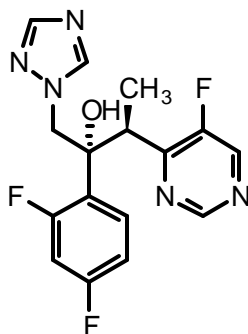Background Document
for the
Antiviral Drug Products Advisory Committee Meeting
October 4, 2001

(voriconazole tablets)
(voriconazole injection)
Pfizer Global Research & Development
NDAs 21-266 and 21-267

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Special Pathogen and Immunologic Drug Products

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Introduction

Pfizer Inc. has submitted a new drug application (NDA) for voriconazole for the indications of: treatment of invasive aspergillosis; empiric antifungal therapy of febrile neutropenic patients; treatment of candida eosophagitis; treatment of serious candida infections; treatment of serious fungal infections caused by *Fusarium* and *Scedosporium* spp.; treatment of serious fungal infections in patients refractory or intolerant to other therapy.

The focus of this Advisory Committee meeting will be to consider the indications of treatment of invasive aspergillosis, and empiric antifungal therapy of patients with febrile neutropenia.

The purpose of this Briefing Document is to provide background information for the Antiviral Drug Products Advisory Committee meeting scheduled for October 4, 2001. The document is organized as follows:

1. **A summary of the preclinical *in vitro* and *in vivo* microbiology data.**

   Overall, we are in general agreement with the Applicant's description of the microbiology information. Essential points to consider are the mechanism of action, *in vitro* and *in vivo* activity against *Aspergillus* and *Candida* species, and potential for cross-resistance with other triazole antifungals.

2. **A summary of selected pharmacology and preclinical toxicology issues**

   Overall, we are in general agreement with the non-clinical toxicological information provided in the Applicant's briefing document. Selected issues related to cardiac, and retinal findings are highlighted.

3. **A summary of the clinical pharmacology of voriconazole**

   Essential points to be considered are the high oral bioavailability, the non-linear pharmacokinetics, the interpatient variability, and the potential for drug-drug interactions. In particular, because voriconazole is both a substrate and an inhibitor of CYP2C19, CYP2C9, and CYP3A4, the interactions between voriconazole and important drugs that are substrates, inducers or inhibitors of these have been evaluated.

4. **Discussion of the efficacy data for voriconazole in the treatment of invasive aspergillosis**

   This indication is supported by the prospective combined analysis of two randomized, open-label active-controlled clinical trials (Studies 307/602), and the comparison of a treated cohort (Study 304) to a retrospectively designed contemporaneous historical control group (Study 1003). In assessing the efficacy please consider the strength and

consistency of the clinical and microbiologic results, as well as whether the studied populations and pathogens are representative of the US population for whom voriconazole is intended to be used.

5. **Discussion of the efficacy data for voriconazole in the empiric antifungal therapy of febrile neutropenic patients.**

The application for this indication is supported by a randomized, open-label, active controlled clinical trial (Study 603), and information from clinical studies evaluating the efficacy of voriconazole in documented infections with relevant pathogens. In addition to effectiveness in the treatment of invasive aspergillosis, we are in general agreement with the Applicant that voriconazole is effective in the treatment of esophageal candidiasis in HIV-infected patients (Study 305). Although, Study 603 failed to meet the statistical primary endpoint for non-inferiority, the totality of the data in this application should be considered in assessing efficacy and safety in this indication. These include, but are not limited to the strength of the efficacy data against the major relevant pathogens, the pattern of breakthrough infections, and the estimated effectiveness of the active control over placebo.

A summary of background information on empiric antifungal therapy of febrile neutropenic patients is also provided in this section. Assessment of the benefit of any antifungal drug over placebo for the treatment of febrile neutropenic patients must take into account: 1) the lack of statistical power in the original studies of the indication; 2) the widespread use of more effective prophylaxis; and 3) the shortened duration of neutropenia in patients currently treated with cytotoxic therapy.

One must also take into account the safety profile of voriconazole, because it is expected that many patients who receive an antifungal drug for empiric therapy while febrile and neutropenic will never develop a fungal infection. In such cases, patients may be exposed to potential adverse events without receiving benefit.

6. **Discussion of the safety of voriconazole in patients enrolled in active controlled clinical studies.**

Selected adverse event categories that are felt to be characteristic of the safety profile of voriconazole are discussed. These include visual findings, rash, and liver function test abnormalities.

Overall, voriconazole's metabolism and potential for drug interactions, may pose a greater safety challenge than some of its individual adverse effects. The Applicant has evaluated the pharmacokinetic interactions between voriconazole and important concomitant medications. We seek the committee's advice on what other interactions should be evaluated.

Preclinical Microbiology

Mechanism of Action

Voriconazole is a triazole antifungal agent. The mechanism of action is the same as for the other approved antifungal azoles, i.e. fluconazole and itraconazole. Voriconazole has been shown to inhibit the cytochrome P-450 dependent 14á-lanosterol demethylase enzyme that is responsible for the removal of the methyl group on the C14 site of lanosterol. Inhibition of this enzyme results in the depletion of ergosterol, a major component necessary for the integrity of the fungal cell wall, and the accumulation of the sterol precursor compounds.

While the mechanism of action of voriconazole is the same as the other approved antifungal azoles, it is necessary to characterize the activity of voriconazole against the different fungal pathogens. This is essential because the composition and content of the different sterols in the cell walls of fungal organisms can vary, thus potentially altering the activity profile and cross resistance pattern of voriconazole from genus to genus and even species to species.

Mechanisms of resistance

There is no single mechanism of resistance for the antifungal azoles. The principal mechanisms, at the molecular level, contributing to antifungal azole resistance include modifications to the ergosterol biosynthesis pathway, molecular changes to the ERG genes and over expression of efflux pumps through either CDR genes of ABC transporters or the MDR1 gene.

***In Vitro* Activity**

Voriconazole is active in vitro against *Aspergillus* and *Candida* species. In 1998 Johnson et al. published data comparing the in vitro activity of voriconazole to that of itraconazole and amphotericin B against filamentous moulds (JAC, 1998,42:741-745). Among other moulds, 10 *A. fumigatus* and 10 *A. flavus* isolates were tested. MICs were determined employing the NCCLS microdilution method. After 48 hours of incubation, when the MICs were read, the microtiter wells demonstrating no growth were plated out and incubated to determine the minimum lethal concentrations (MLC). The MLC was defined as the lowest drug concentration where 95% of the inoculum was killed after additional 48 hours incubation. Table 1 shows the MIC and MLC ranges and MIC_{90} and MLC_{90} values for *A. fumigatus* and *A. flavus* isolates. For the limited number of isolates tested, itraconazole and voriconazole MLCs were comparable to MICs.

Table 1 Voriconazole and Itraconazole MIC and MLC values for *A. fumigatus* and *A. flavus*

	Aspergillus fumigatus (n=10)		*Aspergillus flavus* (n=10)	
	Itraconazole	Voriconazole	Itraconazole	Voriconazole
MIC range (μg/ml)	0.25-0.5	0.25-0.5	0.12-0.25	0.25-1.0
MIC_{90}(μg/ml)	0.5	0.5	0.25	0.5
MLC range(μg/ml)	1.0-2.0	0.25-2.0	0.12-0.5	0.5-2.0
MLC_{90}(μg/ml)	1.0	0.5	0.5	1.0

MIC=minimum inhibitory concentration; MLC=minimum lethal concentration

The inhibitory and cidal activity of three antifungal agents was determined using NCCLS susceptibility testing methods and time kill curves, respectively (Manavathu et al.,1998, AAC 42:3018-21). Table 2 shows amphotericin B, itraconazole and voriconazole MICs for various *Aspergillus* and *Candida* isolates tested. For the *Aspergillus* isolates evaluated voriconazole and itraconazole MICs ranged from 0.125-2.0 μg/ml and 0.25-4.0 μg/ml, respectively. The voriconazole MICs were 2 fold higher than the itraconazole MICs for the various *Aspergillus* species tested.

Voriconazole and itraconazole MICs against the Candida isolates ranged from 0.015-0.5μg/ml and 0.031-0.5μg/ml. However, the MICs for both drugs were 8-32 fold higher for the non-albicans species versus *C. albicans*. The MIC data suggest that the inhibitory effect of voriconazole is comparable to that of itraconazole. In addition, the activity of both azoles is greater against *C. albicans* than non-albicans *Candida* and *Aspergillus* isolates.

Table 2

TABLE 2. Susceptibilities of microorganisms tested[a]

Microorganism	Source[b]	MIC (µg/ml)[c]		
		AMB	ITZ	VCZ
A. fumigatus W73355	DMC	0.5	0.5	0.5
A. fumigatus F55064	DMC	0.5	0.25	1
A. fumigatus H52950	DMC	1	0.25	0.5
A. fumigatus T52654	DMC	0.5	0.25	0.5
A. fumigatus Z88896	DMC	1	0.5	1
Aspergillus niger S11338	DMC	4	4	1
A. niger F51729	DMC	1	4	1
A. niger I71775	DMC	1	4	1
A. niger W7884	DMC	2	0.25	0.25
A. niger T57275	DMC	2	0.5	2
Aspergillus flavus I65850	DMC	0.5	0.25	1
A. flavus I65680	DMC	8	0.25	0.5
A. flavus W69597	DMC	4	0.25	0.5
A. flavus S47511	DMC	4	0.5	0.25
A. flavus W72335	DMC	4	0.25	0.25
Aspergillus sp. M65388	DMC	0.5	0.5	0.5
Aspergillus sp. I35077	DMC	1	0.5	0.25
Aspergillus sp. R26451	DMC	2	4	0.5
C. albicans 90028	ATCC	0.02	0.031	0.015
Candida guilliermondii 9390	ATCC	0.25	0.5	0.25
Candida lusitaniae 40438	DMC	0.5	0.25	0.5
Candida parapsilosis CM205.95	DMC	0.5	0.125	0.125
Candida kefyr LK061.90	DMC	0.5	0.125	0.125
Candida stellatoidea GW575.90	DMC	0.125	0.125	0.125
Candida tropicalis 44508	ATCC	0.5	0.25	0.25
Candida glabrata 33554	ATCC	0.5	0.5	0.5

[a] Results shown are from a typical experiment. Each value represents the mean of two independent determinations. MIC determinations were repeated at least once, and the results were within ±1 dilution.
[b] DMC, Detroit Medical Center; ATCC, American Type Culture Collection.
[c] AMB, amphotericin B; ITZ, itraconazole; VCZ, voriconazole.

Growth inhibition studies were conducted to determine the cidal activity of voriconazole. Figure 1 shows the time killing curves of amphotericin B, itraconazole and voriconazole against the conidial form of n *A. fumigatus* isolate. At 24 hours a 5µg/ml concentration of itraconazole and voriconazole killed 87-96% and 95-99% of the cells, respectively. Amphotericin B produced the greatest cidal activity. Neither azole obtained a killing activity of 99.9%; the quantity of killing traditionally designated to define cidal activity. It is also of interest to note that the killing activity was determined at 24 hours not 48

hours. The cidal response should have been determined at 48 hours, as some of the fungal elements may not have had adequate time to sporulate.
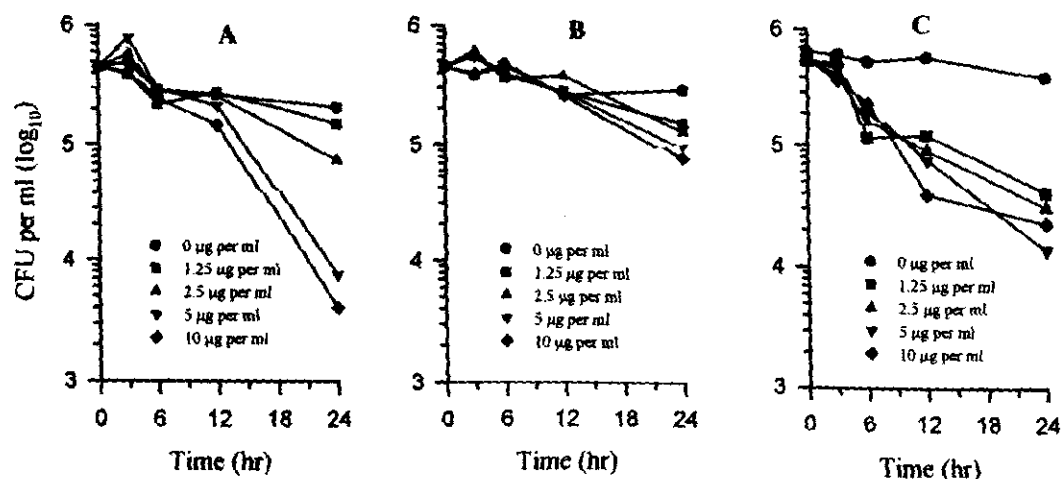
Figure 1

FIG. 1. Comparison of the fungicidal activities of amphotericin B (A), itraconazole (B), and voriconazole (C) against *A. fumigatus* W73353. Each point represents the mean of two independent determinations. Experiments were repeated three times with similar results; the data shown here are from a typical experiment

Cidal activity was also determined for various *Candida* species. Table 3 clearly demonstrates that neither voriconazole nor itraconazole are cidal against all of the *Candida* species tested.

Table 3

TABLE 3 Fungicidal or fungistatic activities of amphotericin B, itraconazole, and voriconazole against *Aspergillus* and *Candida* species[a]

Microorganism	10^5 CFU/ml at T_0	10^5 CFU/ml at T_{24} (% change)[b]		
		AMB	ITZ	VCZ
A. fumigatus (n = 5)	8.52 ± 2.67	0.071 ± 0.091 (−99.2)	0.195 ± 0.297 (−97.7)	0.096 ± 0.055 (−98.9)
A. niger (n = 5)	4.19 ± 1.85	0.074 ± 0.097 (−98.2)	0.541 ± 0.349 (−87.1)	0.224 ± 0.140 (−94.7)
A. flavus (n = 5)	9.06 ± 4.78	0.173 ± 0.288 (−98.1)	0.317 ± 0.223 (−96.5)	0.376 ± 0.243 (−95.9)
Aspergillus sp. (n = 3)	5.57 ± 5.08	0.081 ± 0.123 (−98.5)	0.207 ± 0.284 (−96.3)	0.052 ± 0.023 (−99.1)
C. albicans	7.35 ± 0.68	0.00005 (−100)	65.3 ± 5.2 (+788.4)	50 ± 7.2 (+580.2)
C. guilliermondii	12.3 ± 4.2	0.00005 (−100)	16.3 ± 7.7 (+32.5)	19.2 ± 15.6 (+56.1)
C. lusitaniae	8.5 ± 2.12	0.028 ± 0.012 (−99.7)	20.1 ± 5.9 (+136.5)	131 ± 39 (+1,441.2)
C. parapsilosis	4.0 ± 1.4	0.129 ± 0.026 (−96.8)	12.8 ± 0.28 (+220.0)	13.2 ± 2.9 (+230)
C. kefyr	25.0 ± 2.4	0.092 ± 0.025 (−99.6)	60.5 ± 20.5 (+142)	66 ± 19 (+164)
C. stellatoidea	12.5 ± 4.2	0.00005 (−100)	84.0 ± 21.4 (+572)	108 ± 43 (+764)
C. tropicalis	11.7 ± 2.5	0.0067 (−99.9)	137 ± 65 (+1,070.9)	150 ± 37 (+1,182.1)
C. glabrata	7.0 ± 0	0.00005 (−100)	152 ± 30 (+2,071.4)	46.5 ± 23.3 (+564.3)

[a] Results shown are from a typical experiment. Each value represents the mean of two independent determinations. T_0 and T_{24} denote the times immediately prior to and 24 h after addition of the antifungal agent, respectively.
[b] Percent change is the decrease or increase from the original inoculum (T_0). AMB, amphotericin B; ITZ, itraconazole; VCZ, voriconazole. All drugs were used at 5 μg/mL

In a separate study investigators (Lass-Florl et. al., 2001, AAC 45:124-128) assessed the cidal activity of voriconazole against the filamentous stage of growth for various species of *Aspergillus*. Utilizing a FUN-1 stain, which turns red when taken up by actively metabolizing fungal cells, investigators were able to differentiate live and dead hyphael elements. Table 4 shows the MFC values for voriconazole and itraconazole against the hyphael phase of growth. The MFCs against the hyphael phase of growth are comparable for voriconazole and itraconazole. These MFC values against the hyphal phase are 8-16 fold higher than the MFCs obtained when Aspergillus conidia were used to calculate the MFC. While the MFCs for voriconazole and itraconazole are similar for the majority of the isolates tested, it should be noted that some Aspergillus isolates had higher MFC for one drug or the other suggesting different mechanisms of resistance may be specific to voriconazole or itraconazole. However, additional data are needed to confirm this observation.

