)	-7.8 (-15.5, -0.1) (-16.6, 1.0)

Reviewer's Comment: *The results of overall response for the high risk group are not sufficient to support an indication of empiric treatment of febrile neutropenia in high risk patients. They may be used to support another study in high risk (relapsed leukemia or allogeneic bone marrow/ peripheral stem cell transplant) patients.*

Results: Safety

A total of 417 patients (99.0%) in the voriconazole group and 423 patients (98.8%) in the L-AMB group had at least one adverse event. The most common adverse events included chills, fever, and abnormal vision. Abnormal vision occurred more frequently in the voriconazole group. The incidence of abnormal vision was statistically significantly higher in the voriconazole group (26.1%) than in the L-AMB group (4.9%) ($p<0.0001$).

Treatment related adverse events occurred in 288 patients (68.4%) in the voriconazole group and 343 patients (80.1%) in the L-AMB group. The most commonly occurring treatment related adverse event in the voriconazole group was abnormal vision. As with adverse events overall, abnormal vision related to study treatment was statistically significantly higher in the voriconazole group (23.8%) than in the L-AMB group (0.9%) ($p<0.0001$).

There were 101 (24.0%) voriconazole patients and 109 (25.5%) L-AMB patients with serious adverse events. Sixty-two (14.7%) voriconazole subjects and 46 (10.7%) L-AMB subjects died during therapy or within 30 days of EOT. Two of the voriconazole deaths were considered as treatment related by the investigator. There were 2 additional deaths in the voriconazole group and 1 additional death in the L-AMB group that occurred more than 30 days after EOT.

For a more detailed review of the safety data, please see the Medical Officer Safety review written by Dr. Rose Mary Tiernan.

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Reviewer's Conclusions (which may be conveyed to the sponsor in the action letter)

1. *There is concern about the comparability of the Study 304 voriconazole treated aspergillosis patients to those of the aspergillosis historical control. Prior to the submission of the results of the randomized comparative study, this concern would have played a large role in the ability to assess the overall efficacy of voriconazole in the treatment of invasive aspergillosis. The results of Study 304, however, do not contradict those seen in the randomized comparative study.*

2. *The results of the global aspergillosis trial, Study 307/602, support the statistical superiority of voriconazole compared to an amphotericin B regimen when assessing global response at Week 12. In addition, voriconazole was shown to have a survival benefit when compared to the amphotericin B regimen.*

3. *The efficacy of voriconazole in the treatment of microbiologically and histopathologically proven esophageal candidiasis was demonstrated by one well-controlled study. Study 305 demonstrated that the efficacy of voriconazole at end of treatment was at least as good as that of fluconazole assuming a non-inferiority margin of -15%.*

4. *The results of Study 603 do not demonstrate the non-inferiority of voriconazole in the empirical treatment of febrile neutropenic patients. The results may be used to support an additional study of patients at high risk of fungal infection i.e. patients with relapsed leukemia or allogeneic bone marrow/ peripheral stem cell transplant.*

5. *Abnormal vision occurred at higher rates in the voriconazole group versus all comparators and was the most frequent adverse event with a suspected or probable relationship to study medication.*

Cheryl Dixon, Ph.D.
Biostatistician, DOB III

Concur: Karen Higgins, Sc.D.
Team Leader, DOB III

cc:
Archival NDA 21-266 VFEND tablets
NDA 21-267 VFEND I.V. for Infusion
HFD-590
HFD-590/ Dr. Goldberger
HFD-590/ Dr. Albrecht
HFD-590/ Dr. Cavaille Col
HFD-590/ Dr. Tiernan
HFD-590/ Dr. Powers
HFD-590/ Dr. Alivisatos
HFD-590/ Dr. Johann-Liang
HFD-590/ Ms. Saliba
HFD-700/ Dr. Anello
HFD-725/ Dr. Huque
HFD-725/ Dr. Higgins
HFD-725/ Dr. Dixon

This review contains 29 pages.

