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APPLICATION NUMBER:

21-506

MEDICAL REVIEW(S)

Medical Team Leader and Division Director Review

APPLICANT: Fujisawa Healthcare, Inc.

DRUG: Micafungin sodium for injection

Trade Name: Mycamine®

NDA/Indication: 21-506/Prophylaxis of candida infections in HSCT
21-754/Esophageal Candidiasis

DATE OF SUBMISSION: April 29, 2002 -- NDAs 21-506 (also —
Resubmission: August 24, 2004 -- NDA 21-506

DATE OF SUBMISSION: April 23, 2004 -- NDA 21-754
Major Amendment: January 31, 2005 – NDA 21-506, NDA 21-754

PDUFA GOAL DATE: May 24, 2005

FORMULATION: Lyophylized powder for intravenous injection (50 mg)

RELATED NDAs:

RECOMMENDATIONS:

The applicant should be issued an approval letter for the following indications:

- Esophageal Candidiasis
- Prophylaxis of *Candida* infections in patients undergoing hematopoietic stem cell transplantation (HSCT)

There are no Phase 4 post-marketing commitments for these two applications, with the exception of deferral of pediatric studies for the indications of esophageal candidiasis and prophylaxis of *Candida* infections in patients undergoing hematopoietic stem cell transplantation — — (HSCT).

During this review cycle, the applicant requested inclusion of — — n the labeling. However, the pharmacokinetic data for pediatric patients 2-17 years of age was unacceptable, because some/many of the blood samples were taken from the infusion port instead peripheral or central vein, and therefore the data were invalid (see clinical pharmacology review). The clinical efficacy and safety data alone were

insufficient to support labeling. Given the need for additional study (studies), the applicant and Division plan to discuss pediatric drug development during spring of 2005.

EXECUTIVE SUMMARY

A. Drug Product Summary

MYCAMINE (micafungin sodium) is an echinocandin antifungal that inhibits the synthesis of 1,3-β-D-glucan, an essential component of the cell wall of susceptible fungi but not mammalian cells. It is active in vitro against *Candida albicans, C. glabrata, C. krusei, C. parapsilosis,* and *C. tropicalis*. Micafungin has shown activity in both mucosal and disseminated murine models of candidiasis. Micafungin, administered to immunosuppressed mice in models of disseminated candidiasis prolonged survival and/or decreased the mycological burden.

The pharmacokinetics of micafungin were evaluated in healthy subjects, hematopoietic stem cell transplant recipients, and patients with esophageal candidiasis. The area under the concentration-time curve (AUC) was proportional to micafungin dose from 50 mg to 150 mg and 3 mg/kg to 8 mg/kg. Steady-state pharmacokinetic parameters are presented below.

Table 1: Pharmacokinetic Parameters of Micafungin in Adult Patients

Population	N	Dose (mg)	Pharmacokinetic Parameters (Mean ± Standard Deviation)			
			C_{max} (mcg/mL)	$AUC_{0\text{-}24}$ (mcg·h/mL)	t½ (h)	Cl (mL/min/kg)
HIV- Positive Patients with EC [Day 14 or 21]	20	50	5.1±1.0	54±13	15.6±2.8	0.300±0.063
	20	100	10.1±2.6	115±25	16.9±4.4	0.301±0.086
	14	150	16.4±6.5	167±40	15.2±2.2	0.297±0.081
		Per kg				
HSCT Recipients [Day 7]	8	3	21.1±2.8	234±34	14.0±1.4	0.214±0.031
	10	4	29.2±6.2	339±72	14.2±3.2	0.204±0.036
	8	6	38.4±6.9	479±157	14.9±2.6	0.224±0.064
	8	8	60.8±26.9	663±212	17.2±2.3	0.223±0.081

EC = esophageal candidiasis; HSCT = hematopoietic stem cell transplant

Micafungin is highly (>99%) protein bound. It is metabolized to M-1 (catechol form), M-2 (methoxy form), and M-5 (hydroxylation at the side chain (ω-1 position). Even though micafungin is a substrate for and a weak inhibitor of CYP3A *in vitro*, CYP3A is not a major micafungin metabolism enzyme *in vivo*. Drug interaction studies with immunosuppressants do not show significant pharmacokinetic interaction. Micafungin is neither a P-glycoprotein substrate nor inhibitor *in vitro*. Fecal excretion is the major route of elimination, accounting for 71% of the dose by 28 days, urinary recovery accounts for an additional 10-15% of the administered dose.

MYCAMINE does not require dose adjustment in patients with renal impairment or patients with moderate hepatic dysfunction (Child-Pugh score 7-9). The pharmacokinetics of MYCAMINE have not been studied in patients with severe hepatic impairment. Since micafungin is highly protein bound, it is not dialyzable.

B. Regulatory History

Fujisawa Healthcare, Inc. originally submitted a New Drug Application for MYCAMINE® on April 29, 2002. The application was administratively split into three NDAs as follows:

- NDA 21-506: Prophylaxis of [redacted] in patients undergoing hematopoietic stem cell transplantation. (HSCT)
- [redacted]
- [redacted]

Fujisawa received an Approvable letter from the FDA on January 29, 2003 for NDA 21-506 and [redacted]

After a series of interactions regarding the deficiencies identified in the approvable letter (see minutes March 28, 2003 and letter May 23, 2003), Fujisawa submitted NDA 21-754 for the indication of esophageal candidiasis on April 23, 2004. This was followed on August 24, 2004 by the resubmission of NDA 21-506 for the now narrowed indication, prophylaxis of candida infections in HSCT recipients, instead of the broader indication, prophylaxis of [redacted] in HSCT recipients. This change is relevant because the control drug in this study, fluoconazole, is approved for prophylaxis of candida infections. The resubmission, the NDA for esophageal candidiasis, and a review of pertinent literature on antifungal prophylaxis constituted a complete response to the agency's approvable letter. Fujisawa included a complete discussion of their prophylaxis study and references by Goodman, et al. [1992] and Slavin, et al. [1995] to support efficacy in prophylaxis.

During the various discussions with Fujisawa it was stated and agreed that approval of the indication, prophylaxis in candida infections in HSCT recipients, would be contingent on first or concurrently obtaining approval for the esophageal candidiasis indication [redacted] would have also have been acceptable indications to support the prophylaxis indication but were not underway or completed) along with addressing the other deficiencies in the approvable letter.

Other therapies currently approved for esophageal candidiasis include:

- Caspofungin, (IV) the only currently approved echinocandin
- Fluoconazole (oral and IV)
- Itraconazole (oral)
- Voriconazole (oral and IV)
- In development - NDA 21-632 (Vicuron) anidulafungin injection for the treatment of esophageal candidiasis. Anidulafungin is a new molecular entity in the echinocandin class of antifungal agents.

Other therapies currently approved for prophylaxis of *Candida* infections

- Fluconazole

C. Efficacy

1. Esophageal Candidiasis Efficacy, NDA 21-754

Fujisawa submitted four clinical studies in support of this indication, three in the original application and the fourth at the time of the 120-day update as summarized in the table below.

Study	Study Design	Number of Patients: age range Treatment Regimens	Study Sites and Location	Duration of Therapy	Time of Relapse Evaluation
03-7-005	Phase 3, randomized, double-blind, comparative	523 patients: ≥ 16 years old micafungin 150mg/day (N=260); fluconazole 200 mg/day (N=258)	35 sites in South Africa, Brazil, and Peru	14-21 days	2- and 4-weeks post-treatment
FG463-21-09	Phase 2, randomized, double-blind, comparative, dose ranging	251 patients: > 18 years old micafungin 50 mg/day (N=65); micafungin 100 mg/day (N=64); micafungin 150 mg/day (n=60); fluconazole 200 mg/day (n=62)	24 sites in Brazil, Peru, and South Africa	14-21 days	2-weeks post-treatment
97-7-003	Phase 2, open-label, non-comparative dose de-escalation study to determine minimum effective dose	120 patients: ≥ 18 years old micafungin 12.5 mg/day (N=26); micafungin 25 mg /day (N=22); micafungin 50 mg/day (N=26); micafungin 75 mg/day (N=22); micafungin 100 mg/day (N=24)	9 sites in South Africa	14 days	2-weeks post-treatment
98-0-047†	Phase 2, non-comparative study for candidemia or invasive candidiasis	357 patients (99 patients with EC) Adults and children	62 sites world-wide	5 days to 6 weeks	6-weeks post-treatment

† Study 98-0-047 was submitted previously with

The original NDA 21-754 submission contained results of studies FG463-21-09 and 97-7-003 that provided dose ranging and comparative data adequate for review and on the surface able to support approval. Study 98-0-047 was a non-comparative study previously reviewed and served to expand the safety database. Fujisawa submitted the results of study 03-7-005 in their 120-day safety update. The review of this study placed added responsibility on the review team, necessitated additional requests for analysis of data late in the course of review regarding safety information, and led to the need to extend the PDUFA due date based on major analyses coming in during the later part of the cycle. Study 03-7-005 was a robust Phase 3 study that increased the efficacy and the safety database and insured that the indication could be approved during the first review cycle.

The primary endpoint in the esophageal candidiasis trials was endoscopic appearance of the esophageal mucosa at the end of treatment. Endoscopic cure was defined as a score of 0 based on the following scale:

Esophageal Mucosal grade	Description
0	No evidence of EC-associated plaques
1	Individual, raised plaques, each 2 mm in size or less
2	Multiple raised plaques more than 2 mm in size
3	Confluent plaques combined with ulceration

The clinical response was a secondary endpoint, evaluated at end of treatment as well as at 2 weeks (and in study 03-7-005 at 4 weeks) after completing treatment. Clinical cure was defined as achieving a score of 0 based on the following symptoms:

Parameter	Grade 0	Grade 1	Grade 2	Grade 3
Dysphagia	Swallows food normally	Swallows solid food with difficulty	Can swallow soft food or liquid only	Can swallow small amounts of liquid or cannot swallow
Odynophagia	None	Food causes pain; little or no pain with liquids	Liquids cause pain; will not eat solids	Small sips of liquids only; or will not swallow; spits
Retrosternal pain	None	Low grade intermittent or continuous pain	Continuous pain, soreness or burning; may require pain medication	Very painful; requires pain medication

In the agency's analysis, therapeutic success was defined as score of 0 (endoscopic cure and clinical cure). This differed from the applicant's approach where outcomes of "success" were considered for patients who had amelioration of endoscopic score or clinical score without complete resolution (i.e., improved). In the comparative and dose ranging studies evaluating the 150 mg/day regimen, in fact most of the patients were cured, and only a minor percentage were considered improved.

Mycological outcome was assessed by biopsy and culture, and interpreted by a fairly complex algorithm that consideration absent results as failures. In fact in study 03-7-005, more than 98% of patients had *Candida albicans* isolated at baseline, with the vast majority having *C. albicans* isolated in the absence of other non-Candida species. Very few patients had *Candida* species other than *C. albicans* isolated at baseline and non-Candida isolates were often found in the presence of *C. albicans*.

Phase 3 study 03-7-005 serves as the cornerstone for the approval of this indication. In study - 005, approximately 90% of patients had HIV/AIDS as their underlying disease most with CD4 counts <100, 70% were black, average age was 37, genders were represented equally. This was the first episode of EC for 85% of patients. The infection was considered severe in 30% of patients. Concomitant medications included antibacterials 50%, TB therapy 20% and antiretrovirals 10%. The study population demographic and disease characteristics were balanced across study arms. The mean and median duration of therapy was 14 days. Efficacy in all categories showed micafungin to be non-inferior to fluconazole at end of treatment and at 2 weeks and 4 weeks after completing treatment, as shown in both of the tables below.

Phase 3 study 03-7-005: Endoscopic, Clinical, Therapeutic and Mycological Outcomes in Esophageal Candidiasis at End-of-Treatment

Outcome in study 03-7-05*	MYCAMINE 150 mg/day IV	Fluconazole 200 mg/day IV	% Difference (95% CI) †
	N=260	*N*=258	
Endoscopic Cure	228 (87.7%)	227 (88.0%)	-0.3% (-5.9, +5.3%)
Clinical Cure	239 (91.9%)	237 (91.9%)	0.06% (-4.6, +4.8%)
Overall Therapeutic Cure	223 (85.7%)	220 (85.3%)	0.5% (-5.6, +6.6%)
Mycological Eradication	141/189 (74.6%)	149/192 (77.6%)	-3.0 % (-11.6, +5.6)

*Endoscopic and clinical outcomes were measured in modified intent-to-treat population, including all randomized patients who received ≥ 1 dose of study treatment. Mycological outcome was determined in evaluable population, including patients with confirmed esophageal candidiasis who received at least 10 doses of study drug, and had no major protocol violations.
†calculated as MYCAMINE - fluconazole

Phase 3 study 03-7-005: Relapse of Esophageal Candidiasis at Week 2 and through Week 4 Post-Treatment in Patients who Were Therapeutic Cure at the End of Treatment

	MYCAMINE 150 mg/day IV	Fluconazole 200 mg/day IV	% Difference (95% CI) *
	N=223	*N*=220	
Relapse† at Week 2	40 (17.9%)	30 (13.6%)	4.3 % (-2.5, 11.1)
Relapse† Through Week 4 (cumulative)	73 (32.7%)	62 (28.2%)	4.6 % (-4.0, 13.1)

*calculated as MYCAMINE – fluconazole
N= number of patients with overall therapeutic success (both clinical and endoscopic cure at end-of-treatment)
†Relapse included patients who died or were lost to follow-up, and those who received systemic antifungal therapy in the post-treatment period.

Phase 2 study FG463-21-09 was a four arm, dose ranging study comparing 3 doses of micafungin to fluconazole 200 mg/d. The population was predominantly patients with HIV/AIDS, median age mid-30s, balanced for gender, about 50% black. HIV was confirmed in about 60% of patients; the mean CD4 count was 68 cells/mm3 and median count was 29 cells/mm3 indicating a significantly immunocompromised population. Approximately one-third of the patients were receiving concomitant antiretroviral therapy, 30% were receiving anti-tuberculous therapy, and 70% were receiving Bactrim, presumably for Pneumocystis prophylaxis. Bactrim has known potential for renal and hepatic toxicity and many of the antituberculous medications are associated with adverse events, including hepatotoxicity. These characteristics were taken into consideration during the review of the safety database for these applications.

The results of this study show a clear dose response in endoscopic clearance between 50 mg and 150 mg/day of micafungin, the 95% CI around the point estimates do not overlap. The clinical cure rates were consistent, but there was an unexpected decline in mycological eradication in the 150 mg/day arm. There was an unexpected increase in the number of adverse events in the 100 mg/day arm, there were numerically more deaths in the micafungin arms (see table below). Therefore, it was important that results of the Phase 3 trial 03-7-005were available for review.

Study FG463-21-09 was not designed to test for non-inferiority to fluconazole, although the 95% CI is (-8.4, +14.7) for the endoscopic outcome. This study supports the results of the Phase 3 study.

Phase 2 study FG463-21-09: Summary of Outcome in Patients with Esophageal Candidiasis

Population	Micafungin 50 mg/day	Micafungin 100 mg/day	Micafungin 150 mg/day	Fluconazole 200 mg/day
Randomized	N = 65	N=64	N=60	N=62
SAFETY				
Adverse event during treatment	3	8	3	4
Death during and after treatment	3	3	4	1
OUTCOME				
FAS (ITT)	N=64	N=62	N=59	N=60
Endoscopic Cure (score = 0) EOT	44/64 (66.8%) [57.4, 80.1]*	48/62 (77.4%) [67.0, 87.9]*	53/59 (89.9%) [82.1, 97.5]*	52/60 (86.7%) [78.1, 95.3]*
Clinical Cure (score = 0)	47/64 (73.4%)	52/62 (83.9%)	51/59 (86.4%)	53/60 (88.3%)
Therapeutic Cure EOT **	39/64 (60.9%)	48/62 (77.4%)	50/59 (84.7%)	51/60 (85%)
Mycological eradication EOT	20/64 (31.3%)	36/62 (58.1%)	28/59 (47.7%)	35/60 (58.3%)
Relapse at 2 weeks ***	13/39 (33.3%)	13/48 (27.1%)	10/50 (20.0%)	8/51 (15.7%)

N= number of patients in specified population
* 95% confidence interval around the point estimate
** Therapeutic Cure = patients classified as both endoscopic cure and clinical cure
***Mycological eradication: Patients with missing values were counted as persistence/failure
Relapse at 2 weeks: Patients with missing values or who receiving systemic antifungal drug during the 2 week follow up are tabulated under relapse.

In summary, two adequate and well controlled studies were submitted for this indication. The results of the Phase 3 study are robust and supported by the results of the Phase 2 study. The other Phase 2 studies provide some supportive information, particularly regarding activity of lower doses of micafungin. It should be noted that the Division's acceptance of the results of the Phase 3 study 03-7-005 at the time of the 120-day safety update, significantly augmented the data for the indication of esophageal candidiasis within NDA 21-754. Inclusion of this data greatly enhanced the likelihood that the application would contain a sufficient experience in esophageal candidiasis to support a successful application for the treatment of esophageal candidiasis during this review cycle.

2. Oropharyngeal Candidiasis Efficacy

Although this indication was not requested, the applicant systematically collected this information for the patients enrolled in study 03-7-005 and FG463-21-09, and evaluated clinical signs and symptoms using the following scale:

OPC Clinical Signs and Symptom Grades

Parameter	Grade 0	Grade 1	Grade 2	Grade 3
Plaques	No evidence of OPC-associated plaques	Individual raised plaques, each 2 mm in size or less	Multiple raised white plaques more than 2 mm in size	Confluent plaques
Inflammation	None	Slightly red	Very red	Dark red/scarlet
Fissures	None	Just visible	Prominent	Deep fissure/ulcers
Mouth pain	None	Slight discomfort	Can still eat	Unable to eat

Analysis of data from 03-7-005 by FDA and the applicant showed that efficacy was comparable to fluconazole at the end of treatment, but relapse rates at both 2 weeks and 4 weeks were higher in the micafungin arm. Specifically, the following information is to be included in the package insert to reflect this information:

> In this study, 459 of 518 (88.4%) patients had oropharyngeal candidiasis in addition to esophageal candidiasis at baseline. At the end of treatment 192/230 (83.5%) MYCAMINE treated patients and 188/229 (82.1%) of fluconazole treated patients experienced resolution of signs and symptoms of oropharyngeal candidiasis. Of these, 32.3% in the MYCAMINE group, and 18.1% in the fluconazole group (treatment difference = 14.2%; 95% confidence interval [5.6, 22.8]) had symptomatic relapse at 2 weeks post-treatment. Relapse included patients who died or were lost to follow-up, and those who received systemic antifungal therapy during the post-treatment period. Cumulative relapse at 4 weeks post-treatment was 52.1% in the MYCAMINE group and 39.4% in the fluconazole group (treatment difference 12.7%, 95% confidence interval [2.8, 22.7]).

Analysis of data from FG463-21-09 also shows that most patients had OPC concomitantly with EC, efficacy appears to have a dose-related pattern, and relapse rates are higher on micafungin than fluconazole:

Time of Assessment	Micafungin 50 mg/day N=64	Micafungin 100 mg/day N=62	Micafungin 150 mg/day N=59	Fluconazole 200 mg/day N=60
OPC at baseline	61/64 (95.3%)	59/62 (95.2%)	53/59 (89.8%)	57/60 (95.0%)
OPC and EC grade 0 at EOT	38/64 (59.4%)	45/62 (72.6%)	46/59 (78.0%)	50/60 (83.3%)
Total OPC Relapse at 2 weeks	18/38 (47.4%)	21/45 (46.7%)	17/46 (40.0%)	13/50 (26.0%)

Relapse rates include patients with missing values and systemic antifungal during 2 week follow up period.

The information on oropharyngeal candidiasis is important to include in labeling because these results indicate that while patient who have both esophageal and oropharyngeal candidiasis respond well in this case to 150 mg/kg/day of micafungin intravenously at the end of treatment, patients who have oropharyngeal candidiasis have a much higher chance of relapse after echinocandin treatment compared to azole treatment and this information is important for clinicians in managing these patients.

This finding is not unique to micafungin, and may represent a class effect for the echinocandin drug class. Wording reflecting significantly higher relapse rates is also included in the caspofungin labeling.

3. Prophylaxis Of *Candida* Infections In Patients Undergoing Hematopoietic Stem Cell Transplantation (HSCT) - Efficacy, NDA 21-506

Phase 3 Study 98-0-050 compared micafungin 50 mg/day IV to fluconazole 400 mg/day IV given as a 1-hour infusion in HSCT recipients. The study alone could not support approval for this indication and evidence of antifungal activity is provided from the esophageal candidiasis studies and non-comparative information on Candida indications submitted to [redacted]. A summary of the regulatory guidance provided to Fujisawa is summarized by Dr. Meyer in her review.

Patients were treated up to a maximum of 42 days after transplant and considered to fail prophylaxis if they developed proven, probable, or suspected infection.
Definitions of Infections

- Proven fungal infection: (a) patients with biopsy-proved (with or without culture) invasive (sinus, lung, liver, brain, etc) or disseminated infection (positive culture). Proven pulmonary fungal infection needed presence of compatible radiographic and clinical findings of infection. (b) Immunocompromised patients with sinusitis or a pulmonary infiltrate and an acceptable positive culture of *Aspergillus* or *Fusarium* or the agents of mucor (zygomycosis) from the upper respiratory tract.
- Probable fungal infection: Immunocompromised patients (neutropenia, chronic steroid therapy, etc) with the characteristic clinical and radiographic (chest x-ray, CT scan, other) picture of pulmonary aspergillosis or chonic disseminated candidiasis.
- Suspected systemic fungal infection: patient who met all three of the following criteria for at least 96 hours: neutropenia (ANC < 500 cells/mm3); persistent or recurrent fever ($\geq$ 100.4°F, $\geq$ 38.0°C) for which there was no known etiology; and failure to respond to at least 96 hours of broad spectrum antibacterial therapy.