Table 4

TABLE 4. Susceptibility of *Aspergillus* hyphae to voriconazole and itraconazole

Aspergillus sp.[a] (no. of isolates tested)	Voriconazole MFC range (μg/ml) at 48 h	Voriconazole staining pattern(s)[b]	Itraconazole MFC range (μg/ml) at 48 h	Itraconazole staining pattern(s)
A. flavus (5)	8->16	VI__D__	4-4	I__D__
	2-2	D	2-2	D
	2-4	D	2-2	D
	8->16	V__D__	4-4	D
	2-4	D	4-8	D
A. terreus (5)	2-4	D	4-4	D
	2-4	I__D__	4-4	I__D__
	16	V__D__	2-2	D
	2-4	D	8->16	V__D__
	2-2	D	4-4	D
A. niger (5)	8-16	I__D__	8->16	V__D__
	4-4	D	4-4	D
	2-2	D	8->16	V__D__
	2-2	D	2-2	D
	2-2	D	2-2	D
A. fumigatus (5)	2-2	D	2-2	D
	2-4	I__D__	2-4	I__D__
	8->16	VI__D__	4-4	I__D__
	4-4	D	2-2	D
	2-2	D	2-4	D
Itraconazole-resistant A. fumigatus (1)	2-2	D	>16	VI__D__

[a] Each isolate was tested three times.
[b] V, Viable hyphae represented by green fluorescent hyphae with red vacuolar structures; I, impaired hyphae represented by green fluorescent hyphae and lack of red fluorescent vacuolar structures; D, dead hyphae represented by green-yellow fluorescence without any vacuolar structures. The predominant patterns are underlined.

In an in vitro study conducted by Ruhnke et.al.(1997, AAC 41:575-7) voriconazole susceptibility testing was performed against fluconazole susceptible and resistant isolates of *C. albicans* obtained from HIV positive patients with oropharyngeal candidiasis. The

NCCLS M27-T method was used where the final concentrations of voriconazole and fluconazole ranged from 0.048 to >100 µg/ml. Susceptibility results were read after 48 hours incubation. While the investigators in this study used different dilution factors than those proposed by the NCCLS, this FDA reviewer chose to evaluate the data using breakpoints closer to those proposed by the NCCLS (MIC of >64 µg/ml) to define resistance instead of the investigators proposed breakpoint of >25 µg/ml. This reviewer chose MICs of < 12.5 µg/ml and > 100 µg/ml to signify fluconazole susceptible and resistant *C. albicans* isolates, respectively.

Using these criteria 24/27 (90%) isolates with a fluconazole MIC > 100 µg/ml had a voriconazole MIC > 0.39 µg/ml. In this study there were 56 *C. albicans* isolates with fluconazole MICs < 12.5 µg/ml. The NCCLS defines fluconazole susceptible *Candida* when the MIC is < 8.0 µg/ml. Of the 56 fluconazole susceptible isolates 44 (79%) and 53 (95%) had voriconazole MICs of < 0.09 µg/ml and < 0.19 µg/ml, respectively. The MIC results as shown in Figure 2 indicate that there is good correlation between fluconazole susceptible and resistant *C. albicans* isolates and voriconazole MICs of < 0.09 µg/ml and > 0.39 µg/ml, respectively. However, it is unclear what voriconazole concentrations would be used to define the dose dependant susceptible (DDS) range.

Figure 2

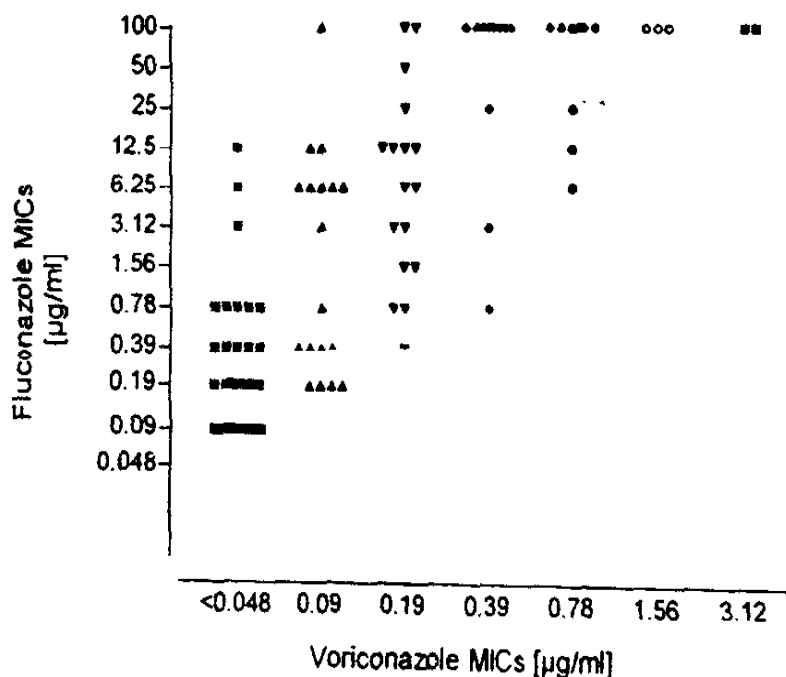FIG. 2 Scatter plots of in vitro susceptibilities to voriconazole versus fluconazole for

105 *C. albicans* isolates tested by M27-T-micro (9) (A) and HR-micro (15) (B). Each datum point represents one experiment. (A) *, $n = 40$; ▲. $n = 18$; ▼. $n = 17$; ◆. $n = 14$; ●. $n = 11$; ○. $n = 3$; ■. $n = 2$. (B) *. $n = 62$; ▲. $n = 2$; ▼. $n = 15$; ◆. $n = 7$; ●. $n = 15$; □. $n = 1$; ○. $n = 3$; ■. $n = 1$.

In vitro susceptibility testing results from Pfizer's in-house studies (data not shown) clearly show voriconazole activity against *Aspergillus* species and *Candida* species are comparable to that of itraconazole. The data from individual isolates also confirm that cross-resistance does occur between itraconazole and voriconazole for the *Candida* species. However, additional data from clinical isolates are needed to determine whether the cross- resistance pattern is partial or total as well as to determine if cross-resistance is exhibited with other fungal pathogens.

In Vivo Studies

The in vivo activity of oral voriconazole was assessed in normal and immunocompromised guinea pigs infected with *A. fumigatus* and *C. albicans isolates*. In normal guinea pigs with established systemic *A. fumigatus* infection (treatment initiated 48 hours post infection) oral voriconazole at 5 mg/kg b.i.d. produced a greater reduction in the fungal burden in kidney tissue than an equivalent dose of itraconazole. Comparable activity was seen for both drugs when administered orally at 10 mg/kg. In neutropenic guinea pigs antifungal therapy was started 1 hour post infection, mimicking a new non-established systemic infection model. After 4 days of therapy oral voriconazole at 5 mg/kg b.i.d. reduced the fungal burden in the liver of animals 2 $\log_{10}$ greater than the same dose of itraconazole. When an *A. fumigatus* isolate demonstrating reduced activity to itraconazole (itraconazole MIC 3.1 μg/ml) was used to produce a systemic infection in immunocompromised guinea pigs, voriconazole at 5 mg/kg and 10 mg/kg significantly reduced the fungal burden in liver tissue. These data suggest that voriconazole retained its activity against an *Aspergillus* strain that exhibited a particular mechanism of resistance to itraconazole.

In vivo studies were also conducted against pulmonary *A. fumigatus* infections in immunocompromised guinea pigs. Animals were treated for 7 days starting 24 hours post infection. In this acute pulmonary infection model, where few untreated infected control animals died, oral voriconazole administered at 8, 4 and 2 mg/kg b.i.d. produced approximately a 1 $\log_{10}$ greater drop in fungal burden in lung tissue than itraconazole at 16 mg/kg b.i.d.

An azole susceptible isolate of *C. albicans* was used to produce a non-established systemic infection in normal guinea pigs. Oral voriconazole, fluconazole and itraconazole were administered b.i.d. for 5 days starting 1 hour post infection. In kidney tissue a 4 $\log_{10}$ drop in fungal burden was observed in animals administered 1 mg/kg b.i.d. fluconazole, 5 mg/kg itraconazole and 5 mg/kg voriconazole.

A second study was conducted where immunocompromised guinea pigs were intravenously infected with a fluconazole susceptible *C. albicans* isolate. Oral b.i.d. dosing was initiated 1 hour post infection and continued for 4 days. The 5 mg/kg b.i.d. dose of itraconazole and the 1 and 5 mg/kg b.i.d. doses of fluconazole produced a 5 $\log_{10}$ drop in fungal burden in the kidney tissue of infected animals. Voriconazole at 5 mg/kg only reduced the fungal burden by 4 $\log_{10}$.

Voriconazole activity was assessed in immunocompromised guinea pigs intravenously infected with a fluconazole resistant strain of *C. albicans*. Oral b.i.d. doses of voriconazole at 10 mg/kg and 20 mg/kg were effective in reducing the fungal burden in the kidneys by approximately 3 $\log_{10}$. Itraconazole and fluconazole at 20 mg/kg were not effective in this animal infection model. These data suggest that the antifungal activity of voriconazole is not affected by this particular azole mechanism of resistance exhibited by this particular *C. albicans* strain. However, it should be noted that the exact mechanism of resistance was not identified or specified in the article.

Normal and immunocompromised guinea pigs were intravenously infected with *C. krusei* and *C. glabrata*, respectively. All animals were treated for 7 days starting 1 hour post infection. In these models oral voriconazole at 10 mg/kg and 20 mg/kg reduced the fungal burden in the kidney by approximately 2 $\log_{10}$. In the *C. krusei* model itraconazole and fluconazole at 20 mg/kg reduced the fungal burden in tissue by 0.4 to 0.6 $\log_{10}$. In the C. glabrata model, itraconazole at 20 mg/kg was not effective, however, fluconazole at 20 mg/kg produced a 2-$\log_{10}$ drop in kidney tissue. The activity of voriconazole was not determined in other tissues such as lung or liver.

Conclusions

Voriconazole, like fluconazole and itraconazole, inhibits the cytochrome P-450 dependent 14á-lanosterol demethylase enzyme that is responsible for the synthesis of ergosterol, a major component necessary for the integrity of the fungal cell wall. It is anticipated that the same mechanisms of resistance seen with fluconazole and itraconazole will also be exhibited by voriconazole. Thus cross-resistance between the various antifungal azole should be expected. However, the extent of this phenomenon (i.e. partial or total cross-resistance) has yet to be determined.

Voriconazole is active in vitro against *Aspergillus* and *Candida* species. In vitro susceptibility testing, employing the National Committee for Clinical Laboratory Standards (NCCLS) M27-A method, demonstrated that in general voriconazole MICs were 2 fold higher than those for itraconazole when tested against various *Aspergillus* and *Candida* species. Voriconazole and itraconazole MICs were the lowest for *Candida albicans* isolates, however, the MICs for both drugs were 8-32 fold higher for the non-albicans strains of Candida. When tested against *Aspergillus* species the MIC values for voriconazole were comparable to that of itraconazole, indicating comparable activity against these moulds. In vitro susceptibility results demonstrated good correlation between fluconazole susceptible (MIC ≤ 12.5 µg/ml) and resistant (MIC ≥ 100 µg/ml) isolates of *C. albicans* and voriconazole MIC values of ≤ 0.09 µg/ml and ≥ 0.39 µg/ml, respectively. Data from individual isolates also confirm that cross-resistance does occur between itraconazole and voriconazole for the *Candida* species.

Growth inhibition time kill studies demonstrated that the cidal activity of voriconazole was not as great as that seen with amphotericin B but was greater than that seen with equal concentrations of itraconazole when tested against the conidial form of *A. fumigatus*. When the cidal activity of voriconazole and itraconazole were tested against

the filamentous stage of growth of various *Aspergillus* species, 8-16 fold higher concentrations of both drugs were required to kill the hyphal phase of growth of the Aspergillus strains. Neither voriconazole nor itraconazole were cidal against the various *Candida* species evaluated.

Voriconazole demonstrated in vivo activity against acute systemic *A. fumigatus* and *C. albicans* infections in immunocompetent and immunocompromised guinea pigs. In newly infected guinea pigs high doses of voriconazole were comparable to itraconazole in reducing the fungal burden of *A. fumigatus* in kidney and lung tissue. Voriconazole also demonstrated activity in immunocompromised guinea pigs infected with an *A. fumigatus* strain demonstrating reduced activity to itraconazole (itraconazole MIC 3.1 µg/ml). Voriconazole exhibited activity in newly infected normal and immunocompromised guinea pigs infected with fluconazole susceptible and resistant strains of *C. albicans.* Voriconazole was also effective in reducing the mycological burden in the kidney of immunocompromised guinea pigs with acute systemic infections produced by *C. krusei* and *C. glabrata* isolates.

Pharmacology/Toxicology

The toxic effects of voriconazole were studied in rodents and nonrodents. Orally administered voriconazole was studied for up to two years, while intravenous voriconazole was studied for up to six months. The toxic effects of voriconazole included insults to the eyes, liver, heart and kidneys. Voriconazole was also shown to be a teratogen and caused adenomas (rats and mice) and adenocarcinomas (rats).

Ocular effects

Voriconazole administration produced dose-related effects in the electroretinogram of dogs exposed to voriconazole plasma levels similar to those measured in human studies. Specifically, dogs experienced reductions in the amplitude and specific time of the a-wave and reduction in the amplitude of the b-wave.

Histopathological examination of the eyes of female rats treated orally, with voriconazole, at 50 mg/kg (equivalent to a human dose of 8 mg/kg based on body surface area conversions), for 24 months, showed a small reduction in the thickness of the outer nuclear layer of the retina.

Cardiac Effects

In a number of studies, high doses of voriconazole have been shown to produce arrhythmia, including premature contractions and prolonged QT intervals. In study CG/1/99, dogs treated with voriconazole (peak plasma level, 24 µg/ml) experienced dose-related increases in QT intervals (up to 7 % increased). In study DI/102/91, nodal premature contractions were associated with voriconazole plasma levels of 86µg/ml and higher. In a one month, dog study of orally administered voriconazole, a dose of 24 mg/kg produced mean plasma levels up to 56 µg/ml on day 16. Ventricular premature contractions with bigeminy were detected in all three male dogs at this dose level.