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

/s/

Cheryl Dixon
11/9/01 09:27:29 AM
BIOMETRICS

Karen Higgins
11/9/01 09:33:03 AM
BIOMETRICS

Fax and 3-13-98 kc

MAR 12 1998

STATISTICAL REVIEW AND EVALUATION

IND #'s: [redacted]

Applicant: Pfizer Central Research

Name of Drug: Voriconazole - Oral
Voriconazole- I. V.

Documents Reviewed: New protocol submitted February 5, 1998

Indication: Treatment of candidemia

Medical Reviewer: Dr. Rigoberto Roca (HFD-590)

I. Background

A new protocol for the study of Voriconazole (I.V. and Oral) has been submitted for review. Protocol No. 150-608 is entitled "A Randomized, Comparative, Multicenter Study of Voriconazole vs. Conventional Amphotericin B in the treatment of Candidemia in Non Neutropenic Subjects. The primary objective of this study is to compare the efficacy and safety of voriconazole and conventional amphotericin B with optional oral fluconazole follow-on therapy, in the treatment of candidemia in non neutropenic subjects.

II. Study Design

This protocol is a prospective, randomized, study of voriconazole compared to amphotericin B with optional follow-on therapy with oral fluconazole in the treatment of candidemia. Subjects will be randomized to receive intravenously either voriconazole or amphotericin B in a 2:1 ratio. After a minimum period of intravenous dosing, subjects may be switched to oral therapy. In the voriconazole arm, subjects can be continued on oral voriconazole in the absence of events contraindicating oral medications. In the amphotericin B arm, subjects can be continued on oral fluconazole provided blood cultures are negative an the signs and symptoms of the infection have resolved.

Baseline assessment will be conducted prior to randomization and start of study medication. Efficacy and safety assessments will be scheduled for all subjects daily on days 1-4 and 7, followed by twice weekly, at the end of therapy (EOT), and 2, 6 and 12 weeks after EOT. End of therapy is defined at the termination of protocol therapy which can occur at least 2 weeks after the complete resolution of all clinical findings of an active infection OR at least 2 weeks after the last positive site culture was taken, whichever is longer.

Subjects with confirmation of *Candida* infection who receive at least one dose of study medication will be eligible for inclusion in the modified intent to treat (MITT) analysis group. The primary analysis of efficacy will be based on the response to antifungal therapy at the final study assessment (12 week follow-up). Subjects who fail or relapse prior to the 12 week follow-up will be discontinued from study, and the failures carried forward. The rate of success is defined as the number of subjects assessed as having a response of cured divided by the total number of subjects eligible for the analysis. The response to antifungal therapy at the final assessment and the rate of success will be summarized for each treatment group by descriptive statistics using data from subjects in the MITT group. The rate of success for subjects treated with voriconazole will be compared to the rate of success for subjects treated with conventional amphotericin B. The goal of this comparison is to demonstrate the therapeutic equivalence of the two treatments. The analysis of the success rates will consist of constructing 95% confidence intervals around the rates for each treatment group and the lower 95% confidence bound for the difference between treatment groups (voriconazole minus amphotericin B).

The response to antifungal therapy at the end of therapy and at the two and six week follow-up visits will also be summarized.. Survival analyses (time to death, time to failure) will be generated by producing non-parametric Kaplan-Meier estimates of the survival function and plotting these estimates against the time from first dose of study medication. Formal statistical analyses will be performed using a Cox proportional hazards model.

A single interim analysis of efficacy may be conducted after at least 30% and no more than 70% of the subjects have completed the study. If this interim analysis is conducted, the level of Type I error to be used for the confidence intervals for the interim and final analyses will be determined based on the Lan and Demets (1994) alpha spending function approximating boundary.

Reviewer's Comment: The method for adjusting the alpha level to be used at the interim and final analyses is acceptable. If one interim analysis is conducted at 30/50/70% enrollment, then the final analysis would be carried out with α= 0.035/0.030/0.027.