Approximately half the patients had allogeneic BMT and half had autologous or syngeneic BMT. Most patients had ANC < 200 cells/mm3, nearly 90% of patients were Caucasian, nearly half were female, and about a quarter of patients had GVHD during study. Based on the applicant's original analysis, micanfungin was marginally superior to fluconazole in preventing fungal infections. Although not a protocol endpoint, examination of the difference between the rates of proven or probably candida infections shows the two products are similar. Micafungin is effective in allogeneic and autologous HSCT. The rates for the outcome of "Absence of Fungal Infection" younger patients are lower than in older patients across both treatment arms. Given the lower rate in the younger patients in both treatment arms, the question is raised whether these differences are due to host factors and/or is the dosage regimen has been sufficiently optimized in this age group. The information is tabulated below.

Phase 3 study Study 98-0-050: Prophylaxis of *Candida* infections in Patients Undergoing Hematopoietic Stem Cell Transplant, applicant's analysis

	MYCAMINE 50 mg/day IV	Fluconazole 400 mg/day IV	
Number of Patients	N=425	N=457	
Absence of Fungal Infection,	340/425 (80%)	336/457 (73.5%)	+6.5%, 95% CI (0.9%, 12%)
All Proven and Probable Breakthrough Systemic Fungal Infection	7 (1.6%)	11 (2.4%)	
Candida infections only	4 (0.9%)	2 (0.4%)	+0.5%, 95% CI (-0.6, 1.6%)
Use of Empirical Antifungal Therapy for Suspected Fungal Infection	64 (15.1%)	98 (21.4%)	
Outcome (Absence of Fungal Infection) by type of HSCT			
Allogeneic	157/220 (71.4%)	175/256 (68.4%)	
Autologous or Syngeneic	181/203 (89.2%)	161/201 (80.1%)	
None	2/2	-	
Outcome (Absence of Fungal Infection) by Age			
< 16 Years	27/39 (69.2%)	24/45 (53.3%)	
≥ 16 Years	313/386 (81.1%)	312/412 (75.7%)	
≥ 65 Years of Age	32/33 (97%)	16/23 (69.6%)	
< 65 Years	308/392 (78.6%)	320/434 (73.7%)	

During the review, it was recognized that there was some confusion between patients classified as having suspected fungal infection and on further review, the following numbers were determined to represent the protocol specified primary endpoint.

Phase 3 study Study 98-0-050: Results from Clinical Study of Prophylaxis of *Candida* Infections in Stem Cell Transplant Recipients

	Micafungin 50 mg/day (n=425)	Fluconazole 400 mg/day (n=457)
Success	**343 (80.7%)**	**337 (73.7%)**
+7.0% difference (micafungin –fluconazole) [95% CI=1.5%, 12.5%]		
Failure	82 (19.3%)	120 (26.3%)
All Deaths[1]	18 (4.2%)	26 (5.7%)
Proven/probable fungal infection prior to death	1 (0.2%)	3 (0.7%)
Proven/Probable fungal infection (not resulting in death)[1]	6 (1.4%)	8 (1.8%)
Suspected fungal infection[2]	53 (12.5%)	83 (18.2%)
Lost to follow-up[1]	5 (1.2%)	3 (0.7%)

[1] Through end-of-study (4 weeks post- therapy)
[2] Through end-of-therapy

In addition, although not counted in the endpoint, the use of systemic antifungal products was examined. In the post treatment period (end of treatment through the 4 week end of study time point), antifungals were used in 42% of the patients, and this use was balanced between the arms as seen in the table below.

Use of systemic antifungal therapy post-treatment	178 (41.9%)	192 (42.0%)
Reason for use post-treatment[1]		
Prophylaxis	160 (89.9%)	174 (90.6%)
Empirical	19 (10.7%)	27 (14.1%)
Treatment	9 (5.1%)	6 (3.2%)
Maintenance	3 (1.7%)	1 (0.5%)

1: patients could have received more than one antifungal agent post-treatment; included use beginning on day of last dose of study drug

As has been documented in the literature, patients undergoing BMT/HSCT benefit from prophylaxis against *Candida* infection and fluconazole has been demonstrated to be superior to placebo in attaining this goal. Therefore, the requested indication was revised from "prophylaxis — ' to "prophylaxis of *Candida* infections". In order to provide support for this indication, the applicant needs to demonstrate that micafungin is non-inferior to fluconazole (along with the other requested data) and this would be supportive of approval. The primary endpoint of the trial actually evaluated all fungal infections, including suspected ones. By the applicant's and FDA analysis, mycafungin was marginally superior to fluconazole in attaining this goal. However, in the absence of a second study showing statistical superiority, it cannot be assumed that micafungin is clinically superior to fluoconazole. In considering just patients with breakthrough proven and probably systemic *Candida* infections, there were 4 *Candida* infections in the mycafungin arm and 2 in the fluconazole arm. The incidence of *Candida* infections was presented in comparison to *Candida* infections from published studies by Goodman and Slavin. These studies were analyzed to justify the lower limit of the confidence interval that would be acceptable, in a study or breakthrough *Candida* infections. This analysis suggested that the proposed lower bound of the margin (fluconazole-micafungin) would be -4% and the applicant calculated that both the 95% CI and 99% CI would fall within than margin thereby meeting the definition of non-inferiority (further described in the applicant's February 18, 2004 submission for March 8, 2004 meeting with the Agency). Thus, the primary endpoint in this trial met its designated margin of 10% and actually showed micafungin to be marginally superior to fluconazole. In addition, though not a designated endpoint, the rate of *Candida* infections in the micafungin arm was shown to be similar to fluconazole.

In the prophylaxis trial, 50 mg/day was shown to be effective while in the EC studies, the 150 mg/day dose was demonstrated to be effective. However, micafungin activity was seen at lower doses in phase 2 studies of EC 97-7-003, FG463-21-09 as well as in noncomparative data from patients with candidemia and invasive candidiasis in study 98-0-047. In these studies, 50 mg/day demonstrated some activity and this finding supports the 50 mg/day dose demonstrated to be non-inferior (statistically superior) to fluconazole. Other factors considered with regards to the 50 mg dose for the prophyalxis of *Candida* infections indication include the following:

- In general, doses needed for prophylaxis are not necessarily the same as doses needed for treatment
- Echinocandins are parenteral agents and doses that are effective systemically are not always equally effective for mucosal oropharyngeal and esophageal infections.
- Plasma concentrations following a 50 mg dose of micafungin are above the concentrations considered effective in murine models of pulmonary aspergillosis and disseminated candidiasis over a 24-hour period.
- Endoscopic cure of esophageal candidiasis shows a clear dose-response and while cure rates with micafungin at 50 mg/day are lower than 150 mg/day, the 60% cure rate observed with the 50 mg/day regimen is higher than the placebo-response rate.
- Non-comparative data in candidemia shows an overall success rate of 74% (ITT) and 86% (PP) with 50 mg/day of micafungin.
- *Candidemia* and disseminated candidiasis can be prevented with lower doses of micafungin because micafungin is readily available in blood or interstitial fluid of the target organ (supported by PK and murine studies).
- Esophageal candidiasis (EC) is a mucosal disease. It is may be more difficult for micafungin to penetrate the keratinized mucosal layer. Therefore, higher doses of micafungin may be required to achieve a clinical cure in EC.

The totality of the evidence supports the conclusion that micafungin 50 mg/day is effective in prophylaxis of *Candida* infections.

D. SAFETY

MYCAMINE is a member of the echinocandin drug class that inhibits fungal cell wall glucan synthesis. Due to the absence of a mammalian structural analogue for the fungal cell wall, the applicant proposes that adverse events are unlikely to occur with MYCAMINE. The review of safety finds that MYCAMINE has a safety profile similar to other echinocandin antifungals, including adverse events such as phlebitis and histamine associated reaction. In addition, some adverse events associated with non-cell wall acting antifungal agents, such as hemolysis and hepatic adverse events also occur with MYCAMINE.

The Medical Officer review of the original NDA concluded a favorable risk profile for MYCAMINE, based on 1368 subjects, the majority of whom received the 50-mg dose of MYCAMINE. The aggregate safety information evaluated in the current review incorporates updated safety data from the original NDA 21-506 (prophylaxis of Candida infections in hematopoietic stem cell transplant recipients), new safety data from the esophageal candidiasis in NDA 21-754 (esophageal candidiasis), several new clinical studies contained in the 120-day safety update, and postmarketing data from Japan. The review team analyzed data from all these submissions, and also consulted with the Office of Drug Safety and Dr. John Senior during the review process. The safety of the 150 mg/day dose of MYCAMINE was more fully characterized in the safety update, consistent with the finding that this was the efficacious dose for the treatment of esophageal candidiasis.

Safety Evaluable Population from the various submissions to NDA 21-506 and 21-754

Duration (Days)	MYCA 50 mg	MYCA 75 mg	MYCA 100 mg	MYCA 150 mg	MYCA 200 mg	Total
Original submission (from Dr. Ibia's reveiw)						
N	974	319	217	111	85	1368
Total	14732	5083	2912	2163	2362	27252
Range	1-135	1-126	1-253	1-127	1-267	1-346
Mean	15.1	15.9	13.4	19.5	27.8	19.9
Re-submission (from ISS NDA 21-754)						
N	1043	269	303	271	197	2085
Total	19920	6819	6575	7599	3238	44151
Range	1-495	1-173	1-490	1-681	2-340	1-681
Mean	19.1	25.3	21.7	28.0	16.4	21.2
120-day Safety Update						
N	1049	270	357	529	197	2402
Total	19926	6846	7.74	112958	3238	48379
Range	1-495	1-173	1-490	1-681	2-340	1-681
Mean	19.0	25.4	19.8	21.4	16.4	20.1

A total of 726 (30%) subjects received $\geq$ 150 mg of MYCAMINE, and of these, the majority (606/726 or 83.5%) received this dose for at least 10 days. The mean duration of treatment for all subjects was 20.1 days (range 1-681 days).

Overall, 2028 of 2402 (84.4%) of subjects (patients and volunteers) who received MYCAMINE experienced an adverse event. Adverse events considered to be drug related were reported in 717 (29.9%) subjects. A comparison of the adverse event profile for MYCAMINE across studies shows that adverse event rates in each category varied widely across the different patient populations studied, highlighting the confounding influence of underlying disease and other factors in evaluating drug safety in severely ill patients. Patients with systemic fungal infections (invasive aspergillosis and candidiasis) represented approximately a third (679/2402 or 28.3%) of the MYCAMINE safety database.

Comparative profile of adverse events in the various populations that received MYCAMINE

	MYCAMINE				FLUCONAZOLE	
AE classification	Study 046 Invasive Aspergillus 75-200 mg (N=326) (%)	Study 047 Invasive candidiasis 75-150 mg (N=353) (%)	Study 050 Prophylaxis In HSCTR 50 mg (N=425) (%)	Study 005 Esophageal candidiasis 150 mg (N=260) (%)	Study 050 Prophylaxis In HSCTR 400 mg (N=457) (%)	Study005 Esophageal Candidiasis 200 mg (N=258) (%)
All Adverse Events (AE)	99.7	96.9	100.0	77.7	100.0	72.1
Serious AEs	75.5	39.9	18.8	13.5	16.2	19.3
Drug-Related AEs	31.9	42.5	15.1	27.7	16.8	21.3
Serious Drug-RelatedAEs	22.1*	6.2	0.9	1.2	2.2	0.3
Discontinuations (D/C)	28.1	20.1	4.2	6.2	7.2	3.9
DRAEs* w/ D/C	2.8	6.8	2.6	2.3	3.5	0.8
Deaths	56.1	29.7	4.2	11.5	5.7	10.9
Hepatic DRAEs*	9.5	16.1	5.2	3.8	6.8	3.1
Renal DRAEs*	3.7	1.7	0.7	0.4	1.3	0
Allergic/histamine DRAEs*	4.3	7.1	3.5	9.2	3.9	3.1
Phlebitis/injection site AEs	0.6	7.2	2.1	3.8	2.2	2.3

* from the original NDA 21-506 submission

The safety of MYCAMINE was compared to fluconazole in two large pivotal studies (Study 03-7-005 and Study 98-0-050) and from supportive studies 97-0-041 (prophylaxis) and FG-463-21-09 (esophageal candidiasis). The overall incidence of treatment emergent adverse events were similar; 91.6% (854/932) in the MYCAMINE-treated group and 90.3% (711/787) in the fluconazole-treated group. The more common adverse events in the studies utilizing fluconazole as a comparator found the following rates for the for the aggregate MYCAMINE treatment group versus the aggregate fluconazole group were diarrhea (41.8% MYCAMINE versus 50.4% fluconazole), mucositis (39.3% versus 47.8%), leukopenia (41.2% versus 46.6%), nausea (38.9% versus 44.6%), vomiting (35.9% versus 42.8%), and thrombocytopenia (38.4% versus 42.8%), respectively.

In the pivotal prophylaxis study (Study 98-0-050) (data shown as in the lightly shaded columns in the above table), the overall event rates in the categories of serious drug AEs, deaths, discontinuations, related hepatic and renal adverse events were numerically more frequent with fluconazole compared to MYCAMINE. By contrast, the dose of MYCAMINE (150 mg) used in the treatment of esophageal candidiasis (data shown as in the lightly shaded columns in the above table) more closely matched that of the comparator fluconazole (200 mg/day). At these dose levels, all AEs, drug related AEs, deaths, discontinuations, related hepatic, renal, injection site and histamine mediated reactions were numerically more frequent with MYCAMINE than fluconazole. A smaller proportion of the adverse events observed in these studies were attributed to drug, compared to patients in the invasive candidiasis or aspergillosis studies, which may indicate a greater tendency to attribute adverse events to the study drug in the less severely ill. For consistency with other antifungal labels, the Division proposes that the label present the common (>0.5%) drug related adverse events in the entire safety database and in the pivotal studies for the esophageal candidiasis and the prophylaxis studies.

Common Drug-Related* Adverse Events in Subjects† who received MYCAMINE in Clinical Trials

Number of Patients[1]	MYCAMINE N=2402
All system	421 (17.5%)
Blood and Lymphatic System Disorders	
Leukopenia	38 (1.6%)
Neutropenia	29 (1.2%)
Gastrointestinal Disorders	
Nausea	67 (2.8%)
Vomiting	58 (2.4%)
Diarrhea	38 (1.6%)
General Disorders and Administration Site Conditions	
Pyrexia	37 (1.5%)
Laboratory Tests	
Aspartate aminotransferase increased	64 (2.7%)
Alanine aminotransferase increased	62 (2.6%)
Blood alkaline phosphatase increased	48 (2.0%)
Liver function tests abnormal	36 (1.5%)
Metabolism and Nutrition Disorders	
Hypokalaemia	28 (1.2%)
Hypocalcemia	27 (1.1%)
Hypomagnesemia	27 (1.1%)
Nervous System Disorders	
Headache	57 (2.4%)
Vascular Disorders	
Phlebitis	39 (1.6%)
Skin and Subcutaneous Tissue Disorders	
Rash	38 (1.6%)

[1]Within a body system, patients may experience more than 1 adverse event
*Determined by the investigator to be possibly, probably, or definitely drug-related
†Subjects included patients and volunteers MedDRA Version 5.0.

Other clinically significant adverse events to include in the product label are the following adverse events:

Hematological and Lymphatic System: , cyanosis, pancytopenia, hemolysis, thrombotic thro cytopenic purpura
Respiratory System: dyspnea, hypoxia, r nonary embolism, apnea
Cardiovascular System: heart arres. hypertension, tachycardia, arrhythmia, myocardial infarct
Digestive System:
Nervous System: convulsion, intracranial hemorrhage, encephalopathy, delirium
Metabolic and Nutritional Disorders: , acidosis, , hyponatremia
Urogenital System: acute kidney failure, oliguria, anuria, kidney tubular necrosis
Skin: skin necrosis, urticaria, erythema multiforme
Muscoskeletal System: arthralgia

The following postmarketing adverse events reviewed by Dr. Singer and by the Office of Drug Safety review team (Drs Melissa Truffa and Adrienne Rothstein) are also proposed for inclusion in the label:[†]

Hepatic: hyperbilirubinemia, hepatic function abnormal, hepatic disorder, hepatocellular damage
Renal: acute renal failure and renal impairment
Hematologic: white blood cell count decreased, hemolytic anemia
Vascular: shock

Safety issues with special labeling

ANAPHYLAXIS
Serious events from the postmarketing Japanese experience included 7 cases of allergy, 5 serious skin reactions and 5 vascular reactions (including anaphylactic shock). Anaphylaxis was not observed to occur in the clinical studies of MYCAMINE, however anaphylactic shock and other anaphylactoid reactions in the postmarketing experience were considered to be at least possibly MYCAMINE related. A WARNING about the possibility of anaphylactoid or anaphylactic reactions during MYCAMINE infusion, is proposed in the label.

"WARNINGS:
Isolated cases of serious hypersensitivity (anaphylaxis and anaphylactoid) reactions (including shock) have been reported in patients receiving MYCAMINE. If these reactions occur, MYCAMINE infusion should be discontinued and appropriate treatment administered. "

HISTAMINE MEDIATED and OTHER ALLERGIC EVENTS
Dose-related histamine release were observed in preclinical studies in rats that received 32 - 100mg/kg of MYCAMINE, but not in rats that received 10 mg/kg. A dose relationships for these events was not established at the doses chosen for the clinical studies. Rashes and vasodilatation were observed in normal volunteers and patients; some of these reactions were serious and required MYCAMINE discontinuation. One event each of erythema multiforme and toxic epidermal necrolysis developed in the clinical studies and postmarketing events, respectively. These adverse events should be described in the Adverse Reactions section of the label as follows:

General
Possible histamine-mediated symptoms have been reported with MYCAMINE, including rash, pruritis, facial swelling, and vasodilatation.

[†] Note: there is available postmarketing experience derived from micafungin use in Japan. Micafungin was approved in Japan in October 2002. The Japanese label describes doses of 50 to 150 mg and also includes a proviso for doses of up to 300 mg/day in selected circumstances.

HEPATIC SAFETY

In *ex-vivo* studies, clinically relevant concentrations of MYCAMINE caused leakage of intracellular enzymes and loss of hepatocyte viability; these effects were intermediate between those observed with amphotericin B and fluconazole. Preclinical studies confirm that the primary target of MYCAMINE toxicity is the liver. In all animal species tested, laboratory and histopathologic evidence of dose-related hepatotoxocicity was noted, including single cell necrosis at 3-5X the human equivalent dose (HED).

Dr. Singer's review of the hepatic safety finds that transient increases in hepatic laboratory function developed in normal volunteers who received MYCAMINE. Most of these transaminase elevations were mild (<3X ULN) and fully reversible. Dr Singer also notes that increases in AST, ALT, alkaline phosphatase and bilirubin were common in MYCAMINE-treated patients; and that the proportion of patients with significant (>3X ULN) conjoint elevation of transaminases and bilirubin was similar in patients who received MYCAMINE or fluconazole.

The applicant's analysis finds no dose- or duration-relationship to the liver function test elevations or the hepatic adverse events that developed in MYCAMINE treated patients, based on multiple analyses of laboratory and clinical hepatic events performed per the FDA-Pharma white paper and in response to requests for additional analyses made by the Agency. On the other hand, the Division notes that while no dose relationship was seen with absolute increases in individual hepatic analytes, a trend suggestive of a dose response was seen with transaminase elevations ≥3X ULN in patients with esophageal candidiasis although these were too infrequent to be statistically significant (see Biopharmaceutics consult by Dr. Dakshina Chilukuri). Some hepatic events were serious, such as the development of hepatic failure or liver damage. These patients had serious underlying illnesses and were receiving concomitant medications along with MYCAMINE. The applicant's panel of hepatic experts concluded that certain serious hepatic events were possibly related to MYCAMINE, a conclusion shared by the Agency's internal expert, Dr. John Senior of the ODS. Similar MYCAMINE related serious hepatic adverse events were noted in the Japanese postmarketing database. The Division's strategy to managing this risk is to propose a HEPATIC PRECAUTION statement, and to plan for postmarketing surveillance in coordination with the ODS. The following wording is proposed for the label:

> PRECAUTIONS:
> Hepatic Effects
> Laboratory abnormalities in liver function tests have been seen in healthy volunteers and patients treated with MYCAMINE. In some patients with serious underlying conditions who were receiving MYCAMINE along with multiple concomitant medications, clinical hepatic abnormalities have occurred, and isolated cases of significant hepatic dysfunction, hepatitis, or worsening hepatic failure have been reported. Patients who develop abnormal liver function tests during MYCAMINE therapy should be monitored for evidence of worsening hepatic function and evaluated for the risk/benefit of continuing MYCAMINE therapy.