Liver effects

Voriconazole effects in the liver included increased transaminase activity, increased liver weight, enlarged, pale or marbled liver, centrilobular hypertrophy, hepatocellular fatty change, single cell necrosis and subcapsular necrosis. Toxicity increased with total dose and so these findings were more common and more severe at higher doses or with longer treatment duration. Increases in relative liver weights were recorded after one month of oral dosing in dogs with doses as low as 3 mg/kg (equivalent to a human dose of 1.6 mg/kg based on body surface area conversions).

Liver tumors

In mice, 24-month oral administration of voriconazole at 50 mg/kg (equivalent to a human dose of 8 mg/kg based on body surface area conversions), resulted in an increase in the incidence of hepatocellular adenoma in both sexes and an increase in

hepatocellular carcinoma in males. In rats, there was an increase in hepatocellular adenomas in high dose females.

Kidney Effects

The vehicle used with voriconazole, sulpho-butly-ether-cyclodextrin (SBECD), is associated with toxic effects in the kidney. Specifically, SBECD administration was associated with cytoplasmic vacuolation in the epithelium of the renal tubules, renal pelvis and urinary bladder. These effects were seen in both drug and vehicle treated animals.

Teratogenicity

In rats, oral voriconazole at10 mg/kg (equivalent to a human dose of 1.6 mg/kg based on body surface area conversions) prolonged the duration of gestation and labor and also produced dystocia. At doses as low as 1 mg/kg (equivalent to a human dose of 0.2 mg/kg based on body surface area conversions), there was an increased incidence of variations and minor anomalies (such as supernumerary ribs) and major visceral anomalies (such as hydronephrosis). At 60 mg/kg (equivalent to a human dose of 9.5 mg/kg based on body surface area conversions), cleft palates were observed at a rate greater than that seen with control animals.

Summary

The toxic effects of voriconazole have been reasonably defined. Knowledge of these preclinical signals allowed the sponsor to monitor these potential adverse effects in their clinical trials. Visual disturbances, as well as cardiac, liver and kidney function were closely monitored.

Clinical Pharmacology

Basic Pharmacokinetics of Voriconazole

Voriconazole exhibits non-linear pharmacokinetics due to saturable metabolism. Exposure, in terms of peak plasma concentration (C_{max}) and AUC increases in a disproportionate manner with dose. For IV dosing a 1.6 fold increase in dose (from 3 mg/kg to 5 mg/kg) results in a 2.4 and 3.1 fold increase in C_{max} and AUC, respectively. For oral dosing, a 2-fold increase in dose (from 200 mg to 400 mg) results in a 2.8 and 3.9 fold increase in C_{max} and AUC respectively.

With repeated dosing, plasma accumulation of voriconazole is substantial due to the non-linear pharmacokinetics. Following multiple dosing with 3 mg/kg IV bid, AUC_τ and C_{max} values are about 2.4 and 1.5 times, respectively, that were seen after single dosing.

Steady state trough plasma concentrations with voriconazole are achieved after 5 days of oral or IV dosing without a loading dose. However, when a loading dose is used, steady state trough plasma concentrations are achieved by Day 3.

Fourteen healthy subjects were administered a loading dose of 6 mg/kg IV bid x 2 doses, followed by 3 mg/kg IV bid x 6 days, followed by 200 mg bid x 6.5 days. The resulting pharmacokinetic parameters of voriconazole are shown below:

Mean (%CV) [Range] Voriconazole Pharmacokinetic Parameters
Following Multiple Dosing

Parameter	3 mg/kg (N=14)	200 mg (N=14)
C_{max} (ng/ml)	3006 (21) [1958 – 4036]	1885 (37) [1072 – 3297]
AUC_τ (ng*h/ml)	13919 (52) [4947 – 34873]	9765 (61) [4473 – 25033]
T_{max} (h)*	1.07 (11) [1.00 – 1.25]	1.50 (29) [1.00 – 2.50]

The systemic clearance of voriconazole is calculated to be 8.7 ml/min/kg following a single 3 mg/kg IV dose and drops to 3.7 ml/min/kg after repeated dosing of 3 mg/kg IV bid for 10 days.

In general, the Phase I pharmacokinetic studies show the inter-subject variability in the estimates of C_{max} and AUC following multiple dosing of 3 mg/kg IV bid and/or 200 mg bid orally is high. Inter-subject variability (expressed as %CV) range from approximately 20% to greater than 100%. In the population pharmacokinetic analysis of 11 Phase I studies, the between subject variability (expressed as %CV) in the predicted steady state estimates of voriconazole AUC following multiple oral (200 mg Q12 hr) or IV (3 mg/kg Q12 hr) administration is 90-100%. As a consequence of this high variability, different patients treated with voriconazole at the same dose can exhibit a wide range of drug concentrations in plasma.

Absorption

The peak plasma concentration (C_{max}) of voriconazole occurs 1-2 hours after dosing in fasted state.

From the sponsor's population pharmacokinetic analysis, the oral bioavailability of voriconazole is estimated to be 96%. Due to the complexities of non-linear pharmacokinetics of voriconazole, this assessment is currently undergoing review. Mean values of C_{max} and AUC following multiple dosing were 37% and 30% lower following oral dosing (200 mg) compared to those obtained following IV dosing (3 mg/kg).

A high fat meal (1000 calories with 50 to 60% of the total caloric content from fat, 25% from carbohydrate and 15% from protein) affects the bioavailability of voriconazole. The exposure after multiple dosing, in terms of mean AUC_τ and C_{max}, is lower (24% and 34%, respectively) in the fed state as compared to the fasted state. Additionally, C_{max} occurs later in the fed state (mean of 2.5 hours fed versus 1.1 hours fasted). It is recommended that oral voriconazole be administered either one hour before or one hour after meals. This is how oral voriconazole was dosed in Phase III clinical trials.

Alterations in gastric pH do not appear to affect the absorption of voriconazole.

Distribution

The volume of distribution of voriconazole is estimated to be 4.6 L/kg.

Plasma protein binding of voriconazole is approximately 60% and is independent of concentrations achieved following single and multiple doses of 200 mg or 300 mg orally bid (approximate range 900 to 15000 ng/ml).

Metabolism

Voriconazole undergoes extensive hepatic metabolism, primarily by three cytochrome P-450 enzymes: CYP2C19, 2C9, and 3A4. *In vitro* metabolism studies using human hepatic microsomal preparations show that voriconazole is both a substrate and inhibitor of these three enzymes. No *in vitro* studies were conducted to evaluate the potential of voriconazole to induce CYP450-mediated substrate metabolism.

A mean of 1.5% of the dose is excreted unchanged in the urine following a single radiolabeled dose in healthy subjects.

The major circulating metabolite in plasma, voriconazole N-oxide, has the potential to inhibit the metabolism of CYP2C9 and CYP3A4 substrates, like the parent voriconazole. The potential for this metabolite to inhibit CYP2C19 substrates appeared to be weaker than that of voriconazole. The inhibition of CYP2C9 and CYP3A4 by voriconazole N-

oxide may contribute to the overall inhibitory effect following parent voriconazole administration.

Voriconazole N-oxide has been shown to have minimal anti-fungal activity.

Elimination

Following IV administration of a single radiolabeled dose of voriconazole, a mean of 80% of the dose is excreted in urine (as voriconazole and metabolites) and a mean of 24% in feces. Similarly, following oral administration a mean of 83% of the dose is excreted in urine and a mean of 22% in feces. Eight metabolites of voriconazole have been identified. All of which are present in urine and two are present in feces. The primary route of metabolism involves N-oxidation of the fluoropyrimidine ring to form UK-121,265 (N-oxide metabolite). The N-oxide metabolite accounts for a mean of 72% of the circulating radiolabeled metabolites in plasma. The metabolites and extent of excretion of radioactivity are similar after oral and IV administration of voriconazole.

The apparent elimination half-life of voriconazole is dose dependent. Following a 200 mg single oral dose the half-life is about 6 hours, but increases up to 12 hours after 400 mg. Following single IV dosing the apparent half-life is about 6 hours with doses of 3 mg/kg and 6 mg/kg and about 6 hours after single and multiple doses of 3 mg/kg IV bid.

Pharmacokinetics of Voriconazole in Special Populations

Age/Gender

Following a single 6 mg/kg IV dose of voriconazole, elderly subjects have a higher mean C_{max} compared to young subjects (mean ratio 121%, 95% CI: 108 to 135). Female subjects have a lower mean C_{max} compared to male subjects (mean ratio 88%, 95% CI: 79 to 98). Elderly male subjects have the highest plasma concentrations. For AUC_t, elderly males have higher values than the other three groups. Compared to young males the mean ratio is 207% (95% CI: 157 to 273) and elderly females compared to elderly males is 64% (95%CI: 48 to 85). In this study there was a difference in mean weight between males and females, therefore the effect of gender can not be separated from the effect of weight.
Following multiple dosing with 200 mg bid, the mean C_{max} and AUC   are lower in young males compared to the other three groups. The ratios of elderly male:young male are 161% (95% CI: 124 to 209) and 186% (95% CI: 126 to 273), respectively and those of young female:young male are 183% (95% CI: 141 to 238) and 213% (95% CI: 145 to 312), respectively. The differences observed in this study between young males and the other three groups were not observed in the single IV dose study.

No dosage adjustment of voriconazole is proposed on the basis of age and/or gender.

Renal Impairment

Following a single 200 mg dose of voriconazole, exposure (AUC and C_{max}) is not affected by various degrees of renal impairment from mild to severe.

Moderate renal impairment (creatinine clearance of 30 to 50 ml/min) has no consistent effect on the pharmacokinetics of voriconazole following multiple IV doses. Although mean voriconazole clearance is higher (and mean drug exposure lower) in subjects with moderate renal impairment compared with subjects with normal renal function, inter-subject variability is high and differences between groups are not statistically significant. This was corroborated by regression analysis, which demonstrated no relationship between voriconazole clearance and the level of renal function.

In subjects with renal impairment and undergoing hemodialysis sessions three times per week, the pharmacokinetic results indicate that exposure, in terms of the concentration at the end of infusion, to voriconazole is 50% lower in dialysis subjects compared with subjects with normal renal function. Voriconazole is dialyzed at a clearance rate of 121 ml/min.

No dosage adjustment of oral voriconazole is necessary in patients with renal impairment. However, accumulation of the IV excipient SBECD (see section on SBECD pharmacokinetics) in patients with moderate to severe renal failure (i.e., creatinine clearance of $\leq$ 50 ml/min), IV voriconazole is not recommended unless the benefit outweighs the risk in an individual patient. Oral voriconazole should be used instead, if possible. Since hemodialysis does not remove a significant amount of voriconazole, no dosage adjustment is necessary in patients undergoing hemodialysis.

Hepatic Impairment

Following a single 200 mg dose of voriconazole, there is a statistically significant increase in exposure to voriconazole in subjects with mild to moderate hepatic impairment (Child-Pugh Class A and B) compared to healthy normal subjects. The AUC is more than three times higher in the impaired group (Child-Pugh Class A and B) compared to the normal subjects. There is no significant difference in C_{max} between the two groups. When evaluating only the subjects with mild hepatic impairment (Child-Pugh Class A) there is still a 2.3-fold increase in exposure compared to normal subjects.

Administration of a multiple oral doses of 100 mg bid to subjects with moderate hepatic impairment (Child-Pugh Class B) results, on average, in a similar exposure (AUC_τ) to voriconazole to those subjects with normal hepatic function who received 200 mg bid.

In patients with mild to moderate hepatic impairment (Child-Pugh Class A and B) a standard loading dose of voriconazole should be given, but the standard maintenance dose should be halved. The pharmacokinetics of voriconazole in patients with severe hepatic impairment (Child Pugh Class C) has not been studied.

Patients

The pharmacokinetics of voriconazole in immunocompromised adults at risk for infection with Aspergillosis is similar to that of healthy adult subjects. In patients receiving voriconazole 300 mg bid, the AUC_τ is approximately two fold higher compared to patients receiving 200 mg bid. On the first day of dosing, the mean C_{max} is approximately two fold higher in patients receiving 300 mg bid compared to patients receiving 200 mg bid. After multiple dosing, the mean C_{max} is approximately two-fold higher in patients receiving 300 mg bid compared to patients receiving 200 mg bid. The accumulation index indicates that there is approximately a five-fold accumulation of voriconazole over 14 days of dosing. There are no apparent differences in accumulation between the 200 mg bid and 300 mg bid doses. On average steady state trough concentrations occurred between 4 and 7 days, but there was no loading dose administered in this study.

Pediatrics

From limited data, plasma profiles and concentrations of voriconazole at the end of a single IV infusion in children appear consistent with those observed in healthy adults who have received the same dose of IV voriconazole (3 mg/kg or 4 mg/kg) in other studies.

Following multiple IV dosing, mean concentrations of voriconazole and voriconazole N-oxide in children 6 years to < 12 years are higher than those for younger children (2 years to < 6 years). There is a large degree of variability in concentrations both between patients and between days within a patient.

Summary of Population Pharmacokinetic Analysis of Voriconazole

A population pharmacokinetics (Pop PK) analysis was performed using a non-linear mixed effects modeling approach on voriconazole plasma concentration-time data combined from 11 Phase I studies in healthy subjects. Subjects included both young and elderly Caucasian males and females, and young Japanese males. Data from a total of 236 subjects were used in the analysis over a range of single and repeated dosing from 1.6 to 6 mg/kg IV (Q12 hr for repeat IV dosing) and from 100 mg to 400 mg orally (Q12 hr for repeat PO dosing).

The primary objectives for the Pop PK analysis were to (1) characterize the PK and the PK variability of voriconazole, and (2) identify the relevant covariates that influence the PK variability of voriconazole.

Voriconazole is extensively metabolized primarily by three hepatic CYP450 enzymes: CYP2C19, CYP2C9, and CYP3A4. CYP2C19 accounts for a large part of voriconazole metabolism and exhibits genetic polymorphism in humans, with approximately 5% of Caucasians exhibiting a deficiency in this enzyme (i.e., poor metabolizers, PM) and

approximately 10-20% of Asians with the PM genotype. The importance of the PM genotype for voriconazole is that plasma concentrations/systemic exposure can be significantly increased compared to those individuals who are either not deficient in this enzyme (i.e., homozygous extensive metabolizers, EM) or who have partial expression of the enzyme (i.e., heterozygous extensive metabolizers, HEM). Thus, in the Phase I studies included for the Pop PK analysis, subjects were genotyped for CYP2C19 expression. There were 145/236 (61%) EM subjects, 69/236 (29%) HEM subjects, and 22/236 (9%) PM subjects. As mentioned above, PK data from Japanese subjects (65/236) were included in the analysis to increase the representation of both HEM and PM genotypes.

A two-compartment PK model with non-linear elimination adequately characterized the plasma concentration-time data. The non-linear feature of the model was to be expected since the primary route of voriconazole elimination is by saturable hepatic metabolic pathways. Thus, the model was characterized incorporating the Michelis-Menton parameters, Km (an affinity constant representing drug concentration at one-half the maximum elimination/metabolic rate) and Vmax (the maximal elimination/metabolic rate).

Effect of CYP2C19 Genotype

Overall, the analysis of the Phase I data shows that the CYP2C19 genotype (i.e., EM, HEM, and PM) is the most influential covariate on the clearance and AUC of voriconazole. CYP2C19 genotype alone accounts for approximately 30% of the overall between subject variability in voriconazole PK. Secondary covariates identified by the Pop PK analysis are gender and age of the subjects. Adding gender and age to the Pop PK model with CYP2C19 genotype accounts for additional variability in PK of approximately 10%.