Assuming a success rate for both treatment groups of 65% and that an interim analysis may be conducted at 70% enrollment, a sample size of 198 subjects (132 assigned to treatment with voriconazole and 66 assigned to treatment with conventional amphotericin B) is adequate to demonstrate equivalence with a delta of 20% and a power of 80% in the MITT analysis of response to antifungal therapy. It is estimated that 15% of the subjects enrolled will be excluded from the MITT population. Therefore, a total of 234 subjects (156 assigned to treatment with voriconazole and 78 assigned to treatment with conventional amphotericin B) will be enrolled in the study.

Reviewer's Comment: The sample size calculated above is based on the method of with an 12.5% increase from equal allocation for the 2:1 randomization. This sample size assumes one interim analysis at 70% enrollment (the largest sample size needed). It needs to be noted, however, for this sample size calculation, the sponsor is stating the goal of the analysis is to demonstrate that the rate of the response to antifungal therapy in subjects randomized to treatment with voriconazole is no more than 20% lower than the rate of response in subjects randomized to treatment with conventional amphotericin B. Thus, all of the useable alpha for the final analysis (0.27) is used in a one-sided fashion. It needs to be determined whether this is acceptable from a clinical standpoint. It is suggested that an equivalence trial design be utilized and two-sided statistical tests be performed.

APPEARS THIS WAY
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Reviewer's Comments (which may be conveyed to the sponsor)

1. *The Sample Size Determination (Appendix G) states that the goal of the analysis os to demonstrate that the rate of response to antifungal therapy in subjects randomized to voriconazole is no more than 20% lower than the rate of response in subjects randomized to treatment with conventional amphotericin B. It is believed that a statement of "no more than 20% lower" contained in the description of this clinical study in a potential label for voriconazole would be misleading: the reader may infer that equivalence has been demonstrated when, in fact, it has not. Therefore, it is recommended that an equivalence trial design be utilized.*

2. *The method used for calculating the alpha levels for the interim and final analyses is acceptable. However, it needs to be ascertained if the one-sided test approach based on the assumption of non-inferiority to the active control is clinically acceptable.*

/S/
3/12/98
Cheryl Dixon, Ph.D.
Biostatistician, DOB IV

/S/
3/12/98
Concur: Aloka Chakravarty, Ph.D.
Acting Team Leader, DOB IV

cc:
Original IND #
Original IND #
HFD-590
HFD-590/ Dr. Goldberger
HFD-590/ Dr. Albrecht
HFD-590/ Dr. Cavaille-Coll
HFD-590/ Dr. Roca
HFD-590/ Ms. Frank
HFD-725/ Dr. Huque
HFD-725/ Dr. Chakravarty
HFD-725/ Dr. Dixon
Chron.

DEC 23 1997

STATISTICAL REVIEW AND EVALUATION

IND #'s: [redacted]

Applicant: Pfizer Central Research

Name of Drug: Voriconazole - Oral
Voriconazole- I. V.

Documents Reviewed: New protocol submitted November 12,1997

Indication: Empirical treatment of systemic fungal infections.

Medical Reviewer: Dr. Teresa Wu (HFD-590)

I. Background

A new protocol for the study of Voriconazole (I.V. and Oral) has been submitted for review. Protocol No. 150-603 is entitled "A Randomized, Open Label Comparative, Multicenter Trial of Voriconazole vs. AmBisome for Empirical Antifungal therapy in Immunocompromised Patients with Persistent Fever and Neutropenia. The objectives of this study are to evaluate

- the efficacy of voriconazole compared to AmBisome® in the empirical treatment of fungal infections in immunocompromised patients with persistent fever and neutropenia.
- the safety and tolerance of voriconazole compared to AmBisome® in the empirical treatment of fungal infections in immunocompromised patients with persistent fever and neutropenia.
- the survival, the incidence of breakthrough deeply invasive infections, and the time to defervescence in subjects treated with voriconazole compared to patients treated with AmBisome®.

The majority of the subjects enrolled in this study will be treated with empirical antifungal medication until recover from neutropenia (typically two weeks), with a follow-up clinical assessment seven days after the last dose of empirical therapy. Subjects who are diagnosed with a deeply invasive fungal infection can be treated until resolution of the infection up to a maximum of 12 weeks.