Safety of concomitant immunosuppressant therapy

The applicant performed several steady-state drug interaction studies with the calcineurin inhibitors (cyclosporine, tacrolimus, sirolimus) and prednisolone in normal volunteers and

finding no drug interaction, proceeded to evaluate the safety of patients receiving concomitant cyclosporine, tacrolimus, sirolimus and prednisolone in the clinical studies of MYCAMINE. In the prophylaxis study, 475 of 882 (53.9%) patients received immunosuppressive medications for treatment or prophylaxis of graft-versus-host disease; of these,198 of 882 (22.4%) patients had documented proven graft-versus-host disease during the study.

Normal volunteers in drug interaction studies that received MYCAMINE with multiple doses of ritonavir, fluconazole, nifedipine, cyclosporine and tacrolimus developed transaminase elevations >3XULN and some that received a single dose of mycophenolate developed transaminase elevations >8-10X ULN. However, the incidence of serious hepatic adverse events in patients who received concomitant MYCAMINE and mycophenolate mofetil was similar to that observed in patients who received MYCAMINE alone. Similar conclusions were derived when the patients that received MYCAMINE with other immunosuppressants were compared to patients that received MYCAMINE or fluconazole alone. The population that required concomitant immunosuppressant therapy was distinct from the group that received MYCAMINE alone, confounding an assessment of attributability. Nonetheless, clinical reviewers were reassured that no serious hepatic events requiring treatment discontinuation occurred in this prospectively evaluated randomized blinded study, with adequate laboratory and clinical documentation of adverse events.

RENAL Adverse Events

Increased BUN and creatinine and decreased creatinine clearance were observed in clinical trials of micafungin completed in Japan. Similar postmarketing renal events supported the listing of serious renal disorders as "Clinically significant adverse reactions" sub-section within the Japanese label. The label further states that renal function should be monitored in patients receiving micafungin and that treatment discontinuation should be considered if abnormalities develop. Dr. Singer performed a careful review of the individual patient data from the NDA and the postmarketing safety database. She notes that while several of these renal adverse events are confounded, there were rare events that appeared to be drug related. She notes that these events were seen at a frequency similar to that of Fluconazole. She also points out that 4 MYCAMINE-treated patients (0.4%) and 4 fluconazole-treated patients (0.5%) had renal adverse events judged to be drug-related by the investigator. To characterize these events, the following wording is proposed in the MYCAMINE label:

> Renal Effects
> Elevations in BUN and creatinine, and isolated cases of significant renal dysfunction or acute renal failure have been reported in patients who received MYCAMINE. In controlled trials, the incidence of drug-related changes in renal function was 0.4% for MYCAMINE treated patients and 0.5% for fluconazole treated patients. Patients who develop abnormal renal function tests during MYCAMINE therapy should be monitored for evidence of worsening renal function.

HEMATOLOGIC

An *in vitro* assay found that MYCAMINE can induce hemolysis of red cells at clinically relevant drug concentrations. One normal volunteer developed acute hemolysis and hemoglobinuria following an infusional event characterized by shortness of breath, diaphoresis and hypotension. In addition, rare events of hemolysis have occurred in patients enrolled in MYCAMINE clinical

trials. The Japanese label lists several hematologic events including neutropenia (1.5%), thrombocytopenia or hemolytic anemia in its "Clinically significant adverse reactions" sub-section and recommends that monitoring for these events be undertaken while on treatment with micafungin. The following wording is proposed for the US product label:

> Hematologic Effects
> Acute intravascular hemolysis and hemoglobinuria was seen in a healthy volunteer during infusion of MYCAMINE (200 mg) and oral prednisolone (20 mg). This event was transient, and the subject did not develop significant anemia. Isolated cases of significant hemolysis and hemolytic anemia have also been reported in patients treated with MYCAMINE. Patients who develop clinical or laboratory evidence of hemolysis or hemolytic anemia during MYCAMINE therapy should be monitored closely for evidence of worsening of these conditions and evaluated for the risk/benefit of continuing MYCAMINE therapy.

OTHER SAFETY ISSUES:

Cardiovascular safety

Mycafungin does not suppress Ikr channel current in hERG transfected cells nor prolong action potential duration. Preclinical studies likewise reveal no increase in QT interval in chronically dosed beagle dogs. Finally, no significant QTc prolongation was observed in normal volunteer studies and no clinical cardiac events related to QT prolongation has been documented in patients who received MYCAMINE.

Drug Interactions

A total of 11 clinical drug-drug interaction studies were conducted in healthy volunteers to evaluate the potential for interaction between MYCAMINE and mycophenolate mofetil, cyclosporine, tacrolimus, prednisolone, sirolimus, nifedipine, fluconazole, ritonavir, and rifampin. In these studies, no interaction that altered the pharmacokinetics of MYCAMINE was observed. There was no effect of single dose or multiple dose MYCAMINE on mycophenolate mofetil, cyclosporine, tacrolimus, prednisolone, and fluconazole pharmacokinetics.

Sirolimus AUC was increased by 21% with no effect on C_{max} in the presence of steady-state MYCAMINE compared with sirolimus alone. Nifedipine AUC and C_{max} were increased by 18% and 42%, respectively, in the presence of steady-state MYCAMINE compared with nifedipine alone. The label should note that patients receiving sirolimus or nifedipine in combination with MYCAMINE be monitored for sirolimus or nifedipine toxicity and doses of sirolimus or nifedipine be reduced if necessary.

MYCAMINE is not an inhibitor of P-glycoprotein and, therefore, would not be expected to alter P-glycoprotein-mediated drug transport activity.

Pregnancy, Lactation

Dr. McMaster concludes that MYCAMINE is a pregnancy category C drug based on the finding of visceral abnormalities in the offspring of the rabbit studies. The following wording is proposed for the label:

Pregnancy Category C

MYCAMINE administration to pregnant rabbits resulted in visceral abnormalities and abortion at 32 mg/kg, a dose equivalent to about four times the recommended dose. Visceral abnormalities included abnormal lobation of the lung, levocardia, retrocaval ureter, anomalous right subclavian artery, and dilatation of the ureter. Animal studies are not always predictive of human response; therefore, MYCAMINE should be used during pregnancy only if clearly needed.

Nursing Mothers

MYCAMINE sodium was found in the milk of lactating, drug-treated rats. It is not known whether MYCAMINE is excreted in human milk. Caution should be exercised when MYCAMINE is administered to a nursing woman.

Pediatric Use

Pediatric safety data was available from 244 pediatric subjects (<16 years of age) in the entire database, including data from 39 patients who received 1mg/kg of MYCAMINE as prophylaxis for Candida infections, and 4 patients who received 3mg/kg of MYCAMINE for the treatment of esophageal candidiasis. A comparison of adverse events occurring in the 244 pediatric patients to those observed in adults (≥16years of age) indicates that reported events were numerically more frequent in pediatric patients. The applicant attributes the difference in adverse event rates to the severity of the underlying disease and the fungal infections in pediatric patients. Nonetheless, age-related efficacy analysis also appears to shows a treatment difference favoring adults in the prophylaxis study. These safety and efficacy concerns, compounded by the limitations of the pharmacokinetic data in pediatric patients, support the recommendation to limit the approved indications to the adult populations.

Geriatric Use

No differences in safety or effectiveness were observed between the 186 subjects 65 years of age or older and those under 65 years of age in the clinical studies of MYCAMINE.

Summary and Recommendation

Safety

Upon review of the resubmission of NDA 21-506 (MYCAMINE 50 mg in the prophylaxis of *Candida* infections in the hematopoietic stem cell transplant recipients) and the new NDA 21-754 (MYCAMINE 150 mg for the treatment of esophageal candidiasis) the Agency's findings include the following with regards to safety:

- rare but serious events of anaphylaxis with MYCAMINE
- a signal for hepatic toxicity with MYCAMINE at a rate similar to that seen with fluconazole, which bears a hepatic warning in its label
- the adverse events of histamine mediated toxicity, infusion related toxicity and phlebitis, especially when MYCAMINE is infused via a peripheral line; events which can be described in the product label for MYCAMINE.
- the adverse events of hemolysis, electrolyte abnormalities and rare renal events considered to be related to MYCAMINE therapy; events which can be described in the product label for MYCAMINE.

- no multi-dose interaction between MYCAMINE and cyclosporine, tacrolimus, sirolimus, prednisolone, mycophenolate mofetil and MYCAMINE that would require dose adjustment for MYCAMINE.
- insufficient information to conclude that a safe dose has been characterized in pediatric patients.

The applicant's submission, which includes *in vitro* studies on hemolysis, hepatic toxicity, action potential and hERG channel assays, as well as the preclinical and normal volunteer safety information, strengthens the validity of the signals identified in the clinical studies and provides a plausible link for drug attribution in evaluating the clinical safety data derived largely from patients with serious underlying illness(es) and usually receiving multiple concomitant medications. The independent assessment by the Office of Drug Safety, the detailed clinical review by Dr. Singer and the availability of postmarketing data strengthens the safety conclusions derived. We address these risks in the label with the addition of a Warning section on anaphylaxis, a precautions statement on hepatic events, statements on hemolysis and renal events. The ODS will monitor these events following the market availability of MYCAMINE.

The applicant has adequately characterized the safety of MYCAMINE in adults and provides valuable information regarding its safe use with several drugs of interest in relation to the approved indications. For esophageal candidiasis, the applicant has performed antiretroviral – MYCAMINE drug interaction studies and for the prophylaxis indication the applicant has evaluated the interaction and safety of concurrent immunosuppressant and MYCAMINE therapy. This information will be useful in the clinical use of MYCAMINE and allow for a risk-benefit evaluation for the individual patient.

Efficacy
In this resubmission, the applicant has successfully demonstrated the efficacy of micafungin in the treatment of esophageal candidiasis at a dose of 150 mg/day intravenously in adult patients. Based upon the satisfactory demonstration of efficacy in the treatment of esophageal candidiasis (a type of established infection due to *Candida* spp.) in NDA 21-754, the result from the prophylaxis study (Study 98-0-050) and the other supportive evidence derived from the aforementioned micafungin NDAs and the related micafungin NDAs, sufficient evidence has been provided to support the efficacy of micafungin in the prophylaxis of *Candida* infection in patients undergoing hematopoietic stem cell transplantation at a dose of 50 mg/day intravenously in adult patients.

Recommendation
The applicant should be issued an approval letter for the following indications:

- Esophageal Candidiasis (NDA 21-754)
- Prophylaxis of *Candida* infections in patients undergoing hematopoietic stem cell transplantation (HSCT) (NDA 21-506)

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/s/

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3/16/05 12:27:41 PM
MEDICAL OFFICER
NDA 21-754, NDA 21-506

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CLINICAL REVIEW

Application Type	21-506
Submission Number	000
Submission Code	SU
Letter Date	August 24, 2004
Stamp Date	August 25, 2004
PDUFA Goal Date	February 25, 2005 (extended to May 25, 2005)
Reviewer Name	Joette M. Meyer, Pharm.D.
Review Completion Date	March 14, 2005
Established Name	Micafungin sodium for injectnion
(Proposed) Trade Name	Mycamine®
Therapeutic Class	Echinocandin Anti-fungal
Applicant	Fujisawa Healthcare, Inc.
Priority Designation	S
Formulation	Lyophilized powder for intravenous infusion
Dosing Regimen	50 mg IV once daily
Indication	Prophylaxis of *Candida* infections in patients undergoing hematopoietic stem cell transplantation
Intended Population	Hematopoietic stem cell transplant recipients

Table of Contents

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

The applicant submitted NDA 21-506 to the FDA on April 29, 2002 and was given a priority review for the indication "micafungin for the prophylaxis of — in patients undergoing hematopoietic stem cell transplantation." The applicant received on Approvable Letter from the FDA on January 29, 2003 for NDA 21-506. The letter stated that Study 98-0-050, the one study submitted in support of prophylaxis of — in patients undergoing hematopoietic stem cell transplantation (HSCT), by itself, did not provide sufficiently robust statistical evidence of superiority of micafungin over fluconazole, a comparator not approved for this indication. Prior to approval of micafungin for prophylaxis, the letter continued, the Agency expects demonstration of the activity of micafungin in the treatment of documented invasive fungal infections.

Fluconazole is approved for a narrower indication "to decrease the incidence of candidiasis in patients undergoing bone marrow transplantation who receive cytotoxic chemotherapy and/or radiation therapy." In addition to demonstration of a mortality benefit in the bone marrow transplant population, fluconazole was also approved based on efficacy in the treatment of systemic fungal infections.

At a face-to-face meeting on March 28, 2003 the applicant requested the indication for prophylaxis — be narrowed to include only *Candida* infections. The indication would be worded: "prophylaxis of *Candida* infections in patients undergoing hematopoietic stem cell transplantation." This new indication is similar to the approved indication for fluconazole.

The current submission (amendment to NDA 21-506), contains a proposed a re-analysis conducted by the applicant of the incidence of proven *Candida* infection in Study 98-0-050 relying on incidence rates of proven breakthrough infections with *Candida* in previously conducted trials in the literature, mainly the Goodman, et al. study [1992] and the Slavin, et al. study [1995].

At the March 28, 2003 meeting, the Agency also stated the applicant would need to have an approval demonstrating both safety and efficacy of micafungin in the treatment of some form of candidiasis, including esophageal candidiasis or other invasive *Candida* infection (including candidemia but not oropharyngeal candidiasis). Such an approval would be necessary to provide sufficient information on the activity of micafungin against *Candida* to support the results seen in Study 98-0-050.

The applicant has submitted a new NDA (21-754) for the treatment of esophageal candidiasis concurrently with the amendment to NDA 21-506, to fulfill the requirement for demonstration of micafungin efficacy in a treatment indication. Unlike the azole class of antifungals (including

fluconazole) the echinocandins (including micafungin) have limited penetration into mucosal tissues. Therefore, demonstration of the efficacy of an echinocandin in esophageal candidiasis is felt by the Agency to be a robust test of efficacy. Upon review of NDA 21-754, the Agency believes that the efficacy of micafungin at a dose of 150 mg, which is three times the prophylaxis dose, has established the efficacy of micafungin for the treatment of esophageal candidiasis.

Other supportive evidence demonstrating the efficacy of micafungin in the treatment of *Candida* infections was included by the applicant in this amendment, including an open-label study of micafungin for the treatment of candidemia (Study 98-0-047, submitted to the original NDA 21-506). In this study, the dose of micafungin was initiated at 75 mg, which is higher than the prophylaxis dose and one-half the dose for esophageal candidiasis.

The applicant's re-analysis of in Study 98-0-050, contained in this amendment to NDA 21-506, changed the emphasis of the primary endpoint from the absence of a fungal infection of any kind, to the incidence of proven *Candida* infections and a new treatment difference was established. Proven *Candida* infections were considered treatment failures while probable/suspected infections and deaths during the study were considered treatment successes. The Clinical and Statistical Reviewers concluded from their review that this approach is statistically inappropriate as a method to determine non-inferiority of micafungin to fluconazole. Additionally, re-defining the primary endpoint from absence of fungal infections during study to incidence of *Candida* infections was also considered by the Reviewers to be statistically invalid.

In choosing an acceptable margin for the re-analysis, the applicant relied on the Goodman and Slavin trials as a clinically relevant historical control. The Clinical Reviewer agreed that the Goodman and Slavin studies, of all those published, best approximate the design, endpoints, etc. of Study 98-0-050. However, it is possible that the risk of developing a fungal infection is lower today than 10 years ago, as evidenced by the lower rate of empirical therapy in Study 98-0-50 compared to the Goodman and Slavin studies. Since Study 98-0-050 did not contain a placebo group, this question of risk remains theoretical.

The Clinical and Statistical Reviewers also re-reviewed the data in the original report for Study 98-0-050 used to generate the primary endpoint, as defined in the protocol. The Reviewers concluded that the applicant defined suspected infections as those who received empirical antifungal therapy rather than adhering to the protocol-defined criteria. A suspected systemic fungal infection defined as patients with neutropenia (ANC <500 cells/mm^3); persistent or recurrent fever (while ANC <500 cells/mm^3) of no known etiology; and failure to respond to at least 96 hours of broad spectrum antibacterial therapy. A persistent fever was defined as four consecutive days of fever greater than 38°C. A recurrent fever was defined as having at least one day with temperatures $\geq$ 38.5 °C after having at least one prior temperature > 38 °C; or having two days of temperatures > 38 °C after having at least one prior temperature > 38°C. In addition, transplant recipients who died or were lost to follow-up during the study were considered failures of prophylactic therapy.

To accurately account for all treatment failures in Study 98-0-050, especially cases of suspected fungal infection, the Division requested from the applicant a detailed breakdown of all patients

who died, were lost to follow-up, developed proven/probable/suspected infections (as defined by the protocol), and those who did not meet the criteria for a suspected fungal infection but did receive empirical antifungal therapy.

As a result of the re-evaluation of failures (deaths, patients lost to follow-up, and proven/probable infections through the end of study and suspected infections through the end of treatment), success was correctly defined as 80.7% in micafungin patients and 73.7% in fluconazole patients (95% CI = 1.5%, 12.5%), as shown in the table below, along with reasons for failure.

The number of proven and probable fungal infections did not change as a result of the re-evalution. The number of proven *Candida* infections was 4 in the micafungin group and 2 in the fluconazole group.

Although not part of the primary endpoint, use of systemic antifungal therapy post-therapy evaluated by the Reviewers, since it also provides a perspective on the efficacy of prophylaxic therapy. The use of systemic antifungals following prophylactic therapy was 42% in both groups.

	Micafungin 50 mg/day (n=425)	Fluconazole 400 mg/day (n=457)
Success	**343 (80.7%)**	**337 (73.7%)**
+7.0% difference (micafungin –fluconazole) [95% CI=1.5%, 12.5%]		
Failure	82 (19.3%)	120 (26.3%)
All Deaths[1]	18 (4.2%)	26 (5.7%)
Proven/probable fungal infection prior to death	1 (0.2%)	3 (0.7%)
Proven/Probable fungal infection (not resulting in death)[1]	6 (1.4%)	8 (1.8%)
Suspected fungal infection[2]	53 (12.5%)	83 (18.2%)
Lost to follow-up[1]	5 (1.2%)	3 (0.7%)

[1] Through end-of-study (4 weeks post- therapy)
[2] Through end-of-therapy

At the time the Approvable letter for NDA 21-506 was written, the Agency did not feel that the results of Study 98-0-050 were robust enough to warrant and indication for prophylaxis of —— —— in HSCT patients, especially since the applicant did not have any data demonstrating efficacy for a treatment indication. However, with the approval of NDA 21-754, the Agency has concluded that micafungin has demonstrated efficacy for the treatment of esophageal candidiasis. Therefore, the results of Study 98-0-050, supported by efficacy of micafungin in the treatment of *Candida* infections, are considered by the Clinical Reviewer to be sufficient to demonstrate non-inferiority of micafungin to fluconazole for the narrower indication of prophylaxis of *Candida* infections in patients undergoing HSCT.

The incidence of drug-related adverse events was similar between micafungin and fluconazole treated patients in Study 98-0-050, including serious events and those resulting in study drug discontinuation.

In summary, micafungin sodium (Mycamine®) for injection, at a dose of 50 mg intravenously once daily, should be approved for prophylaxis of *Candida* infections in adult patients undergoing hematopoietic stem cell transplantation.

However, insufficient data are contained within this submission to provide evidence of the safety and efficacy of micafungin sodium (Mycamine®) for injection— The number of pediatric patients exposed to a 1 mg/kg mg dose of micafungin in Study 98-0-050 was relatively small (N=39) and fungal efficacy rates for prophylaxis or treatment success were lower in pediatric patients than in adults, as shown in Studies 98-0-050 and 98-0-047. Safety data on 244 pediatric patients enrolled across all micafungin clinical trials showed a higher incidence of adverse events in major organ systems compared to fluconazole. Finally, the pharmacokinetics in pediatric patients aged 2 to 17 years has not been adequately characterized. Therefore, micafungin sodium (Mycamine®) for injection should not be approved for —

1.2 Recommendation on Postmarketing Actions

There are no recommendations for risk management activity or required Phase 4 studies at this time.

1.2.1 Risk Management Activity

None.

1.2.2 Required Phase 4 Commitments

None.

1.2.3 Other Phase 4 Requests

None.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

This amendment to NDA 21-506 has three major components.

- The first is a review of the literature as requested by the Division at the meeting with Fujisawa on March 8, 2004 (see Section 2.5 "Presubmission Regulatory Activity"); including meta-analyses and review articles as well as a detailed review of studies using antifungal prophylaxis, especially use of fluconazole, over the prior 20 years (see Section 11: *Appendix I: Review of Antifungal Prophylaxis in Clinical Trials*).
- The second is a detailed review of the design of Study 98-0-050, a reanalysis of the results from this study demonstrating the non-inferiority of micafungin to fluconazole with respect to *Candida* infection, and a summary of key design features and results between Study 98-0-050 and the Goodman et al. [1992] and Slavin et al. [1995] trials (see Section 12: *Appendix II: Comparison of Study 98-0-050; Goodman et al. and Slavin et al. Trials* and Section 13: *Appendix III: Reanalysis of Study 98-0-050*).
- The third component contains responses to other FDA inquiries regarding the appropriate dose of micafungin for prophylaxis of *Candida* infections (see Section 14: *Appendix IV: Other Issues*).

1.3.2 Efficacy

1.3.2.1 Literature Review

The results of published meta-analyses and comprehensive review articles demonstrate that prophylaxis with fluconazole significantly reduces the incidence of invasive yeast infections in cancer patients with neutropenia. These analyses further showed that the benefit of prophylaxis was most evident in patients undergoing BMT/HSCT. The period of greatest risk for an infection, especially due to *Candida* species, is the neutropenic, pre-engraftment phase in BMT recipients. Beyond engraftment, other fungal pathogens emerge, most notably *Aspgergillus* and *Cryptococcus* and patients who develop graft versus host disease appear to be at greatest risk for developing a fungal infection.