Overall, the Pop PK analysis of the Phase I data indicates that PM subjects have the highest plasma voriconazole concentrations, followed by HEM subjects then EM subjects. Following oral and IV doses of 200 mg and 3 mg/kg Q12 hr, respectively, average steady state plasma concentrations and AUC estimates in PM subjects are approximately 4-times those of EM subjects, while in HEM subjects they are approximately 2-times those of EM subjects.

The variability in plasma concentrations/systemic exposure between subjects of varying genotype is quite high. The between subject variability (expressed as %CV) in the predicted steady state estimates of voriconazole AUC following oral ($20_{0\ mg}$ Q12 hr) or IV (3mg/kg Q12 hr) administration is >90%. This implies that the range of plasma exposures to voriconazole will show considerable overlap between subjects.

As was mentioned earlier, plasma accumulation of voriconazole following repeated dosing is extensive. The Pop PK analysis also shows that the magnitude of this accumulation is dependent on CYP2C19 genotype. As might be expected, plasma accumulation following 200 bid orally is highest for PM subjects (approximately 6-times

vs. single dose), intermediate for HEM subjects (approximately 3-times vs. single dose), and lowest for EM subjects (approximately 2-times vs. single dose).

It is noteworthy to mention that no Pop PK analyses were performed in the Phase III clinical program because the Phase III trials were already ongoing when it was discovered that the CYP2C19 genotype was the major covariate influencing the PK of voriconazole. It was not possible to retrospectively assess the genotype of patients in the Phase III trials.

Effects of Gender and Age

From the Pop PK analysis of the Phase I data, it appears that both gender and age may have some additional influence of the PK of voriconazole. Females appear to have higher plasma exposure than males (i.e., AUC 30% to 100% higher) and greater extent of plasma accumulation than males (i.e., accumulation ratio 20% to 50% higher) at the 200 mg Q12 hr dose regimen. A similar trend is apparent for elderly females vs. elderly males. However, plasma voriconazole concentration-time data collected from 10 Phase II/III studies of patients (N=1053) indicates that plasma concentrations of voriconazole are relatively similar between young females and young males and between elderly females and elderly males. There is a trend for both elderly males and females to have slightly higher plasma concentrations than their younger counterparts.

The proposed labeling recommends no adjustment in voriconazole dosage for either gender or age.

Effect of Body Weight

Although not identified as a significant covariate in the Pop PK model, there is a weak relationship between weight and voriconazole AUC following repeated dosing. With repeated dosing for longer periods of time (i.e., > 1-week duration), the AUC estimates show a trend to increase as the subjects' body weights became lower. Subject body weights in the Phase I datasets ranged from approximately 50 kg to 95 kg. Thus, although subjects with body weights < 50 kg were not included in the Pop PK analysis, a decision was made for the Phase III studies to reduce the dose by one-half in patients with body weights < 40 kg. The plasma concentration data obtained from the 10 Phase II/III trials of patients shows similar average steady state plasma concentrations following oral voriconazole administration between patients with body weights < 40 kg who received one-half the recommended dose versus those patients with body weights ≥ 40 kg.

The proposed labeling recommends a reduction in the recommended voriconazole dosage by one-half
patients with body weights < 40 kg.

Race

Influence of race in the Pop PK of the Phase I data was limited to an analysis of Japanese versus Caucasian race. Race has no significant influence on voriconazole PK after accounting for CYP2C19 genotype and body size/weight in the model.

Summary of Pediatric Population Pharmacokinetic Analysis for Voriconazole

A population pharmacokinetic analysis of voriconazole plasma concentration data was performed using data from one single dose and one multiple dose Phase I studies in pediatric patients ranging in age from 2 to 11 years (N = 35). Two single IV doses of voriconazole (3 mg/kg and 4 mg/kg) were evaluated in one study. For the multiple dose study, a loading dose of 6 mg/kg IV bid x 2 doses followed by maintenance IV doses of 3 mg/kg or 4 mg/kg was investigated.

The pediatric subjects were genotyped for CYP2C19 expression. There were 2/35 (6%) homozygous poor metabolizers (PM), 11/35 (31%) heterozygous extensive metabolizers (HEM), and the rest were homozygous extensive metabolizers (EM).

The sponsor's overall conclusion from this analysis is that pediatric subjects have similar exposure to adults given comparable doses of voriconazole. The review of this analysis is currently ongoing.

Drug Interactions

In vitro hepatic microsomal studies indicate that voriconazole is both a substrate and inhibitor of the CYP2C9, CYP2C19, and CYP3A4 enzymes in the liver. *In vitro* comparisons between voriconazole and ketoconazole or itraconazole demonstrate that voriconazole is a substantially less potent inhibitor of CYP3A4 metabolism than the other two azoles.

The potential for *in vivo* drug interactions was evaluated using drugs that are most likely to be co-administered with voriconazole in the clinical setting of fungal infections and that are also substrates, inhibitors, and/or inducers for these three CYP450 enzymes. In addition, other studies were conducted where an interaction might be expected on a mechanistic basis.

The Effect of Other Drugs on the Pharmacokinetics of Voriconazole

The most significant interactions and recommendations for co-administration are listed in Table 1. All the interacting drugs were chosen to investigate CYP450-based mechanisms of interaction. The following drugs were also selected based on the potential for CYP450-based interactions with voriconazole, but did not result in a significant interaction: omeprazole, indinavir, erythromycin, and cimetidine. Azithromycin and ranitidine were also selected to evaluate their effect on voriconazole based on non-CYP mechanisms of interaction and did not show a significant interaction with voriconazole.

TABLE 1
Effect of Other Drugs on the Steady State PK of Voriconazole
Interaction Studies Investigating CYP450-Based Mechanisms

Study # Subjects	Mech.	Drug Dose & Duration	Vori Dose & Duration	Results		Sponsor's Recommendations for Co-Administration *(undergoing review)*
				Vori Cmax Point Est. (90% CI)	Vori AUC Point Est. (90% CI)	
150-228 N=8 healthy young males	CYP450 Induction	**Rifampin** 600mg QD x 23 days	200mg BID x 14 days	↓92% ↓(90%, 94%)	↓96% ↓(94%, 97%)	Rifampin is **contraindicated** with voriconazole
			400mg BID x 7 days	↓66% ↓(46%, 79%)	↓81% ↓(76%, 85%)	
150-228 N=8 healthy young males	CYP450 Induction	**Rifabutin** 300mg QD x 23 days	200mg BID x 14 days	↓67% ↓(57%, 77%)	↓79% ↓(68%, 85%)	If benefit outweighs risk, rifabutin may be co-administered with voriconazole if the voriconazole maintenance dose is increased to 5mg/kg IV BID or to 400mg PO BID (from 200mg PO BID)
			350mg BID x 7 days (N=3)	↓4% (↓55%, 5%↑)	↓32% (↓54%, 0%)	
150-1024 N=10 healthy young males	CYP450 Induction	**Rifabutin** 300mg QD x 14 days	400mg BID + Rifabutin x 7 days	2.0 (1.6, 2.6) vs. Vori 200mg BID + PBO*	1.87 (1.5, 2.4) vs. Vori 200mg BID + PBO	
150-233 N=10 healthy young males	CYP450 Induction (primarily CYP3A4)	**Phenytoin** 300mg QD x 21 days	200mg BID x 14 days (N=10)	↓49% ↓(34%, 61%)	↓69% ↓(60%, 76%)	Increase voriconazole maintenance dose to 5mg/kg IV BID or to 400mg PO BID (from 200mg PO BID)
			400mg BID x 7 days (N=7)	1.34 (0.89, 2.0) vs. Vori 200mg BID Alone	1.39 (0.97, 1.98) vs. Vori 200mg BID Alone	

*PBO = Placebo

The Effect of Voriconazole on the Pharmacokinetics of Other Drugs

The most significant interactions and recommendations for co-administration with voriconazole are listed in Table 2. All the interacting drugs were chosen based on their potential for a CYP450-based interaction. The potential for a non-CYP450 mediated interaction between mycophenolic acid and digoxin was also studied. The pharmacokinetic parameters of these drugs did not change significantly when co-administered with voriconazole.

TABLE 2
Effect of Voriconazole on the PK of Other Drugs
Interaction Studies Investigating CYP450-Based Mechanisms

Study # Subjects	Mech.	Drug Dose & Duration	Vori Dose & Duration	Results		Sponsor's Recommendations for Co-Administration *(undergoing review)*
				Drug Cmax Point Est. (90% CI)	**Drug AUC Point Est. (90% CI)**	
150-239 N=13 healthy young males	CYP2C9 Inhibition	**Warfarin 30mg Single Dose**	300mg BID x 12 days	PT ↑8 sec ↑(5, 12 sec)	AUEC for PT ↑929 sec•hr ↑(574, 1283 sec•hr)	Monitor PT / other suitable anti-coagulation tests; adjust warfarin dosage if warranted
150-241 N=6 healthy young males	CYP2C9 Inhibition	**Phenytoin** 300mg QD x 17 days	400mg BID x 10 days	1.67 (1.44, 1.93) vs. Phenytoin + PBO*	1.81 (1.56, 2.10) vs. Phenytoin + PBO	Monitor phenytoin concentrations and monitor for phenytoin related AEs with co-admin
150-1013 N=16 healthy young males	CYP2C9 / CYP3A4 Inhibition	**Omeprazole** 40mg QD x 7 days	200mg BID x 7 days	2.16 (1.78, 2.64) vs. Omeprazole + PBO	3.81 (3.28, 4.41) vs. Omeprazole + PBO	Reduce omeprazole dose by 1/2 when initiating therapy with voriconazole
150-1024 N=10 healthy young males	CYP3A4 Inhibition	**Rifabutin** 300mg QD x 14 days	400mg BID + Rifabutin x 7 days	2.95 (2.19, 3.97) vs. Rifabutin + PBO	4.31 (3.47, 5.36) vs. Rifabutin + PBO	(**See also Table 1**) Monitor CBC and AEs associated with rifabutin (e.g., uveitis) when co-admin with vori
150-1009 N=12 healthy young males	CYP3A4 Inhibition	**Tacrolimus** 0.1 mg/kg Single Oral Dose	200mg BID x 7 days	2.17 (1.86, 2.52) vs. Tacrolimus + PBO	3.21 (2.69, 3.83) vs. Tacrolimus + PBO	Reduce tacrolimus dose by 1/3 when initiating therapy with voriconazole; monitor tacrolimus concentrations frequently
150-1015 N=15 healthy young males	CYP3A4 Inhibition	**Sirolimus** 2mg Single Oral Solution Dose	200mg BID x 9 days	6.56 (5.73, 7.52) vs. Sirolimus + PBO	11.14 (9.87, 12.58) vs. Sirolimus + PBO	Sirolimus is **contraindicated** with voriconazole
150-235 N=7 male	CYP3A4 Inhibition	**Cyclosporine** BID x 8 days	200mg BID x 8 days	1.13 (0.90, 1.41)	1.67 (1.47, 1.98)	Reduce cyclosporine dose by 1/2 when

and female renal transplant patients		(patients on stabilized therapy)		vs. Cyclosporine + PBO	vs. Cyclosporine + PBO	initiating therapy with voriconazole; monitor cyclosporine concentrations frequently

*PBO = Placebo

Drugs Not Studied

Voriconazole may be predicted to interact with other drugs based on results from *in vitro* and *in vivo* studies of similar drug substrates/inhibitors/inducers for a given CYP450 enzyme (or enzymes). Therefore, it is recommended that the following drugs be contraindicated with voriconazole:

- Carbamazepine and Long Acting Barbiturates: Potent inducers of CYP450 metabolism and likely to significantly reduce voriconazole plasma concentrations/systemic exposure.

- Ergot Alkaloids: Inhibition of metabolism by voriconazole can lead to increased ergot alkaloid concentrations.

Careful monitoring and/or dosage adjustment of the following drugs is recommended with voriconazole co-administration:

- Sulfonylureas, Statins, Benzodiazepines, Vinca Alkaloids: CYP450 substrates, where increased plasma concentrations are likely when co-administered with voriconazole via metabolic inhibition.

Summary of Pharmacokinetic/Pharmacodyanmic (PK/PD) Analysis for Voriconazole

As discussed previously, the pharmacokinetics of voriconazole in humans are characterized by non-linearity due to saturable metabolism, wide intersubject variability, and extensive hepatic metabolism by CYP450 enzymes, namely CYP2C19, which exhibits genetic polymorphism. Because of these features, patients treated with voriconazole at a given dose can be exposed to a wide range of drug concentrations in plasma. Therefore, exploratory pharmacokinetic/pharmacodyanmic (PK/PD) analyses were performed by the sponsor to evaluate the relationships between plasma exposure to voriconazole (i.e., C_{max}, AUC, mean plasma concentrations) and safety and efficacy endpoints. Liver function test (LFT) results and visual adverse events were chosen as the relevant safety endpoints. The efficacy endpoint was a sponsor-assessed response at end of treatment. Two separate PK/PD analyses were conducted, one with data from healthy subjects in Phase I studies and the other with data from patients in Phase II/III trials. The sponsor's analyses included graphical and tabular presentations as well as multiple linear and logistic regression, and survival analyses (for time-to-event data).

Results from Phase I Studies in Healthy Subjects

Twenty-nine (29) Phase I studies were used in the analyses and included PK and PD (i.e., clinical laboratory test) data from 547 subjects treated with single and/or multiple doses (PO and/or IV) of voriconazole and 55 subjects with placebo (PBO). Of the 547 voriconazole-treated subjects, multiple doses were administered to 402 subjects. Doses ranged from 0.9 mg/kg to 6 mg/kg IV and from 100 mg to 400 mg PO. The following covariates were explored in the PK/PD modeling of the Phase I data: time on treatment, age, gender, weight, study, health status (healthy subjects or subjects with renal/hepatic impairment), route of administration, and use of loading dose.

Relevant PK parameters from the Phase I studies are summarized in the tables below:

Voriconazole C_{max} and AUC after Single and Multiple Doses

Subject Demographics	Single Dosing (N=300)		Multiple Dosing (N=457)	
	Mean C_{max} (μg/mL)	Mean AUC (μg$\cdot$hr/mL)	Mean C_{max} (μg/mL)	Mean AUC (μg$\cdot$hr/mL)
All Young Healthy Subjects*	2.43 ± 2.40 (99%) [9.16]	10.6 ± 14.3 (135%) [85.7]	2.33 ± 1.73 (74%) [9.46]	15.6 ± 16.7 (107%) [133.2]
Young Healthy Males	2.06	8.7	2.19	14.4
Young Healthy Females	5.09	24.3	3.93	29.5
Renal Impairment / Hepatic Impairment (Cirrhotic)	1.17	11.0	Not Reported	Not Reported

*Mean ± SD (%CV); [Maximum Value]

Voriconazole Average Plasma Concentrations and C_{max} at Steady State after Multiple Doses

	Average Steady State Conc. N=402 (μg/mL)	Maximum Conc. (C_{max}) N=402 (μg/mL)
Minimum	**0.14**	**0.45**
25th Percentile	0.58	1.58
Median	**0.95**	**2.25**
75th Percentile	1.91	3.30
Maximum	**11.1**	**9.46**

<u>Exposure – LFT Relationships from Multiple Dose Studies in Healthy Subjects</u>
Increases in both ALT and AST from baseline were related to the increases in the C_{max} and the AUC of voriconazole. Modeling the PK/PD relationships for ALT and AST indicated that C_{max} and AUC are strongly associated with these two LFT indices. Increases in ALT and AST appeared to be most pronounced starting at C_{max} values of approximately 5.0 to 6.0 μg/mL and at AUC values starting at approximately 40 to 50 μg$\bullet$hr/mL. In the few subjects with the greatest changes in ALT or AST from baseline, the C_{max} and AUC values were also the highest at approximately 8.0 μg/mL and 80 μg$\bullet$hr/mL and higher, respectively. The greatest changes in ALT and AST were approximately a 1700% and 700% increase from baseline, respectively, at C_{max} and AUC

of approximately 8.5 μg/mL and 85 μg•hr/mL, respectively. From the relationships of ALT and AST with C_{max}, it would appear that maximum plasma concentrations of voriconazole should not exceed 5.0 μg/mL following multiple dose administration.