II. Study Design

This protocol is a prospective, centrally randomized, open-label clinical trial of voriconazole compared to AmBisome® for empirical treatment of fungal infections in immunocompromised subjects with persistent fever and neutropenia. Subjects will be

randomized to receive either variconazole or AmBisome® stratified by risk of fungal infections (allogeneic bone marrow/ allogeneic peripheral stem cell transplant or relapsed leukemia vs. other underlying condition) and systemic antifungal prophylaxis (yes vs. no). Subjects randomized to receive voriconazole will be treated with intravenous voriconazole for at least 3 days, followed by oral voriconazole, until recovery from neutropenia. Subjects randomized to receive AmBisome® will be treated with intravenous AmBisome® until recovery from neutropenia.

Baseline assessment will be conducted prior to randomization and start of study medication. For all subjects, assessments will be performed twice weekly until recovery from neutropenia. Subjects without baseline or breakthrough deeply invasive fungal infections will have follow-up assessments performed seven days after the last dose of study medication. For subjects with baseline or breakthrough deeply invasive fungal infections, additional assessments will be performed every four weeks while on study medication, at the end of treatment (EOT), and at four weeks after EOT.

Subjects who receive at least one dose of study medication and for whom adequate information is collected to confirm the investigator's assessment of overall response to empirical therapy will be eligible for inclusion in the modified intent to treat analysis group. The primary analysis of efficacy will be based on the overall response to empirical therapy. The rate of success is defined as the number of subjects assessed as having a response of success divided by the total number of subjects eligible for the analysis. A subject is categorized as success in the overall response to empirical therapy if all of the following criteria are satisfied: survival for at least 7 days after discontinuation of study medication, absence of breakthrough fungal infection during the period of neutropenia and for at least seven days after the discontinuation of study medication, defervescence during the period of neutropenia, not discontinued from randomized study medication due to toxicity or lack of efficacy prior to recovery of neutropenia, and for subjects with baseline fungal infections only: global response assessed as complete or partial at EOT. Overall response to empirical therapy and the rate of success will be summarized for each treatment group by descriptive statistics using data from subjects in the MITT group. The rate of success for subjects treated with voriconazole will be compared to the rate of success for subjects treated with AmBisome®. The goal of this comparison is to demonstrate the therapeutic equivalence of the two treatments, the analysis of the success rates will consist of constructing 95% confidence intervals around the rates for each treatment group and for the difference between treatment groups. Overall response to empirical therapy and the rate of success will also be summarized for each treatment group by the following: prior systemic antifungal prophylactic treatment, risk of fungal infections, and duration of neutropenia.

The number and percent of subjects who have defervesced during neutropenia will be summarized for each treatment group. The number of subjects who develop breakthrough deeply invasive fungal infection will be summarized by organism and treatment group. The overall rate of breakthrough deeply invasive fungal infections will

be compared for the two groups using Fisher's Exact Test. For subjects who have baseline or breakthrough deeply invasive fungal infections, global response at EOT and four weeks after EOT will be summarized for each treatment group and each infection. The following survival analyses will be performed: time to death, time to discontinuation of therapy due to toxicity/intolerance, and time to defervescence. These survival analyses will be generated by producing non-parametric Kaplan-Meier estimates of the survival function. Formal statistical analyses will be performed using a Cox proportional hazards model. The covariates to be considered for the model are treatment group, prior systemic antifungal prophylactic treatment, risk of fungal infections, and duration of neutropenia.

Reviewer's Comment: The covariates to be included in the Cox model are acceptable.

Assuming a success rate for both treatment groups of 50%, a sample size of 786 subjects (393 per treatment group) is adequate to demonstrate equivalence with a delta of 10% and a power of 80% in the analysis of overall response to empirical treatment. It is estimated that 10% of the subjects enrolled will be excluded from the MITT population. Therefore, a total of 866 subjects (433 per treatment group) will be enrolled in the study.

Reviewer's Comment: Sample size based on the composite variable, overall response, is sufficient. The calculation based on the method of . is acceptable.