Prophylaxis may also be beneficial in populations other than BMT/HSCT who are at higher risk of infection: non-BMT settings where the incidence of invasive infection is expected to exceed 15% when prophylaxis was not used, and in patients with neutropenia for more than 7 days. Although not clear from the literature, the incidence of invasive fungal infections in neutropenic patients may be decreasing over time and has definitely decreased with the institution of routine triazole prophylaxis. Prevention of infection has become the most important parameter impacting overall outcome.

There was a wide range in the incidence of invasive fungal infections across the placebo-controlled studies, which likely reflects the heterogeneity of the patient populations and treatment modalities. However, two large placebo-controlled trials [Goodman et al, 1992; Slavin et al, 1995] demonstrated the benefit of fluconazole prophylaxis versus placebo in BMT/HSCT patients with an estimated treatment effect for overall systemic fungal infections of 11% to 13%. These two studies provide the best estimates of the treatment effect of fluconazole compared to placebo during the pre-engraftment neutropenic time period of HSCT and serve as an appropriate

basis for estimating a new treatment difference for the analysis of noninferiority for proven *Candida* infections in Study 98-0-050.

The incidence of proven systemic *Candida* infections in Study 98-0-050 was 0.9% in the micafungin group and 0.4% in the fluconazole group. Incidence rates for proven invasive *Candida* infections (excluding urinary tract infections) were 1.7% for the Goodman study and 1.3% for the Slavin study for patients enrolled on the active drug (fluconazole). The slightly lower incidence of systemic *Candida* infections in Study 98-0-050 compared to the Goodman and Slavin studies is likely partially reflective of changes in transplant methodology as well as improvements in the supportive care management of BMT/HSCT complications.

A more complete review of antifungal prophylaxis trials submitted by the applicant can be found in Appendix I (see Section 11). Details on how the Goodman and Slavin trials compare to Study 98-0-050 can be found in Appendix II (see Section 12).

1.3.2.2 Study 98-0-050

This was a multicenter, randomized (1:1), stratified (by center, age, type of transplant, and risk for transplant-related mortality), double-blind study of micafungin compared to fluconazole in adult and pediatric patients (≥ 6 months of age) scheduled to undergo an autologous or syngeneic (for hematologic malignancies) or allogeneic hematopoietic stem cell transplant (HSCT).

Study drug was administered in an inpatient or outpatient setting. Patients received either micafungin, 50 mg per day (1 mg/kg per day for patients weighing < 50 kg), or fluconazole (400 mg per day or 8 mg/kg for patients < 50 kg) once daily as a 1-hour infusion.

Prophylaxis with study drug was to continue until one of following occurred: the patient experienced neutrophil recovery to a post nadir ANC of ≥ 500 cells/mm^3 (study drug could be continued for up to 5 days post-neutrophil recovery at the investigator's discretion); the patient developed a proven, probable, or suspected fungal infection; the patient developed unacceptable toxicity; the investigator decided that it was in the best interest of the patient to discontinue; the patient declined further study participation; death occurred; or the patient received prophylactic treatment to a maximum of 42 days after transplant (day +42 after transplant).

The criteria for diagnosing a proven fungal infection included a positive biopsy (with or without culture) for invasive or disseminated fungal infection. A probable infection was diagnosed radiographically (chest x-ray, CT scan, other) or clinically (characteristics of pulmonary aspergillosis, plus a positive BAL specimen).

A suspected systemic fungal infection was diagnosed in patients with neutropenia (ANC <500 cells/mm^3); persistent or recurrent fever (while ANC < 500 cells/mm^3) of no known etiology; and failure to respond to at least 96 hours of broad spectrum antibacterial therapy. A persistent fever was defined as four consecutive days of fever greater than 38°C. A recurrent fever was defined as either having at least one day with a temperature ≥ 38.5 °C after having at least one

prior temperature > 38 °C; or having two days of temperatures > 38 °C after having at least one prior temperature > 38°C. Patients who died or were lost to follow-up during the study were considered failures of prophylaxis.

All patients who received at least one dose of study drug were included in the full analysis set, which was the primary data set for analysis of efficacy.

The primary efficacy endpoint was success, defined as the absence of a proven, probable, or suspected systemic fungal infection through the end of therapy (mean 18 days; range 1 to 51 days), and the absence of a proven or probable systemic fungal infection through the end of the 4-week post-therapy period.

Success was achieved in 80.7% of micafungin patients and 73.7% of fluconazole patients (95% CI = 1.5%, 12.5%), as shown in the table below (along with other study endpoints).

The number of breakthrough *Candida* infections was 4 in the micafungin and 2 in the fluconazole treatment groups. The use of systemic antifungals post-therapy was 42% in both groups.

	Micafungin 50 mg/day (n=425)	Fluconazole 400 mg/day (n=457)
Success	**343 (80.7%)**	**337 (73.7%)**
+7.0% difference (micafungin –fluconazole) [95% CI=1.5%, 12.5%]		
Failure	82 (19.3%)	120 (26.3%)
All Deaths[1]	18 (4.2%)	26 (5.7%)
Proven/probable fungal infection prior to death	1 (0.2%)	3 (0.7%)
Proven/Probable fungal infection (not resulting in death)[1]	6 (1.4%)	8 (1.8%)
Suspected fungal infection[2]	53 (12.5%)	83 (18.2%)
Lost to follow-up[1]	5 (1.2%)	3 (0.7%)

[1] Through end-of-study (4 weeks post- therapy)
[2] Through end-of-therapy

A summary of the proven or probable systemic fungal infections during the study based on protocol-specified diagnostic criteria is presented by organism in the table below.

Organism	**FK463 (n=425)**		**Fluconazole (n=457)**	
Proven	**6**	**(1.4%)**	**8**	**(1.8%)**
Aspergillus species	0	(0.0%)	4	(0.9%)
Candida species	4	(0.9%)	2	(0.4%)
Fusarium species	1	(0.2%)	2	(0.4%)

Zygomyces species	1	(0.2%)	0	(0.0%)
Probable	**1**	**(0.2%)**	**3**	**(0.7%)**
Aspergillus species	1	(0.2%)	3	(0.7%)

Baseline fungal surveillance cultures were taken from the oropharynx only. During therapy the oropharynx, urine and stool or perirectal area were to be cultured once weekly. The oropharyngeal colonization pattern was similar at baseline for the two groups. At baseline the most common species of *Candida* were *C. albicans*, *C. glabrata*, and non-albicans *Candida*. At the end of therapy, overall colonization from any site was seen in 57.2% (243/425) of micafungin patients and 39.8% (182/457) fluconazole patients. Of the *Candida* species, *C. albicans* was noted in more micafungin patients (55.1%) compared to fluconazole patients (30.2%). However, *C. glabrata* was noted in more fluconazole patients (32.4%) than micafungin patients (4.9%). Other species of *Candida* were not present in substantial numbers at the end of therapy, with the exception of *C. parapsilosis* (6.6% micafungin and 2.2% fluconazole) and *C. krusei* (4.1% and 1.6%, respectively).

Of note, in the open-label study of candidemia (Study 98-0-047), infections due to non-albicans species of *Candida* required treatment with a higher dose of micafungin (100 mg, as opposed to 75 mg). The need for higher doses of micafungin to treat non-albicans species has implications for the types of breatkthough infections which may occur in patients receiving micafungin as prophylactic therapy.

1.3.2.3 Reanalysis of Study 98-0-050

In changing emphasis from the absence of either a yeast or mold infection, as in the original NDA, to the incidence of breakthrough proven *Candida* infections, a new efficacy difference was established by the applicant in the current submission. In choosing an acceptable margin, the applicant relied on the Goodman and Slavin trials as a clinically relevant historical control.

The analysis considered breakthrough *Candida* infections as failures of prophylaxis while all other breakthrough infections and deaths during the study were considered successes. The Clinical and Statistical Reviewers consider this approach statistically inappropriate as a method to determine non-inferiority of micafungin to fluconazole. Additionally, the applicant's re-defining of the primary endpoint from absence of fungal infections during study to incidence of *Candida* infections is also statistically invalid.

Details of the applicant's reanalysis of Study 98-0-050 and a comparison to the Goodman, et al. study [1992] and the Slavin, et al. study [1995] can be found in Appendix III (Section 13).

1.3.2.4 Response to other FDA Inquiries

The applicant submitted supporting data to demonstrate that the 50 mg dose is appropriate for use in prophylaxis and why higher doses (100 mg to 150 mg) are required for esophageal candidiasis (EC). In part, *Candidemia* and disseminated candidiasis may be prevented with lower doses of micafungin (50 mg) because micafungin is readily available in blood or

interstitial fluid of the target organ (supported by pharmacokinetic and murine studies). However, in EC, which is a mucosal disease, it is more difficult for micafungin and the other echinocandins in general, to penetrate the keratinized mucosal layer. Therefore, unlike with other drug classes, higher doses of micafungin, or other echinocandins, are required to achieve a clinical cure in EC.

The results from patients with confirmed candidemia in Study 98-0-047/FG-463-21-02 (an uncontrolled study) provide additional evidence of the efficacy of micafungin 50 mg per day in *Candida* infections. The success rate for all monotherapy patients (non-efficacy failure plus efficacy failure) with candidemia receiving a maximum dose of 50 mg per day was 73.8% (48/65, Full Analysis Set) and 86.3% (44/51, Per Protocol Set).

Clinical Reviewer's Comment: The overall success rate of micafungin monotherapy (non-efficacy failure plus efficacy failure) in the candidemia study, using the full analysis set and including daily doses of 1 mg/kg mg and higher, was 83.8.% (155/185) in adults compared to 64.8% (11/17) in pediatric patients < 16 years of age (see Section 8.4.2). These results suggest that micafungin may have less efficacy in pediatric patients compared to adults.

Details on how the applicant addressed the other FDA inquiries can be found in Appendix IV (Section 14).

1.3.2.5 Summary

Given the efficacy of micafungin in the treatment of esophageal candidiasis (NDA 21-754), the non-inferiority of micafungin compared to fluconazole for the primary end point in Study 98-0-050, and supportive evidence of the efficacy of micafungin in the treatment of invasive candidiasis; the applicant has demonstrated efficacy of the 50 mg dose in the prophylaxis of *Candida* infections in patients undergoing hematopoietic stem cell transplant.

1.3.3 Safety

A 50 mg dose (1 mg/kg in patients weighing < 50 kg) of micafungin was used in three clinical studies: 98-0-047 (candidemia or invasive candidiasis), FG-463-21-09 (esophageal candidiasis), and 98-0-050 (prophylaxis of fungal infections in HSCT recipients). A total of 770 patients received at least one dose of micafungin and 517 patients who received at least one dose of fluconazole as the comparator (60 received 200 mg of fluconazole and 457 received 400 mg of fluconazole).

In Study 98-0-050, a total of 18/425 (4.2%) of micafungin and 26/457 (5.7%) of fluconazole treated patients died during the study period. Two deaths occurred while on study drug therapy, both in the fluconazole group. None of the deaths were considered by the investigators to be related to study drug.

A total of 80/425 (18.8%) of micafungin and 74/457 (16.2%) of fluconazole treated patients experienced a serious adverse event other than death during the study. The more common

serious adverse events occurring in the micafungin patients included sepsis (3.3%), fever (3.1%), and hypotension (2.1%). The more common serious adverse events occurring in the fluconazole patients included sepsis (2.8%) and dyspnea (1.8%). A total of 14 patients (4 micafungin patients [0.9%] and 10 fluconazole patients [2.2%]) experienced an adverse event other than death that was considered to be related to study drug.

Drug-related adverse events resulting in drug-discontinuation were reported in 18/425 (4.2%) of micafungin and 33/457 (7.2%) of fluconazole treated patients. Of the 11 micafungin patients who discontinued due to an adverse event considered related to study drug, 4 patients discontinued due to hepatic-related events, 4 patients due to events associated with rash or urticaria, and 1 patient due to increased creatinine. The remaining two patients discontinued for the following reasons: heart palpitations, and jaw and joint pain.

All patients who received micafungin (425) and all patients who received fluconazole (457) experienced at least one adverse event during the study. Drug-related adverse events occurred in 64/425 (15.1%) and 77 (16.8%) of patients in the micafungin and fluconazole groups, respectively. The incidence of particular drug-related adverse events was similar between the groups. Common drug-related adverse events (>1% in the micafungin group) included bilirubinemia (3.3% micafungin, 3.1% fluconazole), nausea (2.4% micafungin, 2.6% fluconazole), diarrhea (2.1% and 3.3%), hypokalemia (1.9%, 1.8%), rash (1.9%, 1.3%), vomiting (1.6%, 1.1%), hypophosphatemia (1.6%, 0.9%), abdominal pain (1.4% and 1.5%), leukopenia (1.2%, 0.9%), and hypomagnesemia (1.2%, 1.3%).

1.3.4 Dosing Regimen and Administration

The dose of micafungin sodium for injection in adult patients to prophylaxis of *Candida* infection in adult patients undergoing hematopoietic stem cell transplant is 50 mg intravenously once daily. No dosing adjustments are required based on race, gender, or in patients with renal or hepatic insufficiency.

The 50 mg dose of micafungin is appropriate for prophylaxis of *Candida* infections in adults, although higher doses are necessary to treat esophageal candidiasis, due to the pharmacokinetic characteristics of the echinocandin class of antifungals (poor penetration into mucosal tissue). In addition to the prophylaxis study (98-0-050), supportive data are available which demonstrates that the 50 mg dose of micafungin is also effective for treatment of documented fungal infections: esophageal candidiasis (Study FG-463-21-09) and candidemia (Study 98-0-047).

Insufficient data are contained within this submission to provide evidence of the safety and efficacy of micafungin in pediatric patients

1.3.5 Drug-Drug Interactions

A total of 11 clinical drug-drug interaction studies in healthy volunteers have been conducted by the applicant to evaluate the potential for interaction between micafungin and drugs commonly used in patients at risk for mucosal or invasive candidiasis, including CYP3A substrates, inhibitors and inducers.

Mycophenolate mofetil, cyclosporine, tacrolimus, prednisolone, sirolimus, nifedipine, fluconazole, ritonavir, and rifampin were evaluated. In these studies, no interaction that altered the pharmacokinetics of micafungin was observed.

There was no effect of single dose or multiple doses of micafungin on mycophenolate mofetil, cyclosporine, tacrolimus, prednisolone, and fluconazole pharmacokinetics. The effect of micafungin on the pharmacokinetics of ritonavir and rifampin was not evaluated.

Sirolimus AUC was increased by 21% with no effect on C_{max} in the presence of steady-state micafungin compared with sirolimus alone. Nifedipine AUC and C_{max} were increased by 18% and 42%, respectively, in the presence of steady-state micafungin compared with nifedipine alone.

1.3.6 Special Populations

Efficacy rates for a 50 mg dose of micafungin do not appear to be affected by gender or race.

Pharmacokinetic data submitted by the applicant were not considered adequate to characterize exposure of the drug in patients between 2 and 17 years. In addition, the number of pediatric patients exposed to a 1 mg/kg mg dose of micafungin in Study 98-0-050 was relatively small (N=39) and fungal efficacy rates for prophylaxis or treatment success were lower in pediatric patients than in adults, as shown in Studies 98-0-050 and 98-0-047 (see Section 8.4.2: *"Pediatric Efficacy"*). Therefore, —

— the **PRECAUTIONS**, Pediatric Use section of the label will reflect the fact that safety and efficacy have not been established in this population. (See Section 9.4: *"Labeling Review"*)

No major differences in adverse events were found based upon in age, gender, or race which would require micafungin dose adjustments for reasons of safety.

Micafungin has not been adequately studied in pregnant human subjects. There is no information in this submission on use of micafungin in pregnant women. Animal studies show that labeled micafungin and/or its metabolites are excreted into the breast milk. The Pharmacology/Toxicology Reviewer has designated micafungin to be Pregnancy Category C, not — . as requested by the applicant (see Section 3.2: *"Animal Pharmacology/Toxicology"*).

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Micafungin sodium, inhibits the synthesis of 1,3-β-D-glucan, an essential component of the cell wall of susceptible fungi but not mammalian cells.

Micafungin sodium exhibits in-vitro activity against a variety of *Candida* (*C. albicans, C. glabrata, C. krusei, C. parapsilosis,* and *C. tropicalis*) species. Standardized susceptibility testing methods for 1,3-β-D-glucan synthesis inhibitors have not been established, and the results of susceptibility studies do not correlate with clinical outcome.

Micafungin has shown activity in both mucosal and disseminated murine models of candidiasis. Micafungin, administered to immunosuppressed mice in models of disseminated candidiasis prolonged survival and/or decreased the mycological burden.

The potential for development of drug resistance is not known.

2.2 Currently Available Treatment for Indication

Fluconazole is approved for the following indication: "to decrease the incidence of candidiasis in patients undergoing bone marrow transplantation who receive cytotoxic chemotherapy and/or radiation therapy."

Guidelines from the Centers for Disease Control (CDC), Infectious Disease Society of America (IDSA) and American Society of Blood and Marrow Transplantation (ASBMT) regarding yeast infections in allogeneic and autologous transplant recipients with underlying hematologic malignancies recommend administration of fluconazole prophylaxis (400 mg oral or IV from the day of HSCT to engraftment) for the prevention of invasive disease with fluconazole-susceptible *Candida* species during neutropenia. [CDC MMWR 2000]

The pivotal study used to obtain the prophylaxis indication for fluconazole was published by Goodman et al [1992]. This publication is discussed further in Section 6 "Integrated Review of Efficacy" and Section 8.6 "Literature Review"

2.3 Availability of Proposed Active Ingredient in the United States

Micafungin is not currently approved for use in the United States.

2.4 Important Issues With Pharmacologically Related Products

2.4.1 Echinocandins

Caspofungin is the only echinocandin that is currently approved for use in the United States. In addition to micafungin, anidulafungin is also being developed. Currently, caspofungin is not approved for prophylaxis of fungal infections in patients undergoing hematopoietic stem cell/bone marrow transplant. However, caspofungin (Cancidas®) is indicated for[1]:

- Empirical therapy for presumed fungal infections in febrile, neutropenic patients.
- Treatment of Candidemia and the following *Candida* infections: intra-abdominal abscesses, peritonitis and pleural space infections. CANCIDAS has not been studied in endocarditis, osteomyelitis, and meningitis due to *Candida*.
- Treatment of Esophageal Candidiasis (see CLINICAL STUDIES).
- Treatment of Invasive Aspergillosis in patients who are refractory to or intolerant of other therapies (i.e., amphotericin B, lipid formulations of amphotericin B, and/or itraconazole). CANCIDAS has not been studied as initial therapy for invasive aspergillosis.

Hepatotoxicity has been seen with caspofungin and the following information is found under the **PRECAUTIONS** section of the label[2]:

> Laboratory abnormalities in liver function tests have been seen in healthy volunteers and patients treated with CANCIDAS. In some patients with serious underlying conditions who were receiving multiple concomitant medications along with CANCIDAS, clinical hepatic abnormalities have also occurred. Isolated cases of significant hepatic dysfunction, hepatitis, or worsening hepatic failure have been reported in patients; a causal relationship to CANCIDAS has not been established. Patients who develop abnormal liver function tests during CANCIDAS therapy should be monitored for evidence of worsening hepatic function and evaluated for risk/benefit of continuing CANCIDAS therapy.

A potential drug interaction exists between caspofungin and cyclosporine and the following **WARNING** can be found in the caspofungin label[3]:

> Concomitant use of CANCIDAS with cyclosporine is not recommended unless the potential benefit outweighs the potential risk to the patient. In one clinical study, 3 of 4 healthy subjects who received CANCIDAS 70 mg on Days 1 through 10, and also received two 3 mg/kg doses of cyclosporine 12 hours apart on Day 10, developed transient elevations of alanine transaminase (ALT) on Day 11 that were 2 to 3 times the upper limit of normal (ULN). In a separate panel of subjects in the same study, 2 of 8 who received CANCIDAS 35 mg daily for 3 days and cyclosporine (two 3 mg/kg doses administered 12 hours apart) on Day 1 had small increases in ALT (slightly above the ULN) on Day 2. In both groups, elevations in aspartate transaminase (AST) paralleled ALT elevations, but were of lesser magnitude (see ADVERSE REACTIONS). Hence, concomitant use of CANCIDAS with cyclosporine is not recommended until multiple-dose use in patients is studied.

1 Cancidas®. Label 9/29/04.
2 Cancidas®. Label 9/29/04.
3 Cancidas®. Label 9/29/04.

2.4.2 Azoles

Fluconazole and itraconazole have been studied for prophylaxis of fungal infections in patients undergoing hematopoietic stem cell/bone marrow transplant, although only fluconazole is approved for this indication ("to decrease the incidence of candidiasis in patients undergoing bone marrow transplantation who receive cytotoxic chemotherapy and/or radiation therapy). Fluconazole (Diflucan®) is also indicated for the treatment of:

- Vaginal candidiasis (vaginal yeast infections due to *Candida*).
- Oropharyngeal and esophageal candidiasis. In open noncomparative studies of relatively small numbers of patients, fluconazole was also effective for the treatment of *Candida* urinary tract infections, peritonitis, and systemic *Candida* infections including candidemia, disseminated candidiasis, and pneumonia.
- Cryptococcal meningitis. Studies comparing fluconazole to amphotericin B in non-HIV infected patients have not been conducted.