C_{max} and AUC of voriconazole were also positively associated with the increase in alkaline phosphatase (ALKP), but the relationships were not as strong as with ALT and AST. Unlike the relationships with ALT and AST, there appeared to be no clear threshold values for C_{max} or AUC of voriconazole with ALKP. The greatest increase in ALKP from baseline was approximately 85% at a C_{max} and AUC of approximately 8.5 μg/mL and 85 μg•hr/mL, respectively.

For total bilirubin, there was little or no relationship with C_{max} or AUC of voriconazole.

It was difficult to adequately assess the time course of LFT abnormalities with respect to voriconazole dosing. This was mainly because the majority of abnormalities were associated with one study. In this study subjects received multiple dose voriconazole that were higher than those usually recommended (i.e., 5 mg/kg IV and 400 mg bid orally) for 14 days duration. Other repeat dose studies employed lower doses (i.e., 3 mg/kg IV and 200 mg bid orally) for a shorter duration of 7 days. Nonetheless, the results from this study suggested that LFT abnormalities may occur after longer duration of therapy (i.e., 7 days or more) and may be associated with higher voriconazole doses and/or plasma concentrations.

Exposure – Visual Adverse Events (VAE) Relationships in Healthy Subjects
Visual adverse events (VAE) from the Phase I studies were classified and evaluated as "any VAE" or as "enhanced/altered visual perception". The overall incidences of these two classifications were higher following multiple doses than with single dose administration. The incidence of any VAE was 46% with multiple doses vs. 24% with single doses; for enhanced/altered visual perception, the incidence was 23% vs. 11%.

Overall, there was a positive association between C_{max} and AUC and the incidence of any VAE and enhanced/altered visual perception with single dose administration of voriconazole. The association between C_{max} and AUC and visual adverse events was weaker with multiple dose administration. It is important to note that there was considerable overlap in the C_{max} and AUC estimates for those subjects reporting VAE and those who did not report any VAE. Nonetheless, mean estimates of both PK parameters were higher for those subjects reporting VAE versus those who did not.

Results from Phase 2/3 Studies in Patients

There were 10 Phase II/III clinical efficacy and safety trials included in the PK/PD analyses. The safety population consisted of 1053 patients who had at least one PK sample drawn for determination of voriconazole concentration in plasma.

Plasma voriconazole concentrations were determined from blood samples collected at various time points during treatment. More than one blood sample may have been

collected during a specific dose interval or on different days of treatment. The PK data were summarized as weekly mean plasma concentrations, with one plasma concentration per weekly window that was 7 days in duration. The median number of weekly mean plasma voriconazole concentrations per subject ranged from 1 to 5 across the studies. The concentration data for voriconazole are summarized in the table below.

Summary Statistics for Voriconazole Plasma Concentrations at Steady State from Phase II/III Studies

	N	Average Conc. (µg/mL)	Maximum Conc. (C_{max}) (µg/mL)
Minimum	**1053**	**<0.1**	**<0.1**
25th Percentile	1053	1.17	1.80
Median	**1053**	**2.49**	**3.40**
75th Percentile	1053	4.38	5.83
Maximum	**1053**	**20.4**	**20.4**

Mean plasma voriconazole plasma levels summarized for all Phase II/III patients over bands of 1.0µg/mL (i.e., 0-1, 1-2, 2-3 µg/mL, etc.) are as follows:

Concentration Bands (µg/mL)	Approximate Frequency (Total N=1053)	Approximate Cumulative Frequency
0 (<0.1) to 1.0	22%	22%
1.0 to 2.0	20%	42%
2.0 to 3.0	17%	59%
3.0 to 4.0	13%	72%
4.0 to 5.0	9%	81%
5.0 to 6.0	7%	88%
6.0 to 7.0	4%	92%
7.0 to 8.0	3%	95%
8.0 to 9.0	3%	98%
>9.0 to 21.0	3%	~100%

As can be seen, the majority of patients (80-90%) have mean plasma levels of 6 µg/mL and less, with about half of the patients with levels of 3 µg/mL and less. Approximately 10-15% of patients had mean concentrations greater than 6 µg/mL.

Exposure – LFT Relationships from Multiple Dose Studies in Patients
Overall, there was an association between the increase in LFT abnormalities and plasma voriconazole concentrations. Median voriconazole plasma levels were generally higher in those patients with increased ALT, AST, alkaline phosphatase (ALKP), and total bilirubin levels than those patients with normal values at weekly intervals from 1 to 12 weeks of voriconazole therapy. The results of the longitudinal logistic regression (odds ratio) and time to event (Cox proportional hazard ratio) modeling analyses are shown in the tables below:

Summary Statistics from Longitudinal Logistic Regression for LFT Abnormalities

	Odds Ratio per 1.0 μg/mL Increase in Voriconazole Plasma Conc.	Lower 95% Bound	Upper 95% Bound
ALT	1.07	0.97	1.19
AST	1.13	1.06	1.20
Alkaline Phosphatase	1.16	1.08	1.25
Bilirubin	1.17	1.08	1.27

Summary Statistics from Time to Event Analyses for LFT Abnormalities

	Hazard Ratio per 1.0 μg/mL Increase in Voriconazole Plasma Conc.	Lower 95% Bound	Upper 95% Bound
ALT	1.09	1.02	1.17
AST	1.14	1.07	1.20
Alkaline Phosphatase	1.15	1.06	1.25
Bilirubin	1.16	1.07	1.25

In the longitudinal regression analyses, the model predicted odds of approximately 7%, 13%, 16%, and 17% in abnormalities of these LFT's for every 1.0 μg/mL increase in plasma voriconazole levels. These odds were statistically significant for AST, ALKP, and total bilirubin ($p<0.001$); the ALT odds ratio was not significant. The time to event analyses showed similar results with respect to the relative risk of LFT abnormalities occurring for every 1.0 μg/mL increase in plasma voriconazole levels. In addition, plasma voriconazole levels and the hazard ratio/relative risk of all LFT abnormalities were significantly associated ($p<0.01$).

Unlike the PK/PD analyses for the subjects in Phase I studies, no threshold concentration(s) for the increase in LFT's were apparent for the patients in the Phase II/III trials. However, it should be noted that maximum frequencies of LFT abnormalities occurred at the highest plasma concentration bands, i.e., 8 to 9 μg/mL and ≥9 μg/mL. The maximal reported occurrences of abnormalities in AST, ALT, ALKP, and total bilirubin over the 12-week evaluation period were approximately 10%, 8%, 5%, and 14%, respectively. The 95% confidence intervals for the statistical ratios shown in the tables above indicated that the odds or risk of an LFT abnormality with every 1 μg/mL increase in plasma voriconazole concentrations may be as low 0% and as high as approximately 30%.

Exposure – Visual Adverse Events (VAE) Relationships from Multiple Dose Studies in Patients
The frequency of visual adverse events varied from approximately 11% to 52% in the 10 Phase II/III trials. Overall, it appeared that median plasma voriconazole concentrations were higher in those patients with VAE than in those patients without VAE over the majority of the weekly evaluation intervals. The incidence in VAE went from

approximately 10 to <20% at plasma concentrations ranging from 0 to 3 µg/mL, then increased to approximately 25% to 40% at voriconazole plasma concentration bands starting at 3 to 4 µg/mL and up to >9 µg/mL. Thus, a threshold concentration of approximately ≥3 µg/mL for VAE in the Phase II/III patients was apparent.

The longitudinal logistic regression analysis revealed a statistically significant relationship between plasma voriconazole concentration and the odds of a VAE (p=0.011). The model predicted approximately a 5% increase in the odds of a VAE occurring for every 1.0 µg/mL increase in plasma voriconazole concentration (95% CI: 1%, 8%).

The percentage of patients with VAE was the highest in the first week of voriconazole dosing ranging from approximately 20% to 40% over plasma concentrations from 0 to >6µg/mL. The incidence decreased by week 2 to approximately 2 to 4% and remained diminished over the subsequent weekly intervals out to week 24.

Exposure – Efficacy Relationship from Multiple Dose Studies in Patients
The efficacy population consisted of 453 patients who had a certainty of baseline fungal infection categorized as "definite" or "probable" and were assessed in the sponsor's Voriconazole Efficacy Response Assessment database (VERA). The efficacy outcome variable was success or failure at the end of treatment. The VERA was a tool that harmonized the efficacy assessments of patients with the same pathogens, but who were enrolled in different studies. These studies commonly had slightly different entry and evaluation criteria. Patients from all studies contributing to the overall efficacy analysis were assessed according to standardized criteria which included the primary underlying condition, hematological risk factors, infecting organism, certainty of infection and outcome at end of therapy.

The sponsor noted that the primary PK/PD analysis for efficacy was conducted omitting one study because of the very high response rate observed (approximately 90%) compared with other studies. After excluding patient data from this study, 280 patients from 6 Phase II/III trials remained in the primary analysis population.

The logistic regression analysis of the primary population (N=280) revealed a statistically significant negative linear relationship between mean plasma voriconazole concentration and the odds of success (p=0.005). Logistic regression analysis using threshold concentration as the explanatory variable showed that the odds ratio for a successful outcome was greatest at the 0.5 µg/mL threshold (ratio: 1.46; 95% CI: 0.63, 3.41). The proportion of successes in patients with mean voriconazole plasma levels below 0.5 µg/mL was approximately 46% compared to approximately 56% of successes in patients with mean plasma levels above 0.5 µg/mL.

An interesting observation was that the mean plasma voriconazole concentration threshold of 6.0 µg/mL was significantly associated with lower success (p=0.001). The odds ratio was lowest at the 6.0 µg/mL threshold (ratio: 0.16; 95% CI: 0.06, 0.47). The proportion of successes in patients with mean voriconazole plasma levels below

6.0µg/mL was approximately 58% compared to approximately 26% of successes in patients with mean plasma levels above 6.0 µg/mL. Further exploration of this latter effect at plasma levels of 6.0 µg/mL was conducted by the sponsor. The finding that treatment failures in these subjects occurred early led to a clinical review that identified hepatic impairment, poor prognosis and early dose escalation as confounding factors.

Overall, due to confounding clinical factors, no definitive conclusions may be made from these 6 Phase II/III studies regarding the relationship between plasma concentrations of voriconazole and efficacy.

Exposure – Visual Adverse Events (VAE) Relationships in Patients
Basic Pharmacokinetics of Voriconazole N-oxide

The mean exposure to voriconazole N-oxide, in terms of C_{max} and AUC, achieved after single and multiple oral dosing with 200 mg bid is compared to that of voriconazole in the following table:

Mean (%CV) Plasma Pharmacokinetic Parameters

		Voriconazole	Voriconazole N-oxide
C_{max} (ng/ml)	Day 1 (n=6)	967 (31)	1580 (23)
	Day 10 (n=5)	2704 (59)	2810 (15)
AUC_{τ} (ng*h/ml)	Day 1 (n=6)	3986 (53)	13290 (21)
	Day 10 (n=5)	18877 (81)	30240 (15)

Following multiple oral dosing with voriconazole 200 mg bid, the C_{max} for voriconazole N-oxide occurs around 2-4 hours, the half-life is about 9 hours, and the mean amount of N-oxide excreted in urine over 12 hours is low (16% of the daily dose).

As with voriconazole, the pharmacokinetics of voriconazole N-oxide do not appear to be affected by renal impairment. Exposure to voriconazole N-oxide following a multiple dose IV voriconazole dosing regimen was similar in subjects with moderate renal impairment (creatinine clearance 30 to 50 ml/min) and subjects with normal renal function.

In subjects with renal impairment and undergoing hemodialysis sessions three times per week, exposure, in terms of the concentration at the end of infusion, to voriconazole N-oxide is 69% lower than in subjects with normal renal function.
The exposure, in terms of mean C_{max} and AUC_{τ} for voriconazole N-oxide in subjects with moderate hepatic impairment (Child-Pugh Class B) is approximately half that seen in subjects with normal hepatic function. These findings are consistent with an approximately 50% lower mean apparent oral clearance of voriconazole in subjects with moderate hepatic impairment.

Basic Pharmacokinetics of Sulphobutyl Ether b-Cyclodextrin (SBECD)

SBECD is a solubilizing excipient used in formulation of IV voriconazole. The exposure to SBECD, in terms of mean C_{max} and AUC_τ, following 6 mg/kg voriconazole (96 mg/kg SBECD) IV bid x 2 doses, then 3 mg/kg voriconazole (48 mg/kg SBECD) IV bid x 5.5 days, is 3200 ng/ml and 3600 ng*h/ml, respectively. The C_{max} occurs about 3 hours after dosing. (150-1016)

There is no accumulation of SBECD between Days 1 and 10, the half-life is about 1.6 hours on Days 1 and 10, and the volume of distribution is about 0.2 L/kg.

However, renal impairment has a significant effect on the pharmacokinetic parameters of SBECD. In subjects with moderate renal impairment (estimated creatinine clearance of 30 to 50 ml/min) the mean C_{max} and AUC increased by almost 50% and 4-fold, respectively, compared to subjects with normal renal function. There was strong correlation between SBECD clearance and creatinine clearance. SBECD has been associated in animal studies with toxic effects in the kidney, specifically cytoplasmic vacuolation in the epithelium of the renal tubules, renal pelvis, and urinary bladder. Therefore, IV voriconazole (containing SBECD) is not recommended in patients with moderate to severe renal impairment (creatinine clearance $\leq$ 50 ml/min) unless the benefit outweighs the risk in an individual patient. Oral voriconazole should be used instead, if possible.

In subjects with renal impairment and undergoing hemodialysis sessions three times per week, the pharmacokinetic results indicate that exposure, in terms of the concentration at the end of infusion, to SBECD is higher (455%) in these subjects than in subjects with normal renal function. SBECD is dialyzed at a clearance rate of 55 ml/min.

Efficacy

The basis of evidence to support the indication of invasive aspergillosis comes from a comparative study 307/602, a non comparative study 304, and a historical control study 1003 which was used as the comparator to study 304.

Treatment of Invasive 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) 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 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.

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 end of randomized therapy and Week 12, and the cause of death (where applicable) in a blinded fashion. Three hundred ninety two patients were enrolled in Study 307/602: 199 voriconazole treated patients and 193 amphotericin B treated patients. 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. The Division is in agreement with the results of this study as presented by the applicant. Global response at week 12 as assessed by the DRC was the primary efficacy endpoint. Voriconazole had a satisfactory global response rate of 52.8% compared to 31.6% for the amphotericin B regimen. The 95% confidence interval for the difference in satisfactory response rates (voriconazole- amphotericin B) stratified by protocol was (9.6, 33.6). Since the lower limit of the confidence interval was greater than –20%, voriconazole is considered to be non-inferior to the amphotericin B regimen. Additional sensitivity analyses were performed and the robustness of these results hold.

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).