An interim analysis of efficacy will be conducted after half of the subjects have completed the study. The interim analysis is intended to insure that no subjects are receiving a significantly inferior treatment. Using the Lan and Demets stopping procedure with an stopping rule, a p-value less than 0.0034 will be considered statistically significant in the comparison of the rates of success in the overall response to empirical therapy between the two treatment groups. No adjustments will be made to the nominal p-values in the final study report.

Reviewer's Comment: Since there is no possibility of making a type I error at the interim analysis i.e., no possibility of rejecting the null hypothesis and claiming equivalence of the two treatments or stopping in favor of voriconazole, the alpha level for the final analysis does not need to be adjusted.

APPEARS THIS WAY
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Reviewer's Comments (which may be conveyed to the sponsor)

1. *The primary efficacy variable, overall response, is a composite endpoint which combines both efficacy and safety assessments. It should be noted that efficacy and safety assessments will be analyzed separately. If opposite conclusions are drawn for the comparison of the two treatments with respect to safety and efficacy, claiming equivalence based on the rate of overall response may not be appropriate. See Medical Reviewer's review for further discussion.*

2. *The sample size calculated is acceptable.*

3. *Adjustment to the nominal p-value at the end of the trial due to the performance of the interim analysis is not necessary since there will be no claim of equivalence or superiority of voriconazole if the trial is stopped early because of an inferior treatment.*

/S/ 12/23/97

Cheryl Dixon, Ph.D.
Biostatistician, DOB IV

/S/
12/23/97

Concur: Aloka Chakravarty, Ph.D.
Acting Team Leader, DOB IV

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Original IND # [redacted]
Original IND # [redacted]
HFD-590
HFD-590/ Dr. Goldberger
HFD-590/ Dr. Albrecht
HFD-590/ Dr. Mann
HFD-590/ Dr. Wu
HFD-590/ Ms. Frank
HFD-725/ Dr. Huque
HFD-725/ Dr. Chakravarty
HFD-725/ Dr. Dixon
Chron.

AUG 1 2 1997

STATISTICAL REVIEW AND EVALUATION

IND #'s: [redacted]

Applicant: Pfizer Central Research

Name of Drug: Voriconazole - Oral
Voriconazole- I. V.

Documents Reviewed: Umbrella protocol and corresponding independent protocols submitted July 21,1997

Indication: Treatment of acute invasive aspergillosis in immunocompromised patients.

Medical Reviewer: Dr. Teresa Wu (HFD-590)

I. Background

Due to the difficulty in enrolling an adequate number of patients in aspergillus trials, the sponsor has submitted an umbrella protocol for combining data from two nearly identical studies of voriconazole versus amphotericin B in the treatment of acute invasive aspergillosis. One study will be conducted in the United States and the other will be conducted in Europe. The two independent aspergillus protocols are entitled:

> Protocol 602 (US protocol)-"An Open Randomized Comparative Multicenter Study of the Efficacy, Safety, and Toleration of Voriconazole Versus Amphotericin B Followed by Other Licensed Antifungal Therapy in the Treatment of Acute Invasive Aspergillosis in Immunocompromised Patients"
> Protocol 307 (European protocol)-" An Open Randomised Comparative Multicentre Study of the Efficacy, Safety, and Toleration of Voriconazole Versus Amphotericin B in the Treatment of Acute Invasive Aspergillosis in Immunocompromised Patients."

These protocols were discussed at the End of Phase II meeting on June 24, 1996. During this meeting, a request for the proposed single combined analysis of the data from these studies was made by the Division of Anti-Viral Drug Products.

The parent protocols have comparable inclusion and exclusion criteria and the schedule of visits and assessments are the same. They are both designed to recruit approximately 250 patients to achieve their objectives with 80% power. The proposed

umbrella protocol details how the results will be pooled and analyzed when the combined number of patients will yield 90% power for the main objectives.