The fluconazole label carries the following bolded **WARNING** regarding hepatotoxicity[4]:

> **Hepatic injury: DIFLUCAN has been associated with rare cases of serious hepatic toxicity, including fatalities primarily in patients with serious underlying medical conditions. In cases of DIFLUCAN-associated hepatotoxicity, no obvious relationship to total daily dose, duration of therapy, sex or age of the patient has been observed. DIFLUCAN hepatotoxicity has usually, but not always, been reversible on discontinuation of therapy. Patients who develop abnormal liver function tests during DIFLUCAN therapy should be monitored for the development of more severe hepatic injury. DIFLUCAN should be discontinued if clinical signs and symptoms consistent with liver disease develop that may be attributable to DIFLUCAN.**

In addition, the fluconazole label also carries a **WARNING** related to serious dermatologic disorders[5]:

> Dermatologic: Patients have rarely developed exfoliative skin disorders during treatment with DIFLUCAN. In patients with serious underlying diseases (predominantly AIDS and malignancy), these have rarely resulted in a fatal outcome. Patients who develop rashes during treatment with DIFLUCAN should be monitored closely and the drug discontinued if lesions progress.

Fluconazole has potentially significant drug interactions with inducers, inhibitors, or substrates of the cytochrome P-450 system, including: Oral hypoglycemics, coumarin-type anticoagulants, phenytoin, cyclosporine, rifampin, theophylline, terfenadine, cisapride, astemizole, rifabutin, tacrolimus, and short-acting benzodiazepines.

2.5 Presubmission Regulatory Activity

- The applicant submitted NDA 21-506 to the FDA on April 29, 2002 and was given a priority review for the indication "micafungin for the prophylaxis of —— in patients undergoing hematopoietic stem cell transplantation."

4 Diflucan® 5% in plastic container. Label 10/07/04.
5 Diflucan® 5% in plastic container. Label 10/07/04.

patients receiving a 150 mg/day dose. The resulting study [Study 03-7-005], as well as Study FG-463-21-09, was reviewed by Dr. Mary Singer, as part of NDA 21-754.

- In a letter dated May 23, 2003 the FDA commented further on the indication for *Candida* prophylaxis and supportive data in patients with esophageal candidiasis (EC). The following advice was given under the heading "Prophylaxis of *Candida* Infections":

  To obtain the more limited indication of prophylaxis of *Candida* infections in patients undergoing hematopoietic stem cell transplantation, you will need to show that the results of Study 98-0-050 demonstrate such activity. There were 14 proven breakthrough fungal infections in this study (i.e., infections due to *Candida* species 6, *Aspergillus* species 4, *Fusarium* species 3, and *Zygomyces* species 1). Four of the 6 proven breakthrough *Candida* infections occurred on the micafungin arm compared to 2 on the fluconazole arm while all 4 proven breakthrough *Aspergillus* infections were on the fluconazole arm. Proven breakthrough *Fusarium* or *Zygomyces* infections were equally distributed between the two arms. All of the remaining endpoints were derived from either probable or possible cases and thus provide limited information on the causal organism. Thus it is neither immediately obvious how much support this study would provide for a *Candida* endpoint nor is it clear that micafungin could be considered superior to fluconazole when the endpoint is narrowed to only consider *Candida* infections. Since fluconazole is approved for the indication of prophylaxis of *Candida* infections in patients undergoing bone marrow transplantation, superiority of micafungin to fluconazole would not be required. However, a result of similar efficacy of micafungin to fluconazole based largely upon possible or probable cases of *Candida* infection would not provide the same level of support as provided by Study 98-0-050 for the original indication.

  While, in principle, results from Study FG-463-21-09 of esophageal candidiasis could support the prophylaxis indication, the Agency is unable to ascertain at this time whether in fact this is the case. The information on this study that you have so far provided to us appears to demonstrate a significantly poorer activity of the 50 mg intravenously once daily (IV QD) dose in the treatment of esophageal candidiasis compared to the 150 mg IV QD dose. Please keep in mind that you would need to provide justification that the efficacy of the proposed dose for treatment of esophageal candidiasis (150 mg IV QD) is relevant to the dose proposed for prophylaxis (50 mg IV QD) when the doses for the two indications are different. Any such justification would need to provide clear evidence of how the 150 mg IV QD dose for treatment of EC bears relevance to the 50 mg IV QD dose for prophylaxis against *Candida* infections in patients undergoing hematopoietic stem cell transplant. This justification is particularly important given our comments about the results in the 98-0-050 study provided above. The results of your Study 97-7-003 suggest that the 50 mg IV QD dose may have activity against esophageal candidiasis; however, the activity appears significantly inferior to the 150 mg IV QD dose and is inconsistent with the observations in FG-463-21-09. The applicability of this data, or any other clinical data at doses greater than the proposed dose of 50 mg IV QD, would require further FDA review.

  Given the aforementioned unresolved issues with the applicability of the data from the treatment of esophageal candidiasis at the dose of 150 mg IV QD to the proposed prophylaxis indication, one option to address the new and narrower indication of "prophylaxis of *Candida* infections in patients undergoing hematopoietic stem cell transplantation" would be for you to conduct another prophylaxis trial designed to show noninferiority of micafungin versus fluconazole with respect to breakthrough *Candida* infections. Another prophylaxis trial would be consistent with the options stated in the January 29, 2003 approvable letter, although the Agency appreciates that this would be a more difficult undertaking. The Agency would be pleased to discuss with you issues of design and dose selection for such a study.

  The Agency wishes to restate that to garner an approval for prophylaxis of *Candida* infections in the targeted population, you will need to have an approval demonstrating both safety and efficacy in the treatment of some form of candidiasis, including esophageal candidiasis or other invasive *Candida*

infection (including candidemia but not oropharyngeal candidiasis). Such an approval is necessary to provide sufficient information on the activity of micafungin against *Candida* to support the results seen in the 98-0-050 study given the issues identified above with the 98-0-050, FG-463-21-09, and 97-7-003 studies. Approval of such a treatment indication would also facilitate including in product labeling information on the activity of micafungin in the treatment of *Candida* infections. We believe that such information would be of value to physicians who care for patients undergoing hematopoietic stem cell transplantation.

Clinical Reviewer's Comment: The May 23, 2003 letter also restated the Division's request for a safety database of at least 300 patients treated with micafungin 150 mg/day for 10 days in order to grant an approval for the treatment of esophageal candidiasis. Later, during a teleconference on July 25, 2003, the Division confirmed that an NDA for the treatment of esophageal candidiasis, supported by the results of Study 97-7-003 and FG-463-21-09 and safety data from at least 300 subjects exposed to micafungin at 150 mg for at least 10 days, would be fileable [see August 8, 2003 – Teleconference Meeting Minutes].

See Medical Officer's review of NDA 21-754, micafungin for the treatment of esophageal candidiasis, by Dr. Mary Singer.

During a Type A meeting with the FDA on March 8, 2004, agreement was reached on the content and format of the proposed response (amendment/resubmission) to the January 2003 Approvable Letter for NDA 21-506. In the briefing document for this meeting, Fujisawa addressed the comments and recommendations listed under the heading "Prophylaxis of *Candida* Infections," in the May 23, 2003 letter. In the briefing document Fujisawa also provided an analysis of the incidence of proven *Candida* infection in Study 98-0-050. They relied on incidence rates of proven breakthrough infections with *Candida* in previously conducted trials in the literature, mainly the Goodman, et al. study [1992] and the Slavin, et al. study [1995]. The FDA's minutes from the March 8, 2004 meeting state:

Fujisawa proposed to submit a new NDA seeking approval of micafungin for the treatment of esophageal candidiasis. They also proposed that the approval of the EC indication, and the already submitted, approvable NDA 21-506, would be adequate for approval of micafungin for the Prophylaxis of *Candida* infections in Patients Undergoing Hematopoietic Stem Cell Transplantation. FDA requested information on the "rationale for comparability of the Goodman *et al.* and Slavin *et al.* trials to study 98-0-050 in terms of patient population, study endpoints, and study designs."

At the meeting, the Division stressed that it was still uncertain how the data presented in the Goodman and Slavin trials compare with study 98-0-050, given secular trends and differences in patient population, study endpoints, and study design. However, the Division acknowledged that this approach might be appropriate but would be a review issue. Fujisawa asked if anything beyond what was submitted in the briefing document would help with the comparability issue.

The Division mentioned two other meta-analysis studies (Kanda *et al.*-2000; Cornely *et al.*-2003) in addition to the Bow *et al.* study presented in the briefing document to offer more insight into the changes in risk-over-time for invasive fungal infections in a neutropenic patient population. Fujisawa agreed to look further into the literature for this additional insight.

Clinical Reviewer's Comment: The current submission (amendment to NDA 21-506) addresses indication-specific issues raised in the Approvable Letter. Non-indication specific issues are addressed in NDA 21-754 (esophageal candidiasis).

- The current submission (amendment to NDA 21-506), in conjunction with approval of NDA 21-574 (micafungin for the treatment of esophageal candidiasis), is considered by Fujisawa as sufficient to fulfill the Division's requirement for approval of micafungin for the "prophylaxis of *Candida* infections in patients undergoing hematopoietic stem cell transplantation."

2.6 Other Relevant Background Information

See the Medical Officer's Review of NDA 21-754 by Mary Singer, M.D. for a description of the efficacy of micafungin for the treatment of esophageal candidiasis and the safety of micafungin doses up to 150 mg.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

The original NDA 21-506 was found approvable from the chemist's perspective. The revised and updated application(s) remain approvable from the chemist's perspective. The following is an excerpt from the CMC Review:

The chemistry, manufacturing and controls for the drug substance and drug product are generally well documented. Fujisawa's drug substance and drug product manufacturing facilities all have acceptable cGMP status based on recent pre-approval inspections and profile updates. The chemistry of FK463 and of the formulated drug product have been thoroughly characterized. The manufacturing processes have been adequately defined. The product specification provides further assurance of the identity, quality, purity and potency of the product. Acceptance criteria for — have tightened at our request. A second — test (' — has been added as requested.

A — expiration dating period was supported in original NDA 21-506. A longer expiration dating period of 36 months for drug product stored at controlled room temperature and protected from light is supported by the updated full shelf-life (— months at 25°C/60% RH) and accelerated — , at 40°C/75% RH) data obtained on the primary stability batches, and by

Analytical methods validation by two FDA laboratories was requested. Validation has only been completed by one laboratory; however this is not an approvability issue. The applicant's continued cooperation to resolve any problems that may be identified is expected.

Several issues identified in the OPS microbiology review of the original application have been satisfactorily addressed by the applicant.

Clinical Reviewer's Comment: See the complete CMC Review for the original NDA 21-506 and for NDAs 21-506/21-754 (esophageal candidiasis).

3.2 Animal Pharmacology/Toxicology

The following is an excerpt from the Pharmacology/Toxicology Review:

The major target organs for micafungin toxicity in animals were the liver and testes, with adverse effects also seen in the spleen, at the injection site, and in clinical chemistry and hematology profiles.

Liver toxicity included enlarged discolored livers with centrilobular hypertrophy, single cell necrosis, acidophilic bodies, nuclear hypertrophy, vacuolation, bile duct proliferation, and mitosis. High doses of micafungin (dosed at 5-10 times clinical exposure, based on body surface area comparisons), administered for prolonged periods produced irreversible changes in the liver in both rats and dogs.

Some renal effects were noted in rats in a 26-week study of micafungin toxicity at a dose of 32 mg/kg micafungin. These changes included pigmentation in proximal tubular epithelium, dilatation of the collecting duct, swelling of the collecting duct epithelium, and increased urine volume.

Injection site reactions in rats included hemorrhage and cellular infiltration of the perivascular tissue. These reactions were less severe when micafungin was infused over 1 hour than with bolus injection. Injection site reactions were not observed in dogs, and a local tolerance study in rabbits demonstrated local tissue reactions comparable to control with several concentrations of micafungin (0.5 -4.0 mg/mL).

Histamine release and related reactions (decreased blood pressure and increased heart rate) were observed in rats who received micafungin by bolus injection of 32 mg/kg. However, repeat micafungin doses up to 32 mg/kg, administered by intravenous infusion over a longer time period did not result in the clinical signs of histamine release, suggesting that the potential effects of histamine release at high doses of micafungin could be minimized by avoiding bolus injections or rapid infusion.

Although increases in plasma histamine were observed in dogs who received high doses of micafungin (100 mg/kg), no effects on blood pressure, heart rate or electrocardiograms were reported.

Micafungin was shown to hemolyze rabbit RBCs *in vitro*, and has known surfactant activity at concentrations of 0.1 to 100 mg/mL. Laboratory changes associated with hemolysis were observed in animals including decreased erythrocytes, hemoglobin and hematocrit, as well as

increased reticulocytes, potassium and bilirubin, along with splenic congestion, pigmentation, and increased weight as well as hypercellularity in the femoral bone marrow. These laboratory and histopathological changes which occurred mostly in the rat, at doses of 10-32 mg/kg micafungin are indicative of hemolysis with this drug. Signs of hemolytic anemia were also observed in dogs following a single dose of 200 mg/kg micafungin; however, splenic congestion was reported less frequently in dogs than in rats.

No evidence of QT prolongation with micafungin was observed in the 4-, 13- and 39-week studies in dogs; and *in vitro* studies at clinically relevant doses demonstrated no effect of micafungin on Ikr current in transfected hERG cells, and did not prolong action potential duration.

In a 39-week study in dogs, seminiferous tubular atrophy and decreased sperm count was reported at about 2 and 7 times the recommended clinical dose, based on body surface area comparisons. Rats treated with micafungin at about twice the recommended clinical dose (based on body surface area comparisons) showed increased epidymal weights and decreased sperm counts. There was no impairment of fertility, however, in the animal studies with micafungin. No impact on human reproductive system and fertility would be expected with the proposed clinical dose of micafungin used in the short term.

Evidence of potential micafungin embryotoxicity was demonstrated in rabbits treated with high doses (32 mg/kg) micafungin, resulting in visceral abnormalities (abnormal lobation of the lung, levocardia, retrocaval ureter, anomalous right subclavian artery, and dilatation of the ureter) and abortion.

Clinical Reviewer's Comment: The applicant requested — for micafungin. However, based upon the the data described above, the Pharmacology/Toxicology Reviewer has designated micafungin as category "C." Caspofungin, the only other approved echinocandin, is also labeled Pregnancy Category C due to embryonic toxicity observed in rats and rabbits at exposures of caspofungin similar to those observed in clinical trials.

There was no evidence of mutagenicity in the Ames test for bacterial reversion, the chromosomal aberration test with cultured Chinese hamster lung cells, or the mouse micronucleus test. Carcinogenicity tests were not performed because chronic use of micafungin is not expected.

Micafungin did not induce delayed or immediate-type hypersensitivity in a skin test, active system anaphylaxis, or passive cutaneous anaphylaxis tests in rodents and guinea pigs. Additionally, a micafungin-guinea pig plasma protein complex did not induce a type I immunological reaction.

The NOAEL in rats was 2.5 to 4.0 mg/kg micafungin in 13 week repeat-dose toxicity studies; and the NOAEL in dogs was 3.2 mg/kg micafungin in a 39 week repeat-dose study, and 10 mg/kg in a 13 weeks study.

The minimum lethal dose of micafungin in rats was 125 mg/kg, equivalent to 8.1 times the recommended human clinical dose for esophageal candidiasis, based on body surface area comparisons. The minimum lethal dose in dogs was > 200 mg/kg micafungin.

Overall, none of the toxicity studies in animals indicated a safety concern at the clinically relevant doses of micafungin (50 or 150 mg/day) in humans. However, as discussed in the integrated summary of safety, potential safety concerns for human use identified in the micafungin safety database include serious allergic reactions, anaphylaxis and anaphylactoid reactions, clinical hepatic adverse events and liver function test abnormalities, hemolysis or hemolytic anemia, renal failure or impairment and abnormalities in serum BUN and creatinine, injection site reactions and allergic or histamine-type reactions.

Clinical Reviewer's Comment: See the complete Pharmacology/Toxicology Review for NDAs 21-506/21-754 (esophageal candidiasis) and the Integrated Summary of Safety in this review (Section 7), as well as the ISS in the Medical Officer's Review of NDA 21-754 for a discussion of potential safety concerns with micafungin in humans.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The data in this review comes from multiple sources:

- Published meta-analyses; review articles; and placebo-controlled trials of antifungal prophylaxis, with special attention to those using fluconazole, including Goodman, et al. [1992] and Slavin, et al. [1995] trials: \\Cdsesub1\n21506\N_000\2004-08-24
- Study 98-0-050 (reanalysis of the results compared to fluconazole with respect to proven breakthrough infections due to *Candida* species): \\Cdsesub1\n21506\N_000\2002-04-29 and \\Cdsesub1\n21506\N_000\2004-08-24
- Efficacy Data from Study 98-0-047 (non-comparative, open-label, multicenter study of non-esophageal *Candida* infections): \\Cdsesub1\n21754\N_000\2004-04-23
- Safety Data on the 50 mg dose of micafungin (including Studies 98-0-047 and FG-463-21-09, in addition to Study 98-0-050): \\Cdsesub1\n21506\N_000\2004-10-25\041025; \\Cdsesub1\n21506\N_000\2005-01-10A; \\Cdsesub1\n21506\N_000\2005-01-10
- Medical Officer's Review of original NDA 21-506 (submitted April 29, 2002)
- Plasma and tissue concentrations of micafungin and animal models of infection (exposure-response data): \\Cdsesub1\n21506\N_000\2004-08-24

4.2 Tables of Clinical Studies

Three clinical trials conducted by the applicant supported the prophylaxis indication and are shown in Table 1 below. In addition, the applicant submitted published meta-analyses; review articles; and placebo-controlled trials of antifungal prophylaxis, which are summarized in tabular form in Section 11: *"Appendix 1: Review of Antifungal Prophylaxis in Clinical Trials."* Detailed

information on the Goodman, et al. [1992] and Slavin, et al. [1995] trials can be found in Section 12: "*Appendix II: Comparison of Study 98-0-050; Goodman et al. and Slavin et al. Trials.*"

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TABLE 1
Clinical Studies Used to Support Prophylaxis Indication
Conducted by Fujisawa

Study #	Population	Design	Number of Patients
98-0-050	Adult and pediatric patients (≥ 6 months old) scheduled to undergo an autologous or syngeneic (for hematologic malignancies) or allogeneic hematopoietic stem cell transplant.	Multicenter, double-blind, randomized, study of 50 mg micafungin (1 mg/kg for patients ≤ 40 kg) compared to fluconazole 400 mg (8 mg/kg for patients < 50 kg)	Micafungin = 425 Fluconazole = 457
FG-463-21-09	HIV positive adult patients with confirmed esophageal candidiasis	Multicenter, double-blind, randomized study of 50 mg, 100 mg, or 150 mg of micafungin versus fluconazole	N=101 total; 50 mg = 64; 100 mg = 62 150 mg = 59 fluconazole = 60
98-0-047	Adult and pediatric patients with candidemia or invasive candidiasis; divided into de novo patients or efficacy failure patients (who received either micafungin alone or in addition to their current antifungal therapy)	Multicenter, open-label, non-comparative	Micafungin 50 mg (1 mg/kg for patients ≤ 40 kg) as initial dose; dose could be increased in 50 mg increments (1 mg/kg) up to 200 mg (4 mg/kg) per day

4.3 Review Strategy

The Clinical Reviewer read the published literature articles submitted by the applicant and focused mainly on the Goodman, et al. [1992] and Slavin, et al. [1995] trials, in an effort to determine their applicability to the study design and results of Study 98-0-050. Information, also provided by the applicant, on plasma and tissue concentrations of micafungin in humans and animal models of infection (exposure-response data) was reviewed to determine whether the results could be extrapolated to humans with *Candida* infections.

The efficacy criteria comprising the composite primary endpoint of Study 98-050, as determined in the original submission of NDA 21-506 and reported in the Medical Officer's review, was re-assessed independently by the Clinical Reviewer, in addition to the reanalysis of proven breakthrough infections due to *Candida* species, as conducted by the applicant.

Efficacy data from Study 98-0-047 (esophageal candidiasis) was reviewed in detail by Mary Singer, M.D., Medical Officer assigned to NDA 21-754.

Safety Data on the 50 mg dose of micafungin (including Studies 98-0-050, 98-0-047 and FG-463-21-09) was requested from the applicant in the form of summary tables and reviewed by the Clinical Reviewer, who compared incidence rates of specific and overall adverse events between the micafungin and fluconazole treated patients. Incidence rates of adverse events in micafungin treated patients were compared across age groups and between males and females and to patients treated with fluconazole in the same subgroup. The safety summary from the applicant's original report of Study 98-0-050 was also reviewed.

4.4 Data Quality and Integrity

As noted by the Medical Officer in the original NDA 21-506, the Division of Scientific Investigations (DSI) conducted an inspection of study sites used in Study 98-0-050 and found no major deficiencies and concluded that the data appeared acceptable for review purposes.

A 10% random sample of CRFs for Study 98-0-050 was also thoroughly assessed in the course of the Medical Officer's review of the original submission of NDA 21-506. Overall, the Medical Officer found that the findings in the 10% random sample were consistent with the findings of the applicant.