Study 304

Study 304 was a multi-center uncontrolled study of voriconazole for the treatment of invasive aspergillosis conducted in Europe. Patients in this study could receive treatment with voriconazole as primary therapy or as salvage therapy. One hundred thirty seven patients were enrolled into the study, 72 primary patients and 65 salvage patients. The expert evaluable population consisted of 112 patients, 58 primary and 54 salvage. The expert's satisfactory global response at end of therapy was 49.1% overall. For primary therapy patients, the satisfactory response rate was 60.3% and for salvage therapy patients it was 37.0%.

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 (5 days or less prior therapy) voriconazole treated patients of study 304. In order to provide the most comparable population, patients 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. Satisfactory global response rates at end of therapy were 52.0% for voriconazole patients and 25.0% for the historical controls. The probability of survival at day 90 was 0.554 voriconazole patients and 0.417 for the historical controls.

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. When the U.S. patients are removed from the historical control group, the global response rate becomes 29.3% and the probability of survival at day 90 becomes 0.573. 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.

The concern about the comparability of the voriconazole treated patients to those of the historical control played a large role in the ability to assess the overall efficacy of

voriconazole in the treatment of invasive aspergillosis, that is, prior to the submission of the results of the randomized comparative study. The results of Study 304, however, do not contradict those seen in the randomized comparative study.

Clinical Microbiology

Study 307/602

Clinical trials 150-307 and 150-602 were designed such that subjects with definite or probable acute invasive aspergillosis, based on disease criteria defined by the Mycoses Study Group (MSG), were eligible to receive either amphotericin B or voriconazole. Because the design of the two clinical trials was essentially identical (307 conducted in Europe and 602 conducted in N. and S. America) the data from both studies were pooled. As per the design of the clinical trials, the data review committee (DRC) determined the global response at week 12. Subjects were categorized as having a satisfactory or unsatisfactory response. Patients with satisfactory responses included those subjects that had a complete or partial response at week 12. Subjects categorized as unsatisfactory had at week 12 a clinical response of either, stable, indeterminate or failure.

The microbiology data show that there were 50/77 (65%) and 41/68 (60%) MITT subjects in the voriconazole and amphotericin B arms, respectively, whom had a single species of Aspergillus recovered from a clinically relevant site. In the voriconazole arm 43/50 (86%) of the infections were due to *A. fumigatus* of which 21/43 (49%) had a satisfactory response at week 12 of the study (See table 1). Only 27/41 (66%) of the MITT subjects in the amphotericin B arm had documented fungal infections due to *A. fumigatus*. A total of 5/27 (19%) had a satisfactory global response at week 12. These response rates in subjects with documented fungal infections clearly demonstrate that voriconazole is more effective in the treatment of fungal infections due to *A. fumigatus* than amphotericin B. However, a major confounding factor in the assessment of the microbiologic efficacy data was the incidence of multiple fungal species recovered from clinically relevant sites. A total of 27/77 (35%) of the subjects in the voriconazole arm and 27/68 (40%) of the subjects in the amphotericin B arm had multiple fungi (yeasts and moulds) from clinically relevant sites.

The response rates in subjects with *A. fumigatus* and other yeasts or moulds were also assessed. In the amphotericin B and voriconazole arms there were 21 and 20 MITT subjects, respectively, meeting this criteria. A satisfactory response was obtained in 6/15 (40%) subjects in both treatment arms who had yeast recovered from clinically relevant sites in conjunction with *A. fumigatus*. In the voriconazole arm a satisfactory response was seen in 4/8 (50%) subjects co-infected with *C. albicans* and 0/4 subjects with *C. glabrata*. While in the amphotericin B arm there were only 4 subjects with *C. albicans* and 0 with *C. glabrata*. One of the 4 subjects with mixed infections due to *C. albicans* responded in the amphotericin B arm. The remaining subjects had various other Candida species isolated from clinical sites, including *C. krusei*, *C. tropicalis*, *C. kyfer*, *C. inconspicum*, *Saccharomyces cerrevisia* and *Geotrichum*.

There were 5 and 7 subjects in the voriconazole and amphotericin B arms, respectively, that had *A. fumigatus* and other moulds isolated from clinically relevant sites. Three of the 5 subjects in the voriconazole arm had a Zygomycete isolated. All 5 subjects in the voriconazole arm had an unsatisfactory response to voriconazole. The majority of the mixed mould cultures in the amphotericin B arm were due to other Aspergillus species of which 3/7 had a satisfactory response by week 12.

In both treatment arms there was a large number of subjects with multiple fungal species being recovered from clinically relevant sites. These numbers were larger than expected. The various combinations of yeast and moulds found in the MITT patients impedes ones ability to directly compare the efficacy of voriconazole to amphotericin B against *Aspergillus* species because many of the fungal isolates (i.e. *C. glabrata*, Zygomycetes, *C. tropicalis)* recovered from clinically relevant sites are typically not susceptible to azole or polyene antifungal agents. However, these data do suggest that voriconazole is not effective against infections due to the Zygomycetes. It is also of interest to note that all of the *C. glabrata* co-infections did not respond to voriconazole either and that there were twice as many *C. albicans* co-infections in the voriconazole arm versus the amphotericin B arm (8 versus 4).

Subjects with culture confirmed infections due to non-fumigatus species of *Aspergillus* were small in both treatment arms. The most common non-fumigatus species of Aspergillus isolated in both treatment arms was *A. flavus*. None of the five subjects in the voriconazole arm with non-fumigatus Aspergillus infections had a satisfactory response while 3/7 ((43%) of those treated with amphotericin B had a satisfactory response. Other Aspergillus species found in the voriconazole arm included 1 *A. terreus*, 3 *A. niger*, 2 Aspergillus species, 1 *A. glacus* and 1 *A. nidulans.* In the amphotericin B arm there were 2 *A. terreus*, 4 *A. niger* and 4 Aspergillus species. While infections due to non-fumigatus *Aspergillus* are increasing it is impossible due to the low incidence of each species to determine the efficacy of voriconazole. However, it is of interest to note that all five of the subjects with *A. flavus* did not respond favorably to voriconazole. Additional clinical cases will have to be evaluated before the therapeutic effect of voriconazole against these non-fumigatus species of *Aspergillus* can be determined.

Table 1

Distribution of Fungal strains Isolated from Patients enrolled in Study 307/602

Fungal Species	**Response to Voriconazole**			**Response to Amphotericin B**		
	Satis-factory	**Unsatis-factory**	**Total**	**Satis-factory**	**Unsatis-factory**	**Total**
Aspergillus fumigatus	21,1$\downarrow$	21	43	5	21	27
Aspergillus flavus		3,2^{Y}	5	2,1$^{Y}\downarrow$	3,1$\uparrow$	7
Aspergillus niger	1^{Y},1	1	3	1	2,1^{Y}	4
Aspergillus terreus		1	1		1, 1$\uparrow$	2
Aspergillus nidulans	1$^{Y}\downarrow$		1			0
Aspergillus glacus	1^{Y}		1			0
Aspergillus species (Not identified)		1^{Y},1	2	1	3	4
A. fumigatus and *A. flavus*		1^{M}	1	2		2
A. fumigatus and *A. niger*	1^{Y},1		2		3	3
A. fumigatus and *A. terreus*	1$\downarrow$		1		1	1
A. flavus and other mould and yeast			0	1	1	2
A. fumigatus and $\geq$1 yeast	6	9	15	5,1$\downarrow$	8,1$\uparrow$	15
A. fumigatus and $\geq$1 non-fumigatus mould		3^{Z}	3	1^{Z}		1

Y=patient who had the defining mould and yeast isolated from clinically relevant sites.

M=patients who had the defining mould and a non-aspergillus mould isolated from clinically relevant sites.

Z=patients who had the defining mould and a Zygomycete isolated from clinically relevant sites.

9= MITT subjects who initially had a satisfactory response at week 12 but had an unsatisfactory response by wk 16.

8= MITT subjects who initially had an unsatisfactory response at week 12 but had a satisfactory response by wk 16.

Of the 145 MIIT subjects with culture confirmed *Aspergillus* infections in vitro susceptibility testing was conducted against only 113 *Aspergillus* isolates. Thirty two isolates were identified at the local laboratory and were not sent for susceptibility testing. The NCCLS M38-P method to employed to determine voriconazole, itraconazole and amphotericin B MICs. Greater than 90% of the *A. fumigatus* isolates had voriconazole MICs between 0.125-0.25 µg/ml. Itraconazole MICs for these isolates ranged from 0.06 to 0.125 µg/ml. The majority of the non-fumigatus species of *Aspergillus* isolated during these clinical trials had voriconazole and itraconazole MICs between 0.5-1.0 µg/ml and 0.06-0.25 µg/ml, respectively. The non-fumigatus Aspergillus species had a 2-4-fold higher voriconazole MIC than for the *A. fumigatus* isolates. Four Zygomycetes were recovered from subjects enrolled in these studies, the voriconazole and itraconazole MICs were 8.0 µ/ml and 1.0 µg/ml, respectively.

The ability to accurately interpret voriconazole susceptibility data obtained from clinical studies 307/602 is complicated by two issues. The first issue is that there is no approved antifungal susceptibility testing methods for the filamentous fungi. The second issue is that breakpoints for the approved azoles and polyenes have not been established for the filamentous fungi. Employing the NCCLS M38-P (a proposed) method, voriconazole MICs for the various Aspergillus species were 2 to 4-fold higher than those found for itraconazole. Higher voriconazole and itraconazole MICs seen for the non-fumigatus species versus *A. fumigatus* isolates may help explain why there were more unsatisfactory response rates seen in those subjects versus those with culture confirmed infections due to *A. fumigatus*. The 8 to 16-fold higher voriconazole and itraconazole MICs obtained with the Zygomycetes versus *A. fumigatus* also correlates with the lack of efficacy seen in the treatment of infections due to these fungi. Additional susceptibility data from subjects with infections due to non-fumigatus species of *Aspergillus* will have to be assessed before the overall efficacy of voriconazole can be determined for the non-fumigatus species of *Aspergillus.*

Study 304

In study 304 there were 137 clinically evaluable subjects. Subjects were classified as having a satisfactory or unsatisfactory global response. For patients infected with *A. fumigatus* 21/40 (53%) had a successful response when treated with voriconazole (See table 2). There were 19 subjects that had infections due to non-fumigatus Aspergillus species. Only 6/19 (32%) subjects with non-fumigatus Aspergillus isolates had a satisfactory response.

Table 2

Pathogens producing infections in clinically evaluable patients enrolled in study 304

	Satisfactory	Unsatisfactory	Unevaluable	Total
A. fumigatus	21	19	0	40
A. fumigatus + mould	2	6	0	8
A. fumigatus + yeast	3	6	0	9
A. flavus	2	7		9
A. terreus	0	2		2
A. niger	3	1		4
A. nidulans	1	3		4
Aspergillus species (no ID)	9	5	2	16
Total	41	49	2	92

These data support those findings found in Aspergillus study 307/602 where voriconazole is effective against *A. fumigatus* but not the other Aspergillus species. This is of particular importance as *A. nidulans*, *A. terreus* and *A. flavus* are new and emerging fungal pathogens.

Organisms found in clinical sites	Satisfactory	Unsatisfactory	Unevaluable	Total
No Micro	11	8	3	22
No Aspergillus	3	1	1	4
Histopath(+)only	8	6	1	15
A. fumigatus	21	9	0	41
A. fumigatus + mould	2	6	0	8
A. fumigatus + yeast	3	6	0	9
A. flavus	2	7	0	9
A. terreus	0	2	0	2
A. niger	3	1	0	4
A. nidulans	1	3	0	4
Aspergillus species (no ID)	9	5	2	16
Total	63	54	7	137

Empiric Antifungal Therapy of Febrile Neutropenic Patients

Introduction

Pfizer Pharmaceuticals is seeking approval of voriconazole (VFEND) injection and tablets for the indication of empiric therapy of febrile neutropenia. The specific wording requested by the applicant in their proposed labeling states that voriconazole is effective in "empirical treatment of presumed fungal infections in febrile immunocompromised patients". In support of this indication, Pfizer has submitted data from one non-inferiority study (Study 603) of voriconazole compared to liposomal amphotericin B (Ambisome, L-AMB) in patients with neutropenia secondary to cancer chemotherapy. The results of the study showed an overall response rate of 26% (108/415) in the voriconazole group and 30.6% (129/422) in the L-AMB group using a composite endpoint in a non-stratified analysis. Using this raw data, the difference in the point estimated of the efficacy of the two therapies was -4.5% with a 95% confidence interval of -10.6% to +1.6%. The study was designed to stratify patients by risk of fungal infection and previous use of antifungal prophylaxis. The stratified results yielded an overall response rate using the same composite endpoint of 23.7% in the voriconazole group and 30.1% in the L-AMB group. The difference in the point estimates the two therapies in the stratified analysis was –6.08% with a 95% confidence interval of –12.0% to –0.1%. The pre-specified lower bound of the 95% confidence interval used to define non-inferiority in this trial was –10%. Thus, in both the raw and stratified analyses, voriconazole did not meet the statistical definition of non-inferiority.

Statistical considerations are one part of the decision making process used by the FDA in determining whether a drug is safe and effective for a given indication. However, the FDA also considers other potential efficacy and safety issues related to a new drug in the light of currently available therapy for that indication. The committee will be asked to consider the potential advantage of fewer numbers of breakthrough infections in the voriconazole group and the adverse experience profile of voriconazole compared to other available therapies for empiric antifungal therapy in febrile neutropenic patients. The committee will also be asked to consider the adverse experience profile of voriconazole given that many patients will receive empiric therapy who will not have fungal infections.

Two other drugs have been FDA-approved for the indication of empiric therapy of fungal infections in febrile neutropenic patients. The studies in febrile neutropenic patients with both liposomal amphotericin B for injection (Ambisome) and itraconazole injection and oral solution (Sporanox) used similar, although not identical, study designs to the current voriconazole Study 603. However, both the Ambisome and Sporanox trials resulted in higher cure rates and both trials met their pre-specified statistical definitions of non-inferiority.

This part of the background package for the committee will discuss the pertinent highlights of Study 603. This section will also discuss some of the potential reasons for the lower cure rates observed in this trial and relate these to the previous studies

performed with Ambisome and Sporanox. This section will also highlight some of the secular trends in cancer chemotherapy and bone marrow transplantation that may impact on the current study and on the overall indication of empiric antifungal therapy in febrile neutropenic cancer patients.

Study 603

Study 603 was designed as a prospective, centrally randomized, open label, comparative (non-inferiority), multicenter study. The applicant conducted the study from March 7, 1998 through September 9, 1999 at 45 centers in the United States and Canada. Eligible subjects were male or female patients 12 years of age or older with neutropenia induced by cancer chemotherapy or bone marrow/ peripheral stem cell transplantation. Subjects had at least 96 hours of neutropenia (defined as a neutrophil count of <500 cells/mm^3 and <250 cells /mm^3 in the 24 hours preceding randomization), temperature of $\geq$ 38°C, and at least 96 hours of systemic empirical antibacterial therapy prior to randomization. Subjects were randomized to receive either voriconazole or L-AMB in a 1:1 ratio. Randomization was stratified according to risk of fungal infection and previous systemic anti-fungal prophylaxis. The study defined high-risk patients as those with allogeneic transplants or relapsed leukemia.

This study was not blinded. The applicant cited the differences in the physical natures of the intravenous formulations of voriconazole and L-AMB and the lack of a suitable oral formulation of L-AMB as reasons for conducting this as an open label trial. The applicant considered administration of dummy infusions of the excipient for each agent to maintain blinding. However, the applicant considered it unethical to administer second intravenous infusions to critically ill patients who may have potential difficulties with fluid balance. The absence of blinding in this trial could introduce potential bias into the study. The toxicities of amphotericin B related products, both renal insufficiency and infusion related events, is well known and clinicians may be more likely to discontinue therapy in patients receiving L-AMB. On the other hand, the efficacy of amphotericin B and related products has been well-established over years of use and clinicians may be more likely to discontinue therapy with a new agent if they are concerned about it's efficacy.