The objective of the umbrella protocol is to conduct a single combined analysis of data from two nearly identical studies of voriconazole versus amphotericin B in the treatment of acute aspergillosis. The aim of the study is to perform the analysis when the combined number of patients eligible for inclusion in the Intent-to-Treat (ITT) week 12 analysis group reaches 276. The sample of 276 patients (138 per group) will provide power of at least 0.90 to

(1) detect a difference of 20% in the rates of satisfactory global response between voriconazole and amphotericin B treatment groups in the ITT analysis at the end of initial randomized single agent therapy (EOT), and
(2) demonstrate equivalence in the rates of satisfactory response between patients randomized to voriconazole and patients randomized to amphotericin B in the ITT analysis at week 12.

After approximately 150 patients have completed treatment in Protocol 307 or 602, the Sponsor will ascertain how many combined patients need to be enrolled in order to obtain the 276 eligible patients. Patients who enter prior to the time the enrollment goal has been met will be considered enrolled in the umbrella protocol and will be eligible for inclusion in the combined analysis. Data collected from patients enrolled in the parent protocols after this total has been met will not be included in the combined analysis.

The rate of satisfactory global response will be used to evaluate efficacy. Global response is ascertained by the Endpoints Committee, based in part on investigator assessments of clinical, mycological, and imaging responses. A complete or partial global response is defined as satisfactory. The analysis of the rates of satisfactory response at EOT and week 12 will consist of constructing 95% confidence intervals around satisfactory response rates for each treatment group and for the difference in satisfactory response rates between treatment groups. For the EOT analysis, the difference between treatments will be considered significant if the 95% confidence interval does not include 0. For the week 12 analysis, the rates of satisfactory response will be considered equivalent if the 95% confidence interval around the difference is within (-20%, 20%). A proportional odds model will be fit to the ordinal global response data for the EOT analysis. A difference between the treatments will be considered significant if $p \leq 0.05$. Survival analyses on time to death and time to discontinuation are also planned.

Since the primary purpose of the umbrella protocol is to pool data from as many as 150 centers world-wide, no formal testing for a difference between centers will be performed. A difference between protocols will be tested by incorporating protocol as a factor in all models.

All patients enrolled in the umbrella protocol who took at least one dose of study medication will be included in the safety summaries.

In order to protect the integrity of the parent protocols, the investigators involved in the running of these protocols will not be informed of the results of the umbrella protocol analysis while the individual protocols are still ongoing. No interim analyses of efficacy are planned for the parent protocols individually. The analysis and decision to file the results of the umbrella protocol in support of regulatory application are not anticipated to effect the conduct or analysis of either of the parent protocols.

APPEARS THIS WAY
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Reviewer's Comments (which may be conveyed to the sponsor)

1. *The sample size of 276 patients is sufficient to detected a difference of 20% with respect to satisfactory response rate between voriconazole and amphotericin B at the 5% significance level with a probability of 0.9. This calculation assumes the expected satisfactory response rate for patients in the voriconazole treatment group to be 55% and the expected satisfactory response rate for patients in the amphotericin B treatment group to be 35%. Since this sample size is sufficient to detect a difference of 20%, it is also adequate to demonstrate equivalence with a delta of 20% and a power of 0.9.*

2. *It needs to be clearly stated whether the primary objective of the study is detecting a difference between voriconazole and amphotericin B, demonstrating equivalence of voriconazole and amphotericin B, or both. If both endpoints are to be considered primary, an adjustment may be necessary.*

3. *The protocol states that 'After approximately 150 patients have completed treatment in 150-307 or 150-602, the Sponsor will ascertain how many combined patients need to be enrolled in order to obtain the 276 eligible patients.' This determination should be blinded to treatment group.*

4. *Further clarification is necessary as to why the evaluable patient analysis is not appropriate for the week 12 analysis.*

5. *It should be noted that all available safety data should be submitted at the time of NDA submission.*

6. *It has been stated that the results of the umbrella protocol will be used to form part of a regulatory submission. It is not clear, though, how the results of the parent protocols will be used. Will there be mention in the reports of the individual protocols that a portion of the data was included in the analysis of the umbrella protocol?*

/S/ 8/12/97

Cheryl Dixon, Ph.D.
Biostatistician, DOB IV

/S/ 8/12/97

Concur: Nancy Paul Silliman, Ph.D.
Acting Team Leader, DOB IV

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