4.5 Compliance with Good Clinical Practices

According to the Medical Officer's review of the original submission of NDA 21-506, trials were conducted in accordance with the Declaration of Helsinki and Good Clinical Practice (GCP) and that written informed consent was obtained from each patient or legal guardian prior to enrollment. No other issues were identified.

4.6 Financial Disclosures

According to the Medical Officer's review of the original submission of NDA 21-506, there were no financial disclosures in the application. The reviewer found no potential financial conflict that could cast doubt on the findings of the application.

5 CLINICAL PHARMACOLOGY

The clinical pharmacology of micafungin was previously described in Clinical Pharmacology and Biopharmaceutics Review for original NDA 21-506. The Approvable letter for NDA 21-506 (January 29, 2003) contained the following clinical pharmacology comments (not deficiciencies):

The following investigations would provide valuable information regarding the safe and effective use of micafungin sodium. You may be able to conduct some of these studies in the course of further development of Mycamine prior to approval; otherwise, they may constitute requests for post-marketing commitments at the time of approval.

- Adequately determine the basic parameter values, dose linearity, and time dependency in micafungin pharmacokinetics at the proposed clinical dosing regimen at steady-state.
- Analyze the effects of age, gender, and race on micafungin pharmacokinetics.
- Determine the complete steady-state pharmacokinetic profiles of the most abundant metabolite (M5) and active metabolites (M1 and M2) in a multiple-dosing regimen.
- Adequately determine the extent of protein binding of parent compound *in vivo*.

The Clinical Pharmacology/Biopharmaceutics review of the amendment to NDA 21-506 (and NDA 21-754, esophageal candidiasis) focuses on the applicant's response to the above comments, as well as a review of exposure-response, an additional mass balance study, additional drug-drug interaction studies, as well as the analytical methods associated with these studies. The results are summarized in Section 5.1 "*Pharmacokinetics*", Section 5.2 "*Pharmacodynamics*", and Section 5.3 "*Exposure-Response Relationships*."

The recommendation of the Clinical Pharmacology/Biopharmaceutics Reviewer is for the applicant to submit new data, as a Phase IV commitment, to adequately assess micafungin pharmacokinetics in pediatric patients aged between 2 and 16 years. As stated in the Clinical Pharmacology/Biopharmaceutics review for the original submission of N21-506, pharmacokinetic blood samples were not adequately collected in the pivotal pediatric study (Study 98-0-043) conducted in patients with febrile neutropenia. An unidentified number of samples appeared to have been drawn from the micafungin infusion port and many samples were not collected at critical time points. The statistical manipulation applied by the Sponsor, at that time, was not felt appropriate to resolve the blood sampling errors.

Clinical Reviewer's Comment: For more information see the complete Clinical Pharmacology and Biopharmaceutics review by Jang-Ik Lee, Ph.D.

5.1 Pharmacokinetics

New pharmacokinetic information submitted since the original NDA 21-506 was reviewed, is summarized below.

5.1.1 Basic Pharmacokinetic Parameters

Micafungin: Table 2 presents the basic pharmacokinetic parameter values of micafungin determined following the first (Day 1) and steady-state (Day 14 or 21) intravenous infusion of micafungin 50 mg, 100 mg, or 150 mg a day over an hour to 54 HIV-positive patients with esophageal candidiasis (Study FG-463-21-09).

TABLE 2
Micafungin Pharmacokinetic Parameters (mean ± SD) Determined Following an 1-hour Intravenous Infusion of Micafungin to HIV-Positive Patients with Esophageal Candidiasis

Time	PK Parameter	50 mg/day (n = 20)	100 mg/day (n = 20)	150 mg/day (n = 14)
After First Dose	Cmax (μg/mL)	4.1 ± 1.4	8.0 ± 2.4	11.6 ± 3.1
	AUCτ (μg-hr/mL)	35.7 ± 8.9	74.5 ± 18.7	104.3 ± 26.3
	AUC∞ (μg-hr/mL)	53.4 ± 17.8	107.9 ± 30.7	150.6 ± 44.6
	CL (mL/hr/kg)	19.3 ± 5.9	19.8 ± 5.4	20.4 ± 5.5
	Vz (mL/kg)	401 ± 124	388 ± 114	407 ± 103
	t½ (hr)	14.9 ± 4.3	13.8 ± 3.0	14.1 ± 2.6
At Steady State	Cmax (μg/mL)	5.1 ± 1.1	10.1 ± 2.6	16.4 ± 6.5
	AUCτ (μg-hr/mL)	54.3 ± 13.1	115.3 ± 24.9	166.5 ± 40.4
	CL (mL/hr/kg)	18.1 ± 4.2	18.1 ± 4.3	17.5 ± 4.8
	t½ (hr)	15.6 ± 2.8	16.9 ± 4.4	15.2 ± 2.2

Micafungin Metabolites: Whereas metabolites M1 and M2 have comparable *in vitro* antifungal activity to the parent compound, metabolite M5 is inactive but most abundant. Table 3 presents pharmacokinetic parameter values for micafungin metabolites M1, M2, and M5 determined following a steady-state intravenous infusion of micafungin 50 mg, 100 mg, or 150 mg over an hour. Exposure to micafungin metabolites was low: M1 and M2 accounted for 11% and 2% of the systemic exposure to parent drug at steady state, respectively. M5 was the predominant metabolite in plasma with AUCτ values ranging between 6% and 24% of those for the parent compound at steady state.

TABLE 3
Pharmacokinetic Parameter Values of Micafungin Metabolites Determined Following a Steady-state Intravenous Infusion of Daily Micafungin Doses Over an Hour to HIV-Positive Patients with Esophageal Candidiasis

Metabolite	PK Parameter	50 mg/day (n = 20)	100 mg/day (n = 20)	150 mg/day (n = 14)
M1	Tmax (hr)	12.6 ± 12.9	6.4 ± 8.1	4.3 ± 6.7
	Cmax (μg/mL)	0.31 ± 0.14	0.62 ± 0.25	0.93 ± 0.34
	AUCτ (μg-hr/mL)	6.0 ± 2.1	12.1 ± 4.0	18.1 ± 4.7
	t½ (hr)	64.6 ± 31.8	62.0 ± 30.6	53.5 ± 15.5
M2	Tmax (hr)	22.9 ± 24.7	21.2 ± 22.6	26.2 ± 26.6
	Cmax (μg/mL)	0.08 ± 0.02	0.10 ± 0.03	0.14 ± 0.04
	AUCτ (μg-hr/mL)	0.98 ± 0.69	1.81 ± 0.55	2.57 ± 0.77
	t½ (hr)	NC	NC	NC
M5	Tmax (hr)	5.7 ± 3.3	6.9 ± 3.8	8.4 ± 3.4
	Cmax (μg/mL)	0.41 ± 0.20	0.63 ± 0.21	1.00 ± 0.29
	AUCτ (μg-hr/mL)	7.84 ± 3.52	12.8 ± 4.5	19.8 ± 5.7
	t½ (hr)	22.7 ± 4.5	25.3 ± 5.2	24.5 ± 9.2

NC, not calculable

5.1.2 Linearity, Accumulation, and Time Dependency in Micafungin Pharmacokinetics

Micafungin pharmacokinetics were linear over the proposed dose range of 50 mg to 150 mg administered once daily: all coefficients (r) for the correlation between micafungin dose, and micafungin C_{max} or AUC following the first and steady-state doses presented in Table 1 were > 0.99. Micafungin accumulation ratios (ratio of micafungin AUCτ at steady state to AUCτ at the first dose) were 1.52, 1.55, and 1.60 at daily micafungin doses of 50 mg, 100 mg, and 150 mg, respectively. The mean values of systemic clearance (CL) and terminal half-life (t½) estimated following 1-hour intravenous infusion of micafungin at steady state were not meaningfully different from the values estimated following the first dose (Table 2). The mean trough concentrations of micafungin measured at Days 3, 7, and 14 remained relatively stable.

5.1.3 Mass Balance

Following a single intravenous infusion of ^{14}C-micafungin 25 mg to 6 healthy subjects, total radioactivity was eliminated primarily in the feces accounting for a mean of 71.0% of the administered dose by the end of the continuous collection period (28 days post dose). However, excretion *via* the feces was very slow with a mean recovery of 60.6% at 14 days post dose. Excretion *via* urine accounted for a mean of 11.6% of the dose by the end of the 28-day collection period. Total radioactivity in feces and urine accounted for a mean of 82.5% of the administered dose.

5.1.4 Protein Binding

When determined in human plasma samples following a single dose of micafungin 100 mg, micafungin binding to plasma protein were approximately 99.8%. Micafungin protein binding in subjects with moderate hepatic dysfunction (Child-Pugh score 7-9) or severe renal impairment (creatinine clearance <30 mL/min) was similar to that of healthy subjects with normal hepatic and renal function. When determined *in vitro*, micafungin was highly bound to plasma proteins (>99%) primarily to albumin and, to a lesser extent, to alpha-1-acid glycoprotein. The extent of plasma protein binding was independent of micafungin concentrations at the range from 10 μg/mL to 100 μg/mL.

5.1.5 Special Populations

Based on the population pharmacokinetic analysis conducted by the applicant, no dosage adjustments are needed in patients with reduced renal function reduced liver function and also no dosage adjustments are needed based on age, race and gender of the patients. These findings were confirmatory of the Phase I pharmacokinetic studies conducted by the applicant.

5.1.6 Drug-Drug Interactions

Mycophenolate mofetil, cyclosporine, tacrolimus, prednisolone, sirolimus, nifedipine, fluconazole, ritonavir, and rifampin were evaluated. In these studies, no interaction that altered the pharmacokinetics of micafungin was observed.

There was no effect of single dose or multiple doses of micafungin on mycophenolate mofetil, cyclosporine, tacrolimus, prednisolone, and fluconazole pharmacokinetics. The effect of micafungin on the pharmacokinetics of ritonavir and rifampin was not evaluated.

Nifedipine and sirolimus were shown to interact with micafungin. The C_{max} and AUC_{∞} of nifedipine determined following a single oral dose of nifedipine 10 mg administered in combination with a steady-state intravenous dose of micafungin 150 mg were increased by 42% and 18%, respectively, compared to those determined following the same dose of nifedipine alone. The $AUC_{0\text{-}72hr}$ of sirolimus determined following a single oral dose of sirolimus 6 mg administered in combination with a steady-state intravenous dose of micafungin 150 mg was increased by 21% compared to the AUC determined following the same dose of sirolimus alone. However, the C_{max} of sirolimus was not affected by micafungin coadministration. Patients receiving sirolimus or nifedipine in combination with micafungin should be monitored for sirolimus or nifedipine toxicity and sirolimus or nifedipine dosage should be reduced if necessary.

The effect of mycophenolate mofetil, cyclosporine, tacrolimus, prednisolone, fluconazole, ritonavir, and rifampin on the pharmacokinetics of micafungin was evaluated and no interactions were observed.

There was no effect of single dose or multiple doses of micafungin on mycophenolate mofetil, cyclosporine, tacrolimus, prednisolone, and fluconazole pharmacokinetics. The effect of micafungin on the pharmacokinetics of ritonavir and rifampin was not evaluated.

5.2 Pharmacodynamics

No new information was submitted by the applicant.

5.3 Exposure-Response Relationships

Dose-effectiveness and dose-toxicity analysis were performed using data from patients with esophageal candidiasis who received doses from 50 mg to 150 mg. The results showed the effectiveness of micafungin for the treatment of esophageal candidiasis increases as dose is increased and maximum effectiveness is seen at the 150 mg dose. There was no relationship between dose of micafungin and liver enzyme elevations.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

Prophylaxis of *Candida* infections in patients undergoing hematopoietic stem cell transplantation.

6.1.1 Methods

The amendment to NDA 21-506 for micafungin has three major parts: literature review, re-analysis of Study 98-0-050, and response to other FDA inquiries.

6.1.2 General Discussion of Endpoints

The primary endpoint in Study 98-0-050 was a composite endpoint defined as: the absence of a proven, probable, or suspected systemic fungal infection through the end of therapy *and* the absence of a proven or probable systemic fungal infection through the end of the 4-week post-therapy period. Both criteria had to be met in order for the patient to be considered a success. Safety parameters, survival, and discontinuation for adverse events related to study drug were removed from the definition of the composite endpoint.

Although the Division agreed on the composite endpoint, after the trial was complete they expressed concern regarding the very low number of infections that emerged from the prophylaxis trial (Study 98-0-050) and reminded the applicant that it must make a good case for antifungal activity (see NDA 21-506 Approvable Letter, January 29, 2003 in Section 2.5 "Pre-submission Regulatory Activity). Results from this trial revealed that the number of emergent infections was numerically low, as was the use of empiric antifungal therapy, raising questions as to the risk of infection in the patient population studied. There were 14 proven breakthrough fungal infections (there were 6 infections due to *Candida* species, 4 due to *Aspergillus* species, 3 due to *Fusarium* species, and one due to *Zygomyces* species).

As a result of further discussions with the FDA, the applicant requested the indication for micafungin be narrowed from "prophylaxis of ' — to "prophylaxis of *Candida* infections in patients undergoing hematopoietic stem cell transplantation".[6] Fluconazole is approved for a similar indication of prophylaxis of *Candida* infection in patients undergoing bone marrow transplantation. Since fluconazole is approved for the indication of prophylaxis of *Candida* infections in patients undergoing bone marrow transplantation, superiority of micafungin to fluconazole would not be required. However, a result of similar efficacy of micafungin to fluconazole based largely upon possible or probable cases of *Candida* infection would not provide the same level of support as provided by Study 98-0-050 for the original indication.[7]

6.1.3 Study Design

Study 98-0-050 was a multicenter, randomized (1:1), stratified (by center, age, type of transplant, and risk for transplant-related mortality), double-blind study of micafungin compared to fluconazole in adult and pediatric patients (≥ 6 months of age) scheduled to undergo an autologous or syngeneic (for hematologic malignancies) or allogeneic hematopoietic stem cell transplant.

6 March 28, 2003 face-to-face meeting
7 May 23, 2003 FDA letter to the applicant

Treatment was administered in an inpatient or outpatient setting. Patients received either micafungin, 50 mg per day (1 mg/kg per day for patients weighing < 50 kg), or fluconazole (400 mg per day or 8 mg/kg for patients < 50 kg) once daily as a 1-hour infusion.

Prophylaxis with study drug was to continue until one of following occurred: the patient experienced neutrophil recovery to a post nadir ANC of ≥ 500 cells/mm3 (study drug could be continued for up to 5 days post-neutrophil recovery at the investigator's discretion); the patient developed a proven, probable, or suspected fungal infection; the patient developed unacceptable toxicity; the investigator decided that it was in the best interest of the patient to discontinue; the patient declined further study participation; death occurred; or the patient received prophylactic therapy to a maximum of 42 days after transplant (day +42 after transplant).

A suspected systemic fungal infection was established if all of the following criteria were met for at least 96 hours: neutropenia (ANC < 500 cells/mm3); persistent or recurrent fever (≥ 100.4°F, ≥ 38.0°C) for which there was no known etiology; and failure to respond to at least 96 hours of broad spectrum antibacterial therapy.

All patients who received at least one dose of study drug were included in the full analysis set and the safety analyses. The full analysis set was the primary data set for analysis of efficacy.

The primary efficacy endpoint was success, defined as the absence of a proven, probable, or suspected systemic fungal infection through the end of therapy, AND the absence of a proven or probable systemic fungal infection through the end of the 4-week post-therapy period.

The secondary efficacy endpoints included the incidence of proven or probable systemic fungal infections during the study (through 4 weeks post-therapy); the incidence of proven, probable or suspected systemic fungal infections through the end of therapy; the incidence of proven or probable systemic fungal infections during the post-therapy period for patients who did not have a systemic fungal infection through the end of therapy; the incidence of proven or probable systemic fungal infections during the study by organism; the incidence of the use of systemic antifungal agents during the post-therapy period; the time to failure during the study; the time to suspected fungal infection; the incidence of superficial fungal infections through the end of therapy; and the incidence of fungal colonization at baseline and at the end of therapy.

Safety assessment was based upon adverse events, laboratory profile, and vital signs. All adverse events through 72 hours after the last administration of study drug, whether ascertained through patient interview, physical examination, laboratory findings, or other means, were recorded. Ongoing adverse events were followed for as long as necessary to adequately evaluate the patient's safety or until the event stabilized.

A total of 889 patients were randomized (426 micafungin, 463 fluconazole); 882 patients were in the full analysis set (425 micafungin, 457 fluconazole); 830 patients were in the per protocol set (397 micafungin, 433 fluconazole).

There were 39 patients in the micafungin group and 45 patients in the fluconazole group less than 16 years of age (mean 7.4 years micafungin and 7.2 years fluconazole).

The mean duration of prophylaxis in patients was 18 days (range 1 to 51 days).

Patient transplant characteristics are shown in Table 4. The definition of high risk and low risk for allogeneic transplants is shown in Table 5.

Clinical Reviewer's Comment: Table 4 was extracted from a larger table in the applicant's original NDA submission.

TABLE 4
Summary of Transplant Characteristics

Characteristic	Classification	Number of Patients (%) of the Total Study Population (N=882)
Baseline Disease Status	Active	365 (41%)
	Remission	326 (37%)
	Relapse	195 (22%)
Type of Transplant*	Allogeneic	476/882 (54%)
	Autologous or Syngeneic	404/882 (46%)
	None	2/882 (< 1%)
Donor Type*	Matched Sibling Donor	291 (33%)
	Other Donor	185 (21%)
	Autologous	404 (46%)
Type of Cells*	Bone marrow cells	244 (85%)
	Peripheral stem cells	606 (69%)
	Cord Blood Cells	30 (3%)
Risk of Transplant-Related Mortality**	High Risk	279 (32%)
	Low Risk	198 (22%)
	Not applicable	405 (46%)

* two patients were not transplanted
** Criteria based on the outcomes from the program and modified by a panel of study investigators.
Source: Table 13.2.6.1 in the applicant's original study report for Study 98-0-050 in NDA 21-506

TABLE 5
ALLOGENEIC TRANSPLANT STRATIFICATION CRITERIA

Diagnosis	Low Risk	High Risk
Acute Myelogenous Leukemia, Acute Lymphocytic Leukemia	Complete Remission 1, 2	Complete Remission 3+ Any relapse
Chronic Myelogenous Leukemia	Chronic Phase 1	Acute Phase Blast Crisis Accelerated Phase Chronic Phase 2+
Chronic Lymphocytic Leukemia	N/A	ALL
Hodgkin's Disease, Non-Hodgkin's Lymphoma	Complete Remission 1, 2 Partial Remission 1, 2	Resistant Relapse Primary Induction Failure Complete/Partial Remission 3+
Multiple Myeloma	Complete Remission 1, 2 Partial Remission 1, 2	Other
Myelodysplasia Syndrome, Myeloproliferative Disease	N/A	ALL
Aplastic Anemia	ALL	N/A
Paroxysmal Noctural Hemoglobinuria	ALL	N/A
Pure Red Cell Aplasia	ALL	N/A
Breast Cancer	Complete Remission 1, 2 Partial Remission 1, 2	Resistant Relapse Complete/Partial Remission 3+
Other Malignancy (carcinoma, ovarian, peripheral neuroectodermal tumor, sarcoma)	N/A	ALL
Congenital Non-Malignant Disease (immunodeficiency disease, inborn errors of metabolism, familial erythrophagocytic disorders)	N/A	ALL
Congenital Non-malignant Disease (congenital hematologic disorders such as sickle cell anemia or thalassemia)	ALL	N/A
Other Non-malignant Disease (autoimmune disease, eosinophilic disorders)	ALL	N/A

Source: Appendix to Protocol for Study 98-0-050 in the applicant's original study report for Study 98-0-050 in NDA 21-506

The more common baseline underlying diseases in the 476 allogeneic transplant patients were: chronic myelogenous leukemia (22%), acute myelogenous leukemia (21%), acute lymphocytic leukemia (13%), and non-Hodgkin's lymphoma (13%). In the 404 autologous and syngeneic transplant patients the more common baseline underlying diseases were: multiple myeloma (37.1%), non-Hodgkin's lymphoma (36.4%), and Hodgkin's disease (15.6%).

6.1.4 Efficacy Findings

Summary of Literature Review: The results of published meta-analyses and comprehensive review articles demonstrate that prophylaxis with fluconazole significantly reduces the incidence of invasive yeast infections in cancer patients with neutropenia. These analyses further showed that the benefit of prophylaxis was most evident in patients undergoing BMT/HSCT, in non-BMT settings where the incidence of invasive infection was expected to exceed 15% when prophylaxis was not used, and in patients with prolonged neutropenia.

There was a wide range in the incidence of invasive fungal infections across the placebo-controlled studies, which likely reflects the heterogeneity of the patient populations and treatment modalities. However, two large placebo-controlled trials [Goodman et al, 1992; Slavin et al, 1995] demonstrated the benefit of fluconazole prophylaxis versus placebo in BMT/HSCT patients with an estimated treatment effect for overall systemic fungal infections of 11% to 13%. These two studies provide the best estimates of the treatment effect of fluconazole compared to placebo during the pre-engraftment neutropenic time period of HSCT.

Treatment effect is directly dependent on the baseline risk of fungal infection. Therefore, the applicant directly compared the study design and patient population in Study 98-0-050 to the Goodman and Slavin studies to demonstrate the comparability of the three studies and support their position that the Goodman and Slavin studies can serve as an appropriate basis for estimating a new treatment difference for the analysis of noninferiority for proven *Candida* infections in Study 98-0-050.