Although the administration of study drug was not blinded, a blinded data review committee (DRC) evaluated all subjects with diagnoses of documented baseline and/or breakthrough deeply invasive fungal infections (DIFIs). Reviewers in the DRC were not provided with information on treatment allocation or dosage.

Subjects who were randomized to voriconazole received an intravenous loading dose of 6mg/kg q12h for the first two doses followed by 3mg/kg IV bid. Subjects randomized to voriconazole received intravenous study drug for a minimum of three days. After three days of intravenous voriconazole, further empirical treatment could be given using oral voriconazole (200mg bid for subjects $\geq$40 kg, 100mg bid for subjects <40 kg). Empirical oral therapy (or continued empirical intravenous therapy) was administered for a maximum of up to three days after recovery from neutropenia (RFN). Subjects diagnosed with baseline or breakthrough DIFI could receive a maximum of 12 weeks of therapy.

L-AMB was administered via intravenous infusion at a dose of 3mg/kg/day, the FDA approved dose for this indication. The protocol specified that L-AMB be infused at a maximum rate of 3mg/kg per hour (i.e. at least 1 hour for a 3mg/kg dose, at least 2 hours for a 6mg/kg dose) if administered through a peripheral vein. Subjects randomized to L-AMB were treated with L-AMB until up to three days after RFN, or resolution of baseline or breakthrough DIFI for a maximum of 12 weeks of therapy, whichever came first.

Dosage of either treatment could be increased in presence of a baseline or breakthrough DIFI, persistence of fever and no improvement in baseline pulmonary infiltrates at least 24 hours after initiation of treatment, or persistence of fever and new pulmonary infiltrates at least 24 hours after initiation of treatment.

For subjects unable to tolerate an escalated dose of intravenous voriconazole, the dose could be reduced by 1mg/kg increments back to the original 3mg/kg q12h. For subjects who were unable to tolerate an escalated dose of oral voriconazole, the dose could be reduced by 50mg decrements to a minimum dose of 200mg bid (subjects weighing ≥40kg) or 100mg PO bid (subjects weighing <40kg).

For subjects randomized to L-AMB unable to tolerate the 3mg/kg/day dose, the dose could be reduced to 1.5mg/kg/day. For L-AMB subjects who were unable to tolerate the escalated 6mg/kg/day dose, the dose could be reduced to 3mg/kg/day and then to 1.5mg/kg/day. Note that the dose of L-AMB could be reduced to less than the original dose but the voriconazole dose could not be reduced below the original dose.

Investigators assessed the overall response to empirical therapy for patients without baseline of breakthrough DIFIs at least seven days after the last dose of study medication. There was no end of treatment (EOT) study assessment for subjects without baseline or breakthrough infections (the empirical therapy only group). The time point for assessment of the overall response for subjects with baseline or breakthrough documented DIFI was at least seven days after the last dose of study medication.

The primary endpoint for this study was the composite variable denoted as overall response. Investigators categorized the overall response as *SUCCESS* if all of the following five criteria were met (regardless of whether subjects were treated empirically or for a baseline DIFI):

1) Survival for at least seven days after discontinuation of study medication

2) Absence of breakthrough fungal infection during the period of neutropenia and for at least seven days after discontinuation of study medication

3) Defervescence during the period of neutropenia or prior to EOT, whichever 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

Investigators categorized the overall response as *FAILURE* if <u>any one</u> of the following criteria was met:

1) Death within seven days after discontinuation of study medication

2) Documentation of breakthrough fungal infection during the period of neutropenia or within seven days after discontinuation of study medication

3) Persistent fever during the period of neutropenia or prior to EOT, whichever occurred first

4) Discontinuation of 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 Stable or Failure at EOT

The definitions of the various components of the overall response to therapy as defined by the applicant were as follows:

- Recovery from neutropenia was defined as ANC >250 cells/mm$^{3.}$
- Time to recovery from neutropenia was defined as the date and time of the first sample with an ANC result of >250 cells/mm^3.
- Defervescence (resolution of fever) during neutropenia was defined as all temperatures of <38.0°C or 100.4°F (excluding those taken within one hour after the infusion of pyrogenic agents) for a continuous period of at least 48 hours preceding recovery from neutropenia (absolute neutrophil count >250 cells/mm^3).
- Time to defervescence was defined as the time from the first dose of study medication until the first time the oral temperature (or equivalent) measured <38.0°C or 100.4°F.
- Baseline infection was defined as any deeply invasive fungal infection that is diagnosed based on results of tests performed at baseline or up to 24 hours after study entry fungal infection.
- Breakthrough infection was defined as any deeply invasive fungal infection diagnosed based on results of tests performed from 24 hours after study entry up to seven days after discontinuation of study medication.

The primary analysis population for this study was the Modified Intent to Treat population (MITT) defined as all patients who had received as least one dose of the study drug and who had sufficient clinical information available to confirm the investigator's assessment of overall response.

The applicant's background package for the committee contains the pertinent information on disposition of patients, patient demographics, and results of the study. Of note, the overall response rate was 26% (108/415) in the voriconazole group and 30.6% (129/422) in the L-AMB group using a composite endpoint in a non-stratified analysis. The difference in the point estimates of the efficacy of the two therapies was -4.5% with a

95% confidence interval of -10.6% to +1.6%. The stratified results yielded an overall response rate using the same composite endpoint of 23.7% in the voriconazole group and 30.1% in the L-AMB group. The difference in the point estimates of the two therapies in the stratified analysis was –6.08% with a 95% confidence interval of –12.0% to –0.1%. The pre-specified lower bound of the 95% confidence interval used to define non-inferiority in this trial was –10%. Thus, in both the raw and stratified analyses, voriconazole did not meet the statistical definition of non-inferiority.

The applicant calculated the sample size for this trial based on expected success rate of approximately 50%, based on the success rates in the trial of empiric therapy of febrile neutropenic patients used to obtain FDA approval for Ambisome when compared to conventional amphotericin B deoxycholate (AMB-D). The lower than expected cure rates could have been one reason for the failure of voriconazole to meet the statistical definition of non-inferiority in this trial.

The main reason for failure in this trial was that many patients did not meet the protocol-specified definition for absence of fever prior to resolution of neutropenia. Only 33% (135/415) of voriconazole treated patients and 36%(154/422) of L-AMB treated patients fulfilled this criteria. This is lower than the rate of resolution of fever in previous trials of empiric antifungal therapy of febrile neutropenic patients with itraconazole compared to AMB-D or L-AMB compared to AMB-D (see following section comparing Study 603 to prior studies in febrile neutropenia). Part of the reason for the high numbers of failures in this component of the composite endpoint may be a more stringent criteria used to define defervescence in this trial. In Study 603, a patient was required to be afebrile for no less than 48 hours prior to recovery of neutropenia. In a previous trial of itraconazole versus AMB-D, their was no time requirement attached to resolution of fever i.e. a patient could be afebrile for less than 48 hours prior to recovery from neutropenia and still fulfill the criteria for a successful outcome. Another reason for the lower than expected rate of patients becoming afebrile prior to recovery of neutropenia was that the duration of neutropenia after randomization to study drug was shorter in this trial compared to previous trials. In the trial of itraconazole vs. AMB-D and the trial of L-AMB versus AMB-D, the median duration of neutropenia was approximately 10 days in both the test and control arms of these trials. In Study 603, the median duration of neutropenia after randomization to study drug was 5.5 days in each treatment arm.

Since many patients who receive empiric antifungal therapy will never have an invasive fungal infection it is important to evaluate the numbers of patients with breakthrough infections in patients receiving empiric therapy. Although one of the components of the composite endpoint, this study was not powered to specifically determine a difference in the number of breakthrough infections. The number of breakthrough infections in the voriconazole arm was 1.9% (8/415) and 5.1% (21/422) in the L-AMB arm. Of the eight (8) breakthrough infections in the voriconazole arm, 4 were caused by Aspergillus species. Thirteen (13) of the 21 breakthrough infections in the L-AMB group were caused by Aspergillus species. Although there were fewer numbers of breakthrough infections in the voriconazole arm, the small number of overall breakthrough infections precludes a definitive comparison.

One of the difficulties with composite endpoints in general is that it merges failures due to toxicity and failures due to lack of efficacy of the drug and may mask important differences between drugs. It is useful, therefore, to examine the numbers of patients discontinued from therapy due to lack of efficacy and the numbers of patients discontinued due to toxicity, keeping in mind the previously-mentioned limitations of a non-blinded trial. In the voriconazole arm, there were 5.3% (22/415) patients discontinued due to lack of efficacy compared to 1.2% (5/422) in the L-AMB arm. More failures due to lack of efficacy were due to persistent fever in the voriconazole group (14/22) than the L-AMB group (2/5). In the voriconazole arm, 4.6% (33/421) of subjects were permanently discontinued due to toxicity compared to 5.5%% (23/422) of subjects in the L-AMB arm. Of note, 5 patients in the voriconazole group were discontinued due to renal toxicity compared to none in the L-AMB group. This observation is complicated by the lack of specific criteria in the protocol for defining renal insufficiency and the absence of specific laboratory criteria for discontinuation of study drug. There were 14 patients temporarily discontinued from therapy in the voriconazole arm compared to 59 patients temporarily discontinued in the L-AMB arm. However, only permanent discontinuations were included as part of the overall composite endpoint. Again, the study was not powered to determine differences in the individual components of the composite endpoint and the small numbers in each group make definitive conclusions difficult.

Other FDA-Approved Drugs for Empiric Antifungal Therapy in Febrile Neutropenic Patients

Two other drugs are FDA-approved for the indication of empiric antifungal therapy of febrile neutropenic patients; intravenous liposomal amphotericin B (Ambisome, L-AMB) and the intravenous and oral solutions formulations of itraconazole (Sporanox). Both L-AMB and itraconazole presented a single study in support of the indication of empiric antifungal therapy in febrile neutropenia patients. The study with L-AMB was a double blind randomized controlled prospective study compared to amphotericin B deoxycholate (AMB-D). The itraconazole study was an open label study comparing intravenous itraconazole followed by itraconazole oral solution versus AMB-D. The important details of the three studies of empiric antifungal therapy in febrile neutropenic patients are presented in the following table.

Details of Empiric Antifungal Therapy Trials

Trial	Trial design	Comparator	Dates
Ambisome N=343 (ITT)	Double blind, randomized	Amphotericin B deoxycholate N=344	January 29, 1995 – July 10, 1996
Itraconazole N=179	Open, randomized	Amphotericin B deoxycholate N=181	March 22, 1996 – December 4, 1997
Voriconazole N=415	Open, randomized	Ambisome N=422	March 7, 1998 - September 9, 1999

The basic study design of the studies used for registration of these two drugs was similar to that used in the current trial with voriconazole. The studies with L-AMB and the itraconazole both used a composite endpoint composed of the same 5 variables used in Study 603. Two multi-disciplinary workshops held in 1994 and 1995 discussed the endpoints for trials of empiric antifungal therapy in febrile neutropenic patients. At these meetings, the participants agreed that the composite endpoint would be most appropriate for studies in this indication.

When one compares results across various trials, one must take into account differences in details in study design and patient demographics as well as secular trends in the care of neutropenic patients over time. Although the basic study designs of all three trials in empiric antifungal therapy of febrile neutropenic patients are similar, there are important differences in the details and demographics of the trials. The itraconazole study excluded patients who received allogeneic bone marrow transplants. The current voriconazole study included patients who received peripheral stem cell transplants that may result in shorter duration of neutropenia. The inclusion criteria for Study 603 also specified that patients have a WBC less than 250 cells/mm^3 in the 24 hours prior to randomization. The other two trials included patients with WBC less than 500 cells/mm^3 but did not include the more stringent criteria in the 24-hour pre-randomization time window. This may also have contributed to the shorter duration of neutropenia after randomization in the voriconazole trial.

There were also some differences in the statistical requirements for the trials. The lower bound of the 95% confidence interval used to define non-inferiority for the itraconazole trial was –15%. The lower bound of the 95% confidence interval used to define non-inferiority in the L-AMB and voriconazole trial was –10%. As the lower bound of the 95% confidence interval specified prior to initiation of a trial impacts on the planned sample size necessary to demonstrate non-inferiority, this in part explains the lower number of patients in the itraconazole trial compared to the L-AMB and voriconazole trials.

Most importantly for the purposes of comparison to Study 603, the definition of defervescence prior to recovery from neutropenia was different in the L-AMB and itraconazole trials. The voriconazole Study 603 required that patients be afebrile for 48 continuous hours prior to recovery from neutropenia. The L-AMB and itraconazole trials did not specify an associated time requirement defervescence prior to recovery from neutropenia.

Although the duration of neutropenia prior to randomization to antifungal study drug was similar in all three trials, the duration of neutropenia after randomization was shorter in the voriconazole trial compared to patients in the L-AMB and itraconazole trials. The shorter duration of neutropenia after randomization in the voriconazole trial resulted in less opportunity for patients to deferevesce. The data on duration of neutropenia in the three trials is presented in the following tables.

Duration of Neutropenia Prior to Randomization

Drug	Study Drug Mean	Range	Control Mean	Range
Ambisome	10	N.A*.	10	N.A.*
Itraconazole	8.9	0,7	9	-5 - 39
Voriconazole	10.7	2.4 - 71.5	9.7	2.4 - 59.7

*data not available

Duration of Neutropenia After Randomization

Drug	Study Drug Median	Range	Control Median	Range
Ambisome	10	N.A.*	10	N.A.*
Itraconazole	10	0 - 35	8	0 - 29
Voriconazole	5.46	0.042 - 57.838	5.52	0.033 – 63.121

*data not available

The combination of the time requirement for defervescence in Study 603 and the shorter duration of neutropenia in this study may explain the lower number of patients in the voriconazole trial who experienced fever resolution prior to recovery from neutropenia in compared to the previous trials with L-AMB and itraconazole. As the failure to defervesce during the period of neutropenia was also the most common reason for failure in Study 603, this may explain the lower overall success rates in Study 603 compared to the previous trials and the failure of voriconazole to meet the statistical definition of non-inferiority in this trial. The following tables present the data on fever resolution and overall success rates in the three trials.

Fever resolution during period of neutropenia

Trial	Study Drug	Comparator
Ambisome	58% (199/343)	58% (200/344)
Itraconazole	73% (131/171)	70% (127/181)
Voriconazole	33% (135/415)	36% (154/422)

Success Rates for Trials in Empiric Antifungal Therapy in Febrile Neutropenic Patients

Drug	Comparator	Success Rate	Comp Success	Delta	95% CI
Ambisome	AMB-D	49.9% (171/343)	49.1% (169/344)	-10%	-6.8%,+8.2%
Itraconazole	AMB-D	47% (84/179)	38% (68/181	-15%	-1%, +20%
Voriconazole	L-AMB	26.0% (108/415) – raw 23.7% - stratified	30.6% (129/422) 30.1%	-10%	-10.6%, 1.6% -12.0%, -0.1%

Background on Empiric Antifungal Therapy in Febrile Neutropenic Patients

To determine whether a drug can be considered non-inferior to a control regimen for a give indication, one must first consider the relative advantage of any drug therapy over placebo in that indication. The lower bound of the 95% confidence interval of the difference between the mean efficacy rates of two drug therapies used to define statistical non-inferiority should not be greater (more negative) than the advantage of the control regimen over placebo. In other words, if a control regimen is 10% more effective than placebo then the lower bound of the 95% confidence interval used to define non-inferiority when this control is compared to a new therapy would have to be less negative than –10%. With this in mind, it is worth examining the rationale for empiric antifungal treatment of febrile neutropenic patient and the previous placebo controlled or no-therapy controlled trials in this indication.

Empiric antifungal therapy for febrile neutropenic cancer patients has evolved as the standard of care over the past 20 years. Autopsy studies of leukemia and bone marrow transplant patients performed in the 1980's and early 1990's showed that fungal infections were identified in 25% of each of these patient groups post-mortem[1]. Many patients with invasive fungal infections at autopsy had no pre-mortem evidence of invasive fungal infections. The greatest risk of fungal infection was in patients with neutropenia, especially the group with neutrophil counts less than 100 cells/mm^3. This laid the groundwork for studies of empiric antifungal therapy in neutropenic patients.

This standard of care for empiric antifungal therapy in febrile neutropenic patients was based on several studies from the 1970's and 1980's, which showed a lower incidence of fungal infections in patients receiving empiric antifungal therapy compared to those receiving no antifungal therapy. In the first trial by Pizzo et al.[2] performed between 1975 and 1979, patients who were receiving cephalothin, gentamicin and carbenicillin were randomized after 7 days of such therapy to discontinue the antibacterial therapy or continue the same antibacterial therapy with or without the addition of AMB-D. The group that received empiric AMB-D in addition to continued antibacterial therapy had 1 breakthrough fungal infection in 18 patients. This one infection was a fatal pulmonary infection due to *Petrillidium* (now *Pseudoallescheria*) *boydii* documented at autopsy. In the group receiving continued antibacterial therapy alone, there were 5 breakthrough fungal infections in 16 patients. Two of these patients died, one with disseminated Aspergillus infection and one with a disseminated Candida and Aspergillus mixed infection. The other 3 infections were severe necrotizing Candida mucositis, Candida esophagitis (with no mention of documentation by endoscopy) and Candida pneumonia. Whether there is a true clinical entity of Candida pneumonia remains debatable even today. The small number of patients in each group, the very small numbers of breakthrough infections, and the questionable diagnoses in several of the patients make

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[1] Bodey G etal. Fungal infections in cancer patients: An international autopsy survey. Eur J Clin Microbiol Infect Dis 1992;11:99-109

[2] Pizzo PA et al. Empiric antibiotic and antifungal therapy for cancer patients with prolonged fever and granulocytopenia. Am J Med 1982; 72: 101-110.

comparison of the groups difficult. In this trial, the median duration of neutropenia after randomization was 24 days, considerably longer than that seen in more contemporary studies of this indication.

In a second study performed by the European Organization for Research and Treatment of Cancer (EORTC)[3], patients receiving various antibacterial regimens were randomized after 4 days of antibacterial therapy to receive AMB-D or no antifungal therapy. Among the 68 patients randomized to receive AMB-D, there was a single documented fungal infection, a fungemia due to *Candida tropicalis.* In the group that did not receive antifungal therapy, there were 6 fungal infections among 64 patients (two fatal candidemias, one caused by *C. tropicalis* and one by *C. albicans*; two severe oropharyngeal *C. albicans* infections; one fatal pulmonary *Aspergillus fumigatus* infections and one fatal disseminated *Mucor* species infection). Although there was no difference between the groups in terms of overall survival at 30 days, there were no deaths attributed to fungal infections in the patients who received AMB-D compared to 4 deaths due to fungal infection in the patients who did not receive empiric antifungal therapy. Again, the number of breakthrough fungal infections in this trial was small.

It is difficult to determine a numerical value for the benefit of empiric antifungal therapy over no therapy based on these two studies. However, despite the statistical limitations of these trials, empiric antifungal therapy in febrile neutropenic patients became the standard of care over the succeeding decades. Although AMB-D became the standard of treatment, the drug was never FDA –approved for this indication. AMB-D, however, was approved in 1956, prior to the current regulations used in drug approval.

Several important changes in therapy have occurred over the intervening years which one should also take into account when comparing current trials of empiric antifungal therapy in febrile neutropenic patients to older studies in this indication. In the EORTC trial a number of patients were receiving off-label antifungal prophylaxis with drug such as ketoconazole and oral AMB-D. The efficacy of these drugs in preventing fungal infections in neutropenic patients was not clear. Today, many bone marrow transplant patients receive therapy with oral triazole drugs such as fluconazole. Fluconazole is indicated to decrease the incidence of candidiasis in patients undergoing bone marrow transplantation who receive cytotoxic chemotherapy and/or radiation therapy. A study of prophylactic fluconazole in neutropenic bone marrow transplantation patients demonstrated a reduction in invasive fungal infections from 18% in the placebo arm to 1% in the fluconazole arms. One must question how the widespread use of fluconazole may change the epidemiology of fungal infections in persistently febrile neutropenic patients receiving antibacterial therapy. It is possible that early Candida infections may become less frequent and later infections with Aspergillus or other filamentous fungi may begin to emerge. Alternately, fungal infections may be limited to high risk patients such as those receiving allogeneic bone marrow transplantation or those who have received several courses of cytotoxic therapy such as patients treated for relapses of leukemia.

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[3] EORTC International Antimicrobial Therapy Cooperative group: Empiric antifungal therapy in febrile granulocytopenic patients. Am J Med 1989;86:668-672.

Another recent development is shortening in the duration of neutropenia in patients receiving cytotoxic chemotherapy. This has the effect of shortening the period during which patients are at greatest risk of developing fungal infections. In the study by Pizzo et al. in the 1970's , the duration of neutropenia after randomization to study drug was 24 days. This is much longer than the 10 days of neutropenia after randomization in the trial supporting the use of itraconazole in febrile neutropenia and even shorter still than the 5.5 days of neutropenia in the current voriconazole trial. The shorter duration of neutropenia may be a consequence of increased use of growth factor therapy to stimulate recovery from neutropenia and/or the advent of peripheral stem cell transplants.

Conclusion

In summary, as assessment of the benefit of any antifungal drug over placebo for the treatment of febrile neutropenic patients should take into account: 1) the lack of statistical power in the original studies of the indication, 2) the widespread use of more effective prophylaxis, 3) the shorter duration of neutropenia in patients currently treated with cytotoxic therapy, 4) the efficacy of the drug in patients with proven infections especially those due to Candida species and Aspergillus species and 5) the potential limitation of benefit to a specific subset of patients at higher risk of fungal infections. The committee should consider the factors in light of the adverse experience profile (presented in the following section of this document) and the knowledge that many patients who receive an antifungal drug for empiric antifungal therapy while febrile and neutropenic will never develop a fungal infection. In such cases the patient would be exposed to potential adverse effects with no benefit.

Clinical Safety

The safety of voriconazole has been assessed in a clinical program incorporating healthy volunteers, empiric antifungal therapy of patients with persistent fever and neutropenia, and patients with fungal infections in both compassionate use studies and controlled clinical trials. In June 2001, Pfizer submitted an updated Integrated Summary of Safety which encompasses a safety database of 3467 healthy volunteers and patients. Although global safety was assessed as part of this NDA review, the present section of the Advisory Briefing package will focus on selected areas that are characteristic of the safety profile of this new drug. Adverse events involving vision, liver function, cardiac toxicity and skin will be addressed.

Ocular Safety

Summary of Ocular Findings

1)   Abnormal vision has generally been reported in more than one out of every three subjects. Included in these ocular reports are decreased vision, photophobia, altered color perception and ocular discomfort.

2)   Results from Study 1501004 demonstrated that in subjects dosed with voriconazole 400 mg q12 x 1 day and 300 mg q12h for 27 additional days there were ocular abnormalities throughout the treatment period consistent with a drug effect on both the retinal rods and cones.

These effects were noted in:
a)   ERG testing (decreased b-wave amplitude, decreased implicit time).
b)   Farnsworth Munsell testing – increased scores in blue-green
c)   Humphrey Visual Field Test

3)   Baseline exams were normal, and the control group remained normal. As demonstrated by the mean scores for the group, the decreased visual function was present after the first day of voriconazole and continued through the 28 days of drug administration. Testing 14 days after the end of treatment generally demonstrated a return to normal function.

4)   Farnsworth Munsell testing and Visual Field Testing are well known to have learning curves. While the scores in the voriconazole group appear to improve at Day 28, this is more likely a reflection of the learning curve.

5)   The number of patients discontinuing due to ocular events has been small (<10) and has included the following reasons: decreased vision, altered color perception and photophobia. It is not known from the submission whether all of these events were completely reversible.

6)   Pupil size was not adequately evaluated since the pupil size was measured after pharmacologic dilation.

7)   Human histopathology has not been performed. Ocular biomicroscopy has not detected ocular lesions.

8)   Effects on ocular function are not known for therapies extending beyond 28 days or for retreatments with voriconazole.

Hepatic Safety

The Applicant fully acknowledges that voriconazole causes clinically significant liver function test abnormalities.

In the Phase I pharmacology studies, the Applicant notes that there were no elevations of alkaline phosphatase in either the voriconazole or placebo patients. The incidence of elevated AST in the voriconazole arm was 0.9% vs. 0.8% in placebo. The incidence of elevated ALT was 1.2% in the voriconazole arm vs. 0% in placebo. The incidence of elevated total bilirubin was 0.5% in the voriconazole arm vs. 1.6% in placebo. The Applicant notes that any hepatic function abnormalities were reversible upon discontinuation of study drug.

In the controlled phase 3 clinical studies (studies 307/602, 603 and 305), the frequency of occurrence of elevated alkaline phosphatase, total bilirubin, AST and ALT, without regard to baseline, was reported in patients receiving voriconazole as follows:

Alkaline phosphatase	6.8-16%
Total bilirubin	4.3-26.5%
AST	5.6-20.3%
ALT	7.8-18.9%

It is important to note that full information regarding individual hepatitis C status and hepatitis B status was not always available.

The Applicant states that liver function test abnormalities (AST, ALT, alkaline phosphatase and total bilirubin) have been associated with plasma voriconazole concentration.   However, no threshold plasma concentrations have been identified above which the risk of an elevated liver function test abnormality was higher compared with plasma concentrations below the threshold.

An additional analysis regarding hepatic adverse events will be presented at the Advisory Committee meeting.

Cardiac Safety

 In the Phase 1 healthy volunteer program, the Applicant maintains that there was no apparent relationship between increases in the rate-corrected QT interval (QTc) and either dose or exposure to voriconazole.

As described by the Applicant, in the phase 3 studies, there was a single cardiac death that was due to ventricular fibrillation that occurred within 30 minutes of the patient's second infusion of voriconazole. Although the patient had underlying left ventricular dilatation and electrolyte abnormalities at the time of the event, voriconazole could not be excluded as a contributing factor.

In the controlled phase 3 trials (aspergillosis study 307/602, candida esophagitis study 305 and febrile neutropenia study 603), examination of cardiac adverse events and discontinuations for cardiac events did not detect a trend toward more events in the voriconazole arm. However, it is also important to remember that these studies were not designed to assess the risk to develop an arrhythmia in a population with underlying heart disease who may be on multiple medications including anti-arrhythmic drugs.

Skin

As outlined by the Applicant, skin rash was observed in 278/1493 (18.6%) of patients in the Therapeutic Studies program. It is important to note that this was a population that contained many patients who were also receiving antihistamines, steroids and immuno-suppressant drugs that might affect the type or severity of skin exanthem observed. In the controlled aspergillosis study 307/602, 124 of 196 patients on voriconazole received immunosuppressants, 134 of 196 patients on voriconazole received steroids and 77 of 196 patients received antihistamines and many patients received combinations of these three types of drugs.

In addition, in study 307/602 the incidence of graft vs. host disease (GVHD) was 4.1% in the voriconazole arm and 2.2% in the amphotericin B/OLAT arm.   In study 603, GVHD occurred in 2.9 % of patients in the voriconazole arm and in 1.4% of patients in the Ambisome arm

Further examination regarding the incidence of discontinuations for skin rashes across the controlled studies was made. No significant differences were noted between voriconazole and the comparator arms.

It is difficult to provide a precise description of the skin rashes that occurred in the clinical studies. No pathognomic type of skin exanthem emerges. The rash was described as "rash", "macular papular exanthem" and numerous other descriptions were used. The severity of rash (mostly mild and moderate) was similar across treatment arms and the median day of onset was 23 days for voriconazole and 19 days for the rashes that developed in the comparator arms for studies 307/602, 603 and 305. Many of these patients were on other concomitant medications that could also cause rash.

There were skin biopsy results available for only 4 patients. Two of those patients received voriconazole and two patients received liposomal amphotericin B. One voriconazole patient had GVHD at day 30 and the other patient on voriconazole had a "lichenoid drug reaction compounded by elements of phototoxicity" at day 138 of therapy. The patients on liposomal amphotericin B both had GVHD at day 21 and at day 35, respectively.

Finally the Applicant has provided data on the most severe episodes of skin rash that emerged during the clinical trials. At this time, we concur with the company that rash, including severe episodes such as Stevens-Johnson syndrome can occur with voriconazole administration. Although most skin rashes were of mild severity, clinical judgment should always dictate when to discontinue drug. The mechanism of action for the development of this skin exanthem has not been identified. There is insufficient information to conclude that these reactions represent photosensitivity.

Summary of Risk/Benefit

The safety database for voriconazole was adequate but was often confounded by factors in the severely ill patient that made it difficult to accurately obtain a picture of the events attributable to drug alone.

At present both the Applicant and the Division agree that visual abnormalities occurred at a frequency of between 24% to 33% in the clinical trial database. Most of these visual symptoms appear to resolve with discontinuation of drug. However, it is important to keep in mind, that we do not have complete follow-up data on all of the patients who discontinued voriconazole for visual symptoms. We also do not know if vision may be compromised upon re-challenge with voriconazole or whether it is safe to use this drug in patients who have underlying eye diseases such as diabetic retinopathy and CMV retinitis.

Voriconazole has the potential for numerous drug interactions because it is both a substrate and an inhibitor of CYP 2C9, 2C19 and 3A4. The Applicant has evaluated potential drug interactions between voriconazole and several important medications. These should guide precautions intended to minimize potential adverse reaction. We look to the Advisory Committee for recommendations regarding whether additional drug interactions need to be explored.

This drug is hepatically metabolized and can elevate liver function tests. Although we have data on the use of this drug in patients with chronic liver disease in Child-Pugh classes A and B, we do not have sufficient data to completely ascertain the safety of using this drug in liver transplantation, or in patients with Child Pugh Class C disease or in patients with hepatitis B or hepatitis C disease. Liver function tests should be monitored.

Regarding cardiac toxicity, the use of this drug in patients with underlying heart disease and on anti-arrhythmic drugs should be done with caution and consideration given to cardiac monitoring during the use of the intravenous preparation. Patients should have electrolyte abnormalities corrected before infusion of this drug.

The mechanism for the skin exanthem remains to be clarified but clinical judgment should dictate if and when this drug should be discontinued.

In conclusion, voriconazole represents an important new addition to our armamentarium of antifungal agents and, in the controlled aspergillosis study 307/602, the drug has demonstrated a survival advantage. Therefore, in treating patients with aspergillus infection with its attendant high morbidity and mortality, one can reconcile taking the risk of exposing the patient to development of a visual, cardiac, liver function abnormality and/or rash.

However, we look to the Advisory Committee for guidance regarding whether less ill populations of patients should be exposed to the risks associated with voriconazole use, especially if less toxic therapy is available for a particular indication.