A more complete review of antifungal prophylaxis trials submitted by the applicant can be found in Appendix I (Section 11). Details on how the Goodman and Slavin trials compare to Study 98-0-050 can be found in Appendix II (Section 12).

Study 98-0-050: As determined by the primary endpoint, 80.0% of the micafungin patients were "successes" (i.e., had an absence of fungal infections as defined by the composite endpoint) as compared with 73.5% of the fluconazole patients, as shown in Table 6. The resulting 6.5% difference had a 95% confidence interval (CI) of 0.9% to 12.0%. This interval was greater than the prespecified 10% non-inferiority margin. This difference was consistent in patients who underwent an allogeneic (3.0%) or an autologous (9.1%) transplant.

In the per protocol set, the overall success rate micafungin (81%; 322/397) remained statistically superior to fluconazole (74.1%, 321/433) with a difference of 7.0% (95% CI of the difference [1.3%, 12.6%]).

Clinical Reviewer's Comment: Table 6 was created by the applicant. The micafungin data is represented by the column labeled "FK463".

TABLE 6
Overall Treatment Success and Treatment Success by Type of Transplant at the End of Study

	FK463 (n=425)	Fluconazole (n=457)	Treatment Difference ††	95% CI †
Overall	340 (80.0%)	336 (73.5%)	+ 6.5%	(0.9%, 12.0%)
Type of Transplant				
Allogeneic	157/220 (71.4%)	175/256 (68.4%)	+ 3.0%	
Autologous or Syngeneic	181/203 (89.2%)	161/201 (80.1%)	+ 9.1%	
None	2/2 (100.0%)	0 (0.0%)	N/A	

Patient base: all randomized patients who received at least 1 dose of study drug (full analysis set).
Treatment success: absence of proven, probable, or suspected systemic fungal infection through the end of therapy and absence of proven or probable systemic fungal infection through the end of study.
† 95% confidence interval for the difference in overall success rate is based on the large sample normal approximation test.
†† FK463 rate - fluconazole rate
N/A: not applicable
Source: Table 12 in applicant's original report for Study 98-0-050

Clinical Reviewer's Comment: During the review, it was determined by the Clinical and Statistical Reviewers that the applicant's definition of success was not appropriate. Patients who did not develop a fungal infection, but died during the study were included as successes, which is not considered acceptable by the Division. Patients who received empirical antifungal therapy were counted as having suspected fungal infections, whether or not they met the protocol-defined criteria for suspected infection. Also, patients who met the protocol-defined criteria for suspected infection, but did not receive a systemic antifungal agent, were not included as failures.

To accurately account for all failures in Study 98-0-050, especially cases of suspected fungal infection, the Division requested from the applicant a detailed breakdown of all patients in the full analysis set according to the following process:

1) All deaths, regardless of causality. Patients who died following a diagnosis of proven/probable infection should be noted.
2) Of the remaining patients (minus deaths), all patients diagnosed (by the blinded, independent reviewer) as having a proven or probable infection.

3) Of the remaining patients (minus deaths and patients with proven/probable fungal infections), all patients who met the protocol definition for suspected fungal infection, regardless of whether or not they received systemic antifungal therapy.

   The original protocol definition of suspected fungal infection consisted of three components:
   - Patients with neutropenia (ANC < 500/mm^3) AND
   - Persistent fever of ≥ 100.4°F (≥ 38°C) for which there is no known etiology OR a recurrent fever of > 100.4°F (> 38°C) on two measurements of temperature at least 3 hours apart or a single measurement of ≥ 101.3°F (≥ 38.5°C) AND
   - Failed to respond to 96 hours of adequate broad spectrum antibacterial therapy.

   For this analysis, the applicant re-reviewed all patients who received empirical antifungal therapy and the applied the protocol definition of suspected fungal infection. The applicant also further clarified the criteria of persistent/recurrent fever, for the purposes of reducing patient ambiguity, as follows:

   A persistent fever was defined as four consecutive days of fever greater than 38°C. A recurrent fever was defined as either having at least one day with a temperature ≥ 38.5 °C after having at least one prior temperature > 38 °C; or having two days of temperatures > 38 °C after having at least one prior temperature > 38°C.

   Additionally, all patients who did not receive empirical antifungal therapy (and who did not die, or have a proven/probable infection) and had at least one day of fever ≥ 38°C during neutropenia, were re-reviewed applying the protocol criteria of suspected fungal infection, as detailed above.

4) Of the remaining patients (minus deaths and patients with proven/probable fungal infections), all patients who were lost to follow-up.
5) Of the remaining patients (minus deaths, patients lost-to-follow-up, patients with proven/probable/suspected infection), all patients who received systemic antifungal therapy. Note, these patients were not included in the calculation of failure, based on the protocol defined primary endpoint.

Results of this re-analysis are shown in the tables below.

Clinical Reviewer's Comment: Tables 6A and 6b were created by the reviewer from a single table submitted by the applicant on February 15, 2005. The information on patients lost to follow-up was added March 7, 2005 after additional communication with the applicant.

TABLE 6A
FDA Requested Re-Analysis of Success in Study 98-0-050

	Micafungin (n=425)	Fluconazole (n=457)
Treatment Success	**343 (80.7%)**	**337 (73.7%)**
+7.5% difference (micafungin – fluconazole) [95% CI=1.5%, 12.5%]		
Treatment Failure	82 (19.3%)	120 (26.3%)
All Deaths	18 (4.2%)	26 (5.7%)
Proven/probable fungal infection prior to death	1 (0.2%)	3 (0.7%)
Proven/Probable fungal infection (not resulting in death)	6 (1.4%)	8 (1.8%)
Suspected fungal infection[1,2]	53 (12.5%)	83 (18.2%)
Lost to follow-up[3]	5 (1.2%)	3 (0.7%)

[1] 10 patients in each group met the criteria for suspected fungal infection, but did not receive empirical systemic antifungal therapy. All other patients met the criteria and received empirical systemic antifungal therapy.
[2] micafungin (0572532), 4 fluconazole patients (0203612, 0512501, 2472101, and 2051002) were included as suspected fungal infections, although they were initiated on empirical systemic antifungal therapy after 72-96 hours, rather than at least 96 hours as defined by the protocol. These patients met the other protocol criteria and therefore, the Clinical Reviewer agrees with including these patients as having a suspected fungal infection.
[3] Patients lost to follow-up: micafungin (0511015, 0571001, 3421016, 4881001, and 4881004), fluconazole (0701002, 0081009, 0703002). These patients were included as failures in the applicant's original analysis.

TABLE 2b
FDA Requested Re-Analysis of Empirical Therapy Use

Use of systemic antifungal therapy post-therapy	178 (41.9%)	192 (42.0%)
Reason for use [1]		
Prophylaxis	160 (89.9%)	174 (90.6%)
Empirical	19 (10.7%)	27 (14.1%)
Treatment	9 (5.1%)	6 (3.2%)
Maintenance	3 (1.7%)	1 (0.5%)

1: patients could have received more than one antifungal agent post-therapy; included use beginning on day of last dose of study drug

A summary of success, using the applicant's original protocol definition, by age is presented in Table 7. Patients in the micafungin group had higher rates of success across all age groups compared to fluconazole. The success rate for pediatric patients was lower than for adults in both groups. All but two pediatric patients in each group underwent an allogeneic transplant, which is considered to be a higher risk population than those who receive autologous transplants. The rates were consistent between the full analysis set and per protocol set (data not shown).

Clinical Reviewer's Comment: Table 3 was created by the applicant. The micafungin data is represented by the column labeled "FK463".

TABLE 7
Treatment Successes at the End of Study by Age

Age Group	FK463 (n=425)		Fluconazole (n=457)		Treatment Difference†
<16 Years	27/39	(69.2%)	24/45	(53.3%)	+15.9%
≥16 Years	313/386	(81.1%)	312/412	(75.7%)	+5.4%
≥ 65 Years of Age	32/33	(97.0%)	16/23	(69.6%)	+27.4%
< 65 Years	308/392	(78.6%)	320/434	(73.7%)	+4.9%

Patient base: all randomized patients who received at least 1 dose of study drug (full analysis set).
Treatment success: absence of proven, probable, or suspected systemic fungal infection through the end of therapy and absence of proven or probable systemic fungal infection through the end of study.
† FK463 rate - fluconazole rate
Source: Table 14 in applicant's original report for Study 98-0-050

A summary of successes, using the applicant's original protocol definition, by gender of the patients is presented in Table 8. The success rate was similar between males and females for both micafungin and fluconazole, although the rates were numerically higher for micafungin than fluconazole for both males and females.

Clinical Reviewer's Comment: Table 8 was created by the applicant. The micafungin data is represented by the column labeled "FK463".

TABLE 8
Treatment Success at the End of Study by Gender

	FK463 (n=425)	Fluconazole (n=457)	Treatment Difference †
Male	203/253 (80.2%)	205/274 (74.8%)	+5.4%
Female	137/172 (79.7%)	131/183 (71.6%)	+8.1%

Patient base: all randomized patients who received at least 1 dose of study drug (full analysis set).
Treatment success: absence of proven, probable, or suspected systemic fungal infection through the end of therapy and absence of proven or probable systemic fungal infection through the end of study.
† FK463 rate - fluconazole rate
Source: Table 15 in the applicant's original report for Study 98-0-050

A summary of successes, using the applicant's original definition, by other subgroups, including race and factors associated with risk of infection (risk of transplant-related mortality and occurrence of GVHD during the study) can be found in Table 9 below.

Clinical Reviewer's Comment: Table 9 was created by the applicant. The micafungin data is represented by the column labeled "FK463".

TABLE 9
Rates of Treatment Success by Subgroup

SUBGROUP	CLASS	FK463 (n=425)	FLUCONAZOLE (N=457)
NEUTROPENIC STATUS (3)	ANC < 200 CELLS/MM^3	332/413 (80.4%)	325/442 (73.5%)
	ANC ≥ 200 CELLS/MM^3	8/ 12 (66.7%)	11/ 15 (73.3%)
TYPE OF TRANSPLANT	NONE	2/ 2 (100.0%)	0
	ALLOGENEIC	157/220 (71.4%)	175/256 (68.4%)
	AUTOLOGOUS OR SYNGENEIC	181/203 (89.2%)	161/201 (80.1%)
AGE GROUP (YEARS)	≤ 12	23/ 33 (69.7%)	20/ 39 (51.3%)
	> 12	317/392 (80.9%)	316/418 (75.6%)
	< 16	27/ 39 (69.2%)	24/ 45 (53.3%)
	≥ 16	313/386 (81.1%)	312/412 (75.7%)
	< 65	308/392 (78.6%)	320/434 (73.7%)
	≥ 65	32/ 33 (97.0%)	16/ 23 (69.6%)
RACE	AMERICAN INDIAN	1/ 2 (50.0%)	0
	BLACK	24/ 30 (80.0%)	28/ 37 (75.7%)
	CAUCASIAN	309/387 (79.8%)	302/411 (73.5%)
	ORIENTAL	5/ 5 (100.0%)	5/ 8 (62.5%)
	OTHER	1/ 1 (100.0%)	1/ 1 (100.0%)
GENDER	FEMALE	137/172 (79.7%)	131/183 (71.6%)
	MALE	203/253 (80.2%)	205/274 (74.8%)
GVHD DURING STUDY	NO	275/329 (83.6%)	278/355 (78.3%)
	YES	65/ 96 (67.7%)	58/102 (56.9%)
COLONIZATION DURING STUDY	NO	129/159 (81.1%)	153/216 (70.8%)
	YES	211/266 (79.3%)	183/241 (75.9%)
DONOR TYPE (4)	MATCHED SIBLING	102/131 (77.9%)	122/160 (76.3%)
	OTHER DONOR	55/ 89 (61.8%)	53/ 96 (55.2%)
RISK OF TRANSPLANT RELATED MORTALITY (4)	HIGH RISK	92/126 (73.0%)	97/152 (63.8%)
	LOW RISK	65/ 94 (69.1%)	78/104 (75.0%)

(1) DEFINED AS ABSENCE OF PROVEN, PROBABLE OR SUSPECTED SYSTEMIC FUNGAL INFECTION THROUGH THE END OF THERAPY AND ABSENCE OF PROVEN OR PROBABLE SYSTEMIC FUNGAL INFECTION THROUGH THE END OF STUDY.
(2) PATIENTS WHO RECEIVED AT LEAST ONE DOSE OF STUDY DRUG. (3) MINIMUM NEUTORPHIL COUNT DURING STUDY.
(4) ALLOGENEIC TRANSPLANT PATIENTS ONLY.
Source: Table 13.4.5.1 in the applicant's original report for Study 98-0-050

A summary of the proven or probable systemic fungal infections during the study based on protocol-specified diagnostic criteria, confirmed by an independent reviewer, is presented by organism in Table 10.

Clinical Reviewer's Comment: Table 10 was created by the applicant. The micafungin data is represented by the column labeled "FK463".

TABLE 10
Proven or Probable Fungal Infections During the Study by Organism Based on Protocol-Specified Diagnostic Criteria

Organism	FK463 (n=425)		Fluconazole (n=457)	
Proven	**6**	**(1.4%)**	**8**	**(1.8%)**
Aspergillus species	0	(0.0%)	4	(0.9%)
Candida species	4	(0.9%)	2	(0.4%)
Fusarium species	1	(0.2%)	2	(0.4%)
Zygomyces species	1	(0.2%)	0	(0.0%)
Probable	**1**	**(0.2%)**	**3**	**(0.7%)**
Aspergillus species	1	(0.2%)	3	(0.7%)

Patient base: all randomized patients who received at least 1 dose of study drug (full analysis set).
Proven: includes biopsy-proven (with or without culture) invasive or disseminated fungal infection
Probable: includes patients with the characteristic clinical or radiological (chest x-ray, CT scan, other) picture of pulmonary aspergillosis plus a positive BAL specimen.
Source: Table 18 in the applicant's original report for Study 98-0-050

Clinical Reviewer's Comment: According to the study protocol, the case report forms for all patients with an investigator-reported proven or probable breakthrough invasive fungal infection were reviewed in a blinded manner using the protocol-specified diagnostic criteria by an independent reviewer. The independent reviewer confirmed all investigator-reported proven invasive fungal infections (6 in the micafungin group and 8 in the fluconazole group, as shown in Table 6). However, there were an additional 12 patients with reported probable invasive fungal infections who did not meet protocol-specified diagnostic criteria (in addition to the 4 patients shown in Table 10). Of these 12 patients:

Two patients died (1253104 and 4181001, both in the fluconazole group).

One patient reported as having a probable infection was re-classified as having a proven infection according to the protocol (0323003 in the micafungin group).

Six patients (0082502, 0203505, 0321009, 0352504, 0523101, 1252103, all in the micafungin group, met the protocol definition of suspected infection.

The remaining three patients, did not meet the protocol definition of suspected infection, but did receive systemic antifungal therapy (micafungin patients 0311006 and 1233502 and fluconazole patient 0892001).

The Reviewer agrees with the independent reviewer that these patients did not meet the protocol definition of probable infection. All these patients, with the exception of the 3 patients who received systemic antifungal therapy, have been classified as failures in the analysis of the primary endpoint, which is also acceptable to the Reviewer.

A summary of the incidence of fungal colonization at baseline and end of therapy for the full analysis set is shown in Table 11. Baseline fungal surveillance cultures were taken from the oropharynx only. During prophylactic therapy the oropharynx, urine and stool or perirectal area were to be cultured once weekly. The oropharyngeal colonization pattern was similar at baseline for the two groups. At baseline the most common species of *Candida* were *C. albicans*, *C. glabrata*, and non-albicans *Candida*. At the end of therapy, overall colonization from any site was seen in 57.2% (243/425) of micafungin patients and 39.8% (182/457) fluconazole patients. Of the *Candida* species, *C. albicans* was noted in more micafungin patients (55.1% compared to fluconazole (30.2%) patients. However, *C. glabrata* was noted in more fluconazole patients (32.4%) than micafungin patients (4.9%). Other species of *Candida* were not present in substantial numbers at the end of therapy, with the exception of *C. parapsilosis* (6.6% micafungin and 2.2% fluconazole) and *C. krusei* (4.1% and 1.6%, respectively).

Clinical Reviewer's Comments: Candida parapsilosis and C. glabrata are susceptible (dose dependent) to fluconazole, but C. krusei is resistant. According to the Microbiology Review for the original NDA 21-506 submission, Candida albicans (MIC_{90} 0.5 μg/mL) and glabrata (MIC_{90} 0.5 μg/mL) are more susceptible to micafungin than are parapsilosis (MIC_{90} > 8 μg/mL) and krusei (MIC_{90} not done, but MIC range 0.06 to 2 μg/mL). Micafungin is not fungicidal against Candida parapsilosis and there was not enough information to determine if micafungin is fungicidal against albicans. No information was provided about glabrata or krusei.

In Study 98-0-047 (invasive candidiasis) infections with non-albicans species required treatment with a higher dose (100 mg) of micafungin, which has potential implications for the types of breaththrough infections which may occur following use of micafungin for prophylaxis.

TABLE 11
Incidence of Colonization at Baseline and End of Therapy

INCIDENCE OF COLONIZATION AT BASELINE AND END OF THERAPY
FULL ANALYSIS SET (1)

PERIOD	ORGANISM (4)	TREATMENT GROUP FK463 (N=425)	TREATMENT GROUP FLUCONAZOLE (N=457)
BASELINE (2)	OVERALL	115 (27.1%)	138 (30.2%)
	CANDIDA ALBICANS	82 (71.3%)	83 (60.1%)
	CANDIDA GLABRATA	12 (10.4%)	18 (13.0%)
	CANDIDA GUILLIERMONDII	1 (0.9%)	1 (0.7%)
	CANDIDA KRUSEI	1 (0.9%)	0 (0.0%)
	CANDIDA LUSITANIAE	0 (0.0%)	2 (1.4%)
	CANDIDA NON-ALBICANS	3 (2.6%)	4 (2.9%)
	CANDIDA PARAPSILOSIS	1 (0.9%)	2 (1.4%)
	CANDIDA SP. NOS	1 (0.9%)	1 (0.7%)
	CANDIDA TROPICALIS	0 (0.0%)	1 (0.7%)
	EXOPHIALA SP. NOS	1 (0.9%)	0 (0.0%)
	FUNGI NON SPECIFIED	2 (1.7%)	0 (0.0%)
	PENICILLIUM SP. NOS	2 (1.7%)	0 (0.0%)
	RHODOTORULA MACILAGINOSA	0 (0.0%)	1 (0.7%)
	SACCHAROMYCES CERRVISIAE	1 (0.9%)	5 (3.6%)
	TRICHOSPORON INKIN	1 (0.9%)	0 (0.0%)
	UNKNOWN	1 (0.9%)	2 (1.4%)
	YEAST SP. NOS	6 (5.2%)	18 (13.0%)
END OF THERAPY (3)	OVERALL	243 (57.2%)	182 (39.8%)
	ACREMONIUM SP. NOS	0 (0.0%)	1 (0.5%)
	ASPERGILLUS FUNIGATUS	2 (0.8%)	1 (0.5%)
	ASPERGILLUS NIGER	1 (0.4%)	0 (0.0%)
	ASPERGILLUS SP. NOS	0 (0.0%)	1 (0.5%)
	AUREOBASIDIUM PULLULANS	1 (0.4%)	0 (0.0%)
	BLASTOSCHIZOMYCES CAPITATUS	1 (0.4%)	0 (0.0%)
	CANDIDA ALBICANS	134 (55.1%)	55 (30.2%)
	CANDIDA FAMATA	0 (0.0%)	1 (0.5%)
	CANDIDA GLABRATA	12 (4.9%)	59 (32.4%)
	CANDIDA GUILLIERMONDII	3 (1.2%)	3 (1.6%)
	CANDIDA KEFYR	2 (0.8%)	0 (0.0%)
	CANDIDA KRUSEI	10 (4.1%)	3 (1.6%)
	CANDIDA LAMBICA	0 (0.0%)	1 (0.5%)
	CANDIDA LUSITANIAE	4 (1.6%)	1 (0.5%)
	CANDIDA MAGNOLIAE	0 (0.0%)	1 (0.5%)
	CANDIDA NON-ALBICANS	8 (3.3%)	5 (2.7%)
	CANDIDA NORWEGENSIS	0 (0.0%)	1 (0.5%)
	CANDIDA PARAPSILOSIS	16 (6.6%)	4 (2.2%)
	CANDIDA RUGOSA	0 (0.0%)	1 (0.5%)
	CANDIDA SP. NOS	3 (1.2%)	1 (0.5%)
	CANDIDA TROPICALIS	6 (2.5%)	2 (1.1%)

(1) PATIENTS WHO RECEIVED AT LEAST ONE DOSE OF STUDY DRUG.
(2) LAST AVAILABLE BASELINE EVALUATION (INCLUDES EVALUATIONS UP TO FIRST DOSE DATE PLUS 3).
(3) LAST AVAILABLE POST BASELINE EVALUATION PRIOR TO OR ON LAST DOSE DAY PLUS 3.
(4) A PATIENT MAY BE INFECTED WITH MORE THAN ONE ORGANISM.

Source Table 13.4.12.1 in the applicant's original report for study 98-0-050

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TABLE 11 (continued)
Incidence of Colonization at Baseline and End of Therapy

INCIDENCE OF COLONIZATION AT BASELINE AND END OF THERAPY
FULL ANALYSIS SET (1)

PERIOD	ORGANISM (4)	TREATMENT GROUP: FK463 (N=425)	TREATMENT GROUP: FLUCONAZOLE (N=457)
END OF THERAPY (3)	CRYPTOCOCCUS ALBIDUS	0 (0.0%)	1 (0.5%)
	CURVULARIA SP. NOS	1 (0.4%)	0 (0.0%)
	FUNGI NON SPECIFIED	1 (0.4%)	0 (0.0%)
	GEOTRICHUM CANDIDUM	1 (0.4%)	0 (0.0%)
	KLUYVEROMYCES SP. NOS	0 (0.0%)	1 (0.5%)
	MALASSEZIA FURFUR	1 (0.4%)	0 (0.0%)
	RHODOTORULA RUBRA	1 (0.4%)	0 (0.0%)
	RHODOTORULA SP. NOS	0 (0.0%)	1 (0.5%)
	SACCHAROMYCES CEREVISIAE	13 (5.3%)	12 (6.6%)
	SCOPULARIOPSIS SP. NOS	1 (0.4%)	0 (0.0%)
	TRICHOSPORON BEIGEL'II	1 (0.4%)	0 (0.0%)
	TRICHOSPORON MUCOIDES	1 (0.4%)	0 (0.0%)
	UNKNOWN	1 (0.4%)	1 (0.5%)
	WANGIELLA DERMATITIDIS	2 (0.8%)	0 (0.0%)
	YEAST SP. NOS	16 (6.6%)	25 (13.7%)

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(1) PATIENTS WHO RECEIVED AT LEAST ONE DOSE OF STUDY DRUG.
(2) LAST AVAILABLE BASELINE EVALUATION (INCLUDES EVALUATIONS UP TO FIRST DOSE DATE PLUS 3).
(3) LAST AVAILABLE POST BASELINE EVALUATION PRIOR TO OR ON LAST DOSE DAY PLUS 3.
(4) A PATIENT MAY BE INFECTED WITH MORE THAN ONE ORGANISM.

Source Table 13.4.12.1 in the applicant's original report for Study 98-0-050

Reanalysis of Study 98-0-050: In changing emphasis from the absence of either a yeast or mold infection, as in the original NDA, to the incidence of breakthrough proven *Candida* infections, a new efficacy difference was established by the applicant in the current submission. In choosing an acceptable margin, the applicant relied on the Goodman and Slavin trials as a clinically relevant historical control.

The analysis considered breakthrough *Candida* infections as failures while all other breakthrough infections and deaths during the study were considered successes. The Clinical and Statistical Reviewers consider this approach statistically inappropriate as a method to determine non-inferiority of micafungin to fluconazole. Additionally, the applicant's re-defining of the primary endpoint from absence of fungal infections during study to incidence of *Candida* infections is also statistically invalid.

Details of the applicant's reanalysis of Study 98-0-050 and a comparison to the Goodman, et al. study [1992] and the Slavin, et al. study [1995] can be found in Appendix III (Section 13).

Response to other FDA Inquiries: The applicant has submitted the following data to demonstrate that the 50 mg micafungin dose is appropriate for use in prophylaxis and why higher doses (100 mg to 150 mg) are required for esophageal candidiasis:

- Plasma concentrations of micafungin in adult BMT patients administered at 50 mg dose of micafungin are above the minimum effective concentration (MEC) based upon murine models of pulmonary aspergillosis and disseminated candidiasis over a 24-hour period.
- Endoscopic cure of esophageal candidiasis shows a clear dose-response. Although the cure rates with micafungin at 50 mg were lower than the higher doses, about 60% of patients were cured, which is higher than the placebo-response rate.
- In a single, non-comparative trial of candidemia, a 50 mg dose was shown to have an overall success rate of 74% (ITT) and 86% (PP).
- *Candidemia* and disseminated candidiasis can be prevented with lower doses of micafungin because micafungin is readily available in blood or interstitial fluid of the target organ (supported by PK and murine studies). In esophageal candidiasis (EC), which is a mucosal disease, it is more difficult of micafungin to penetrate the keratinized mucosal layer and it is not excreted well into saliva (supported by a rabbit model with anidulafungin; extrapolated to micafungin based on the similarity in molecular size of the two compounds). Therefore, higher doses of micafungin may be required to achieve a clinical cure in EC.

Details on how the applicant addressed the other FDA inquiries can be found in Appendix IV (Section 14).

6.1.5 Clinical Microbiology

No new clinical microbiology information was included in this submission.

Clinical Reviewer's Comment: See Microbiology Review for the original NDA 21-506 and for NDA 21-754 (esophageal candidiasis).

6.1.6 Efficacy Conclusions

Micafungin was shown to be non-inferior to fluconazole for the prophylaxis of fungal infections in Study 98-0-050. The reanalysis of the primary endpoint focusing on proven *Candida* infections in the micafungin group compared to the fluconazole group and compared to the difference seen between fluconazole and placebo in the Goodman and Slavin trials was not acceptable from a statistical point of view. Given the non-inferiority of micafungin compared to fluconazole for the primary end point in Study 98-0-050, the efficacy of micafungin in the treatment of esophageal candidiasis (NDA 21-754) and supportive evidence of efficacy in the

treatment of candidemia, the applicant has demonstrated efficacy of the 50 mg dose in the prophylaxis of *Candida* infections in adult patient undergoing hematopoietic stem cell transplant.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

A 50 mg dose of micafungin was used in three clinical studies:

- Study 98-0-47: a phase II, non-comparative, open-label, multicenter study of micafungin in adult and pediatric patients newly diagnosed or refractory non-esophageal *Candida* infections (candidemia or invasive candidiasis)
- Study FG-463-21-09: a phase II, randomized, double-blind, multicenter, active controlled, dose ranging study of micafungin (50, 100, and 150 mg) versus fluconazole in adult patients with esophageal candidiasis.
- Study 98-0-050: a phase III, randomized, double-blind, multicenter, active controlled study of micafungin versus fluconazole in adult and pediatric patients undergoing hematopoietic stem cell transplant at risk for fungal infections.

The following patients from the above studies were included in the safety database* for this submission:

- Study 98-0-047: adult patients (≥ 16 years) who received 50 mg/day of micafungin and pediatric patients who received between 0.8 and 1.2 mg/kg/day of micafungin.
- Study FG-463-21-09: patients who received 50 mg/day of micafungin and all fluconazole (200 mg) treated patients
- Study 98-0-050: all micafungin (50 mg/day in adults and 1 mg/kg/day in patients weighing < 50 kg) and all fluconazole (400 mg and 8 mg/kg/day for patients weighing < 50 kg) treated patients

*Only adverse events that began during the time period from earliest dose of 50 mg/day until the last dose of 50 mg/day plus 3 days were reported for patient selection described above.

Overall: A total of 770 patients received at least one dose of micafungin and 517 patients who received at least one dose of fluconazole (60 received 200 mg of fluconazole and 457 received 400 mg of fluconazole).

By age: Of the 770 micafungin treated patients, 41 patients were < 6 years, 31 patients were 6-12 years, 16 patients were 13 to 17 years, and the remaining 682 were ≥ 18 years old.

By Race: No breakdown by race was provided by the applicant.

Clinical Reviewer's Comment: The safety of micafungin in Study 98-0-050 was previously reviewed in the original submission of NDA 21-506 (see Medical Officer Review). No effect of

race was seen on the adverse event profile of micafungin. Therefore, the Reviewer did not request an additional safety analysis of micafungin based on race for this resubmission.

By Sex: Of the 770 micafungin treated patients, 323 were females and 447 were males.

Clinical Reviewer's Comment: The applicant was asked by the Reviewer to provide incidence rates of adverse events, using number of patients as the denominator, as listed below, for studies using the micafungin 50 mg oral dose and/or 1 mg/kg dose (patients ≤ 40 kg). These studies include: 98-0-050, FG-463-21-09, and 98-0-047.

- *All Treatment-Emergent AEs by COSTART Term - including AEs for fluconazole, as a comparator, by dose*
- *Treatment-related adverse events – including fluconazole*
- *Deaths*
- *Serious AEs*
- *Discontinuations due to AEs*
- *Renal AEs*
- *Hematologic AEs (including hemolysis, neutropenia, leukopenia, and thrombocytopenia)*
- *Allergic Reactions, including rash - for micafungin and fluconazole*
- *All Treatment-Emergent AEs by COSTART Term, broken down by age (i.e., < 6 years; 6 to < 13 years; 13 to < 18 years; and 18 years and older) - including AEs for*
- *fluconazole by age and by dose*
- *All Treatment-Emergent AEs by COSTART Term, broken down by sex (males and*
- *females) - including AEs for fluconazole by sex and by dose*

The resulting data below was submitted by the applicant in response to the Reviewer's request.

In addition to the tables provided by the applicant, the Reviewer had attempted to summarize textual information on AEs for Study 98-0-050, as reported in the original NDA 21-506 submitted April 29, 2002.

For additional information regarding Study FG-463-21-09 see Medical Officer Review of NDA 21-754 by Mary Singer, M.D.

7.1.1 Deaths

Study 98-0-050: A total of 18/425 (4.2%) of micafungin and 26/457 (5.7%) of fluconazole treated patients died during the study. Two deaths occurred while on study drug therapy, both in the fluconazole group. None of the deaths were considered by the investigators to be related to study drug.

Clinical Reviewer's Comment: As noted in the Medical Officer's Review of the original NDA 21-506, there were two additional deaths in the micafungin group, not captured by the original study report. However, both patients died following completion of the study and should not be

reported in the number of deaths which occurred during the study. Information on these two patients is included here for completeness:

Patient 0352504 was a 33 years female who received an allogeneic transplant and 13 days of micafungin at which time she was discontinued and begun on empiric treatment for a suspected fungal infection. She completed the study and 8 days later died following alveolar hemorrhage, acute heart failure, and secondary multiorgan failure. No autopsy was performed.

Patient 1233502 was a 42 year old female who received an allogeneic transplant and 30 days of micafungin. She completed the study and died about 2 months later of a suspected CNS infection. The site investigator diagnosed her with probable fungal infection of the brain/central nervous system, but the independent, blinded reviewer considered that the protocol-specified criteria for such diagnosis were not met.

Table 12 shows the adverse events leading to death across all three studies compared to fluconazole.

TABLE 12

INCIDENCE OF PRIMARY CAUSE OF DEATHS (INCLUDING NON-TREATMENT EMERGENT) IN PATIENTS WITH 50 MG FK463 AND FLUCONAZOLE
ALL TREATED PATIENTS (1)

BODY SYSTEM (2) COSTART TERM	FK463 (N=770)	FLUCONAZOLE 200 MG (N=60)	FLUCONAZOLE 400 MG (N=457)	FLUCONAZOLE TOTAL (N=517)
ALL SYSTEMS	106(13.8%)	1(1.7%)	26(5.7%)	27(5.2%)
CARDIOVASCULAR SYSTEM				
ANY AE	36(4.7%)	0	7(1.5%)	7(1.4%)
SHOCK	25(3.2%)	0	4(0.9%)	4(0.8%)
HEART ARREST	3(0.4%)	0	2(0.4%)	2(0.4%)
SUBDURAL HEMATOMA	0	0	1(0.2%)	1(0.2%)
CONGESTIVE HEART FAILURE	2(0.3%)	0	0	0
ENDOCARDITIS	2(0.3%)	0	0	0
HEART FAILURE	2(0.3%)	0	0	0
HEMORRHAGE	1(0.1%)	0	0	0
INCREASED CAPILLARY FRAGILITY	1(0.1%)	0	0	0
RESPIRATORY SYSTEM				
ANY AE	23(3.0%)	0	6(1.3%)	6(1.2%)
RESPIRATORY DISTRESS SYNDROME	1(0.1%)	0	3(0.7%)	3(0.6%)
PNEUMONIA	4(0.5%)	0	1(0.2%)	1(0.2%)
PULMONARY MYCOSIS	1(0.1%)	0	1(0.2%)	1(0.2%)
RESPIRATORY FAILURE	13(1.7%)	0	1(0.2%)	1(0.2%)
DYSPNEA	1(0.1%)	0	0	0
EMPHYSEMA	1(0.1%)	0	0	0
PULMONARY EMBOLUS	1(0.1%)	0	0	0
RESPIRATORY DISORDER	1(0.1%)	0	0	0
BODY AS A WHOLE				
ANY AE	28(3.6%)	0	4(0.9%)	4(0.8%)
SEPSIS	10(1.3%)	0	3(0.7%)	3(0.6%)
RELAPSE OF PRIMARY MALIGNANCY	0	0	1(0.2%)	1(0.2%)
AIDS	2(0.3%)	0	0	0
CACHEXIA	2(0.3%)	0	0	0
CARCINOMA	3(0.4%)	0	0	0
DEATH	1(0.1%)	0	0	0
GRAFT REJECTION	1(0.1%)	0	0	0
GRAFT VERSUS HOST DISEASE	2(0.3%)	0	0	0
MONILIASIS	1(0.1%)	0	0	0
NECROSIS	1(0.1%)	0	0	0
NEOPLASM BENIGN	1(0.1%)	0	0	0
PERITONITIS	1(0.1%)	0	0	0
TUBERCULOSIS AGGRAVATED	2(0.3%)	0	0	0
TUBERCULOSIS REACTIVATED	1(0.1%)	0	0	0

(1) STUDIES INCLUDED: 98-0-050, FG-21-09, AND 98-0-047. STUDY 98-0-047 ONLY INCLUDES PATIENTS < 16 YEARS OLD WHO RECEIVED 1 MG/KG/DAY (BETWEEN .8 AND 1.2 MG/KG/DAY), AND >= 16 YEARS OLD WHO RECEIVED 50 MG/DAY DOSE OF FK463.
FOR STUDY 98-0-050, NON-FUNGAL INFECTIONS WERE EXCLUDED.
(2) WITHIN A BODY SYSTEM A PERSON MAY EXPERIENCE MORE THAN ONE ADVERSE EVENT.

Corresponds to Table R62 in the applicant's submission dated January 10, 2005.
FK463 = micafungin

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TABLE 12 (continued)

INCIDENCE OF PRIMARY CAUSE OF DEATHS (INCLUDING NON-TREATMENT EMERGENT) IN PATIENTS WITH 50 MG FK463 AND FLUCONAZOLE
ALL TREATED PATIENTS (1)

BODY SYSTEM (2) COSTART TERM	FK463 (N=770)	FLUCONAZOLE 200 MG (N=60)	FLUCONAZOLE 400 MG (N=457)	FLUCONAZOLE TOTAL (N=517)
DIGESTIVE SYSTEM				
ANY AE	4(0.5%)	0	4(0.9%)	4(0.8%)
GASTROINTESTINAL HEMORRHAGE	2(0.3%)	0	2(0.4%)	2(0.4%)
COLITIS	0	0	1(0.2%)	1(0.2%)
HEPATIC FAILURE	1(0.1%)	0	1(0.2%)	1(0.2%)
GASTROINTESTINAL CARCINOMA	1(0.1%)	0	0	0
HEMIC AND LYMPHATIC SYSTEM				
ANY AE	6(0.8%)	0	3(0.7%)	3(0.6%)
ACUTE MYELOBLASTIC LEUKEMIA	1(0.1%)	0	1(0.2%)	1(0.2%)
LEUKOPENIA	0	0	1(0.2%)	1(0.2%)
LYMPHOMA LIKE REACTION	0	0	1(0.2%)	1(0.2%)
ACUTE LEUKEMIA	1(0.1%)	0	0	0
CHRONIC LYMPHOCYTIC LEUKEMIA	1(0.1%)	0	0	0
LEUKEMIA	2(0.3%)	0	0	0
THROMBOCYTOPENIA	1(0.1%)	0	0	0
NERVOUS SYSTEM				
ANY AE	6(0.8%)	1(1.7%)	2(0.4%)	3(0.6%)
CONVULSION	0	0	1(0.2%)	1(0.2%)
DEMENTIA	0	1(1.7%)	0	1(0.2%)
INTRACRANIAL HEMORRHAGE	1(0.1%)	0	1(0.2%)	1(0.2%)
BRAIN EDEMA	1(0.1%)	0	0	0
CEREBRAL HEMORRHAGE	1(0.1%)	0	0	0
CEREBRAL INFARCT	1(0.1%)	0	0	0
CEREBROVASCULAR ACCIDENT	1(0.1%)	0	0	0
MENINGITIS	1(0.1%)	0	0	0
METABOLIC AND NUTRITIONAL DISORDERS				
ANY AE	2(0.3%)	0	0	0
ACIDOSIS	2(0.3%)	0	0	0
UROGENITAL SYSTEM				
ANY AE	1(0.1%)	0	0	0
ACUTE KIDNEY FAILURE	1(0.1%)	0	0	0

(1) STUDIES INCLUDED: 98-0-050, FG-21-09, AND 98-0-047. STUDY 98-0-047 ONLY INCLUDES PATIENTS < 16 YEARS OLD WHO RECEIVED 1 MG/KG/DAY (BETWEEN .9 AND 1.2 MG/KG/DAY), AND >= 16 YEARS OLD WHO RECEIVED 50 MG/DAY DOSE OF FK463. FOR STUDY 98-0-050, NON-FUNGAL INFECTIONS WERE EXCLUDED.
(2) WITHIN A BODY SYSTEM A PERSON MAY EXPERIENCE MORE THAN ONE ADVERSE EVENT.

Corresponds to Table R62 in the applicant's submission dated January 10, 2005.
FK463 = micafungin

7.1.2 Other Serious Adverse Events

Study 98-0-050: A total of 80/425 (18.8%) of micafungin and 74/457 (16.2%) of fluconazole treated patients experienced a serious adverse event other than death during the study. The more common serious adverse events occurring in the micafungin patients included sepsis (3.3%), fever (3.1%), and hypotension (2.1%). The more common serious adverse events occurring in the fluconazole patients included sepsis (2.8%) and dyspnea (1.8%). A total of 14 patients (4 micafungin patients [0.9%] and 10 fluconazole patients [2.2%]) experienced an adverse event other than death that was considered to be related to study drug.

Table 13 shows serious adverse events across all three studies compared to fluconazole.

TABLE 13

INCIDENCE OF SERIOUS TREATMENT EMERGENT ADVERSE EVENTS OF 50 MG FK463 AND FLUCONAZOLE
ALL TREATED PATIENTS (1)

BODY SYSTEM (2) COSTART TERM	FK463 (N=770)	FLUCONAZOLE 200 MG (N=60)	FLUCONAZOLE 400 MG (N=457)	FLUCONAZOLE TOTAL (N=517)
ALL SYSTEMS	169(21.9%)	5(8.3%)	74(16.2%)	79(15.3%)
BODY AS A WHOLE				
ANY AE	65(8.4%)	0	26(5.7%)	26(5.0%)
SEPSIS	24(3.1%)	0	13(2.8%)	13(2.5%)
FEVER	16(2.1%)	0	6(1.3%)	6(1.2%)
GRAFT VERSUS HOST DISEASE	4(0.5%)	0	3(0.7%)	3(0.6%)
ABDOMINAL PAIN	2(0.3%)	0	2(0.4%)	2(0.4%)
ASTHENIA	1(0.1%)	0	1(0.2%)	1(0.2%)
NECK PAIN	0	0	1(0.2%)	1(0.2%)
PAIN	1(0.1%)	0	1(0.2%)	1(0.2%)
PRIMARY GRAFT DYSFUNCTION	1(0.1%)	0	1(0.2%)	1(0.2%)
TRANSFUSION REACTION	1(0.1%)	0	1(0.2%)	1(0.2%)
ABSCESS	2(0.3%)	0	0	0
ALLERGIC REACTION	1(0.1%)	0	0	0
ANAPHYLACTOID REACTION	1(0.1%)	0	0	0
ASCITES	1(0.1%)	0	0	0
CACHEXIA	2(0.3%)	0	0	0
CARCINOMA	1(0.1%)	0	0	0
CHILLS	1(0.1%)	0	0	0
INFECTION	11(1.4%)	0	0	0
NECROSIS	1(0.1%)	0	0	0
PERITONITIS	1(0.1%)	0	0	0
PROCEDURAL COMPLICATION	2(0.3%)	0	0	0
TUBERCULOSIS AGGRAVATED	3(0.4%)	0	0	0
TUBERCULOSIS REACTIVATED	1(0.1%)	0	0	0
DIGESTIVE SYSTEM				
ANY AE	28(3.6%)	1(1.7%)	25(5.5%)	26(5.0%)
DIARRHEA	4(0.5%)	0	6(1.3%)	6(1.2%)
NAUSEA	2(0.3%)	0	6(1.3%)	6(1.2%)
VOMITING	4(0.5%)	0	5(1.1%)	5(1.0%)
MUCOSITIS	2(0.3%)	0	4(0.9%)	4(0.8%)
VENOOCCLUSIVE LIVER DISEASE	3(0.4%)	0	3(0.7%)	3(0.6%)
HEPATIC FAILURE	0	0	2(0.4%)	2(0.4%)
LIVER FUNCTION TESTS ABNORMAL	5(0.6%)	0	2(0.4%)	2(0.4%)
ESOPHAGITIS	0	0	1(0.2%)	1(0.2%)
GASTROENTERITIS	0	0	1(0.2%)	1(0.2%)
GASTROINTESTINAL ANOMALY	0	1(1.7%)	0	1(0.2%)
GASTROINTESTINAL HEMORRHAGE	1(0.1%)	0	1(0.2%)	1(0.2%)
HEPATITIS, NONSPECIFIC	0	0	1(0.2%)	1(0.2%)

(1) STUDIES INCLUDED: 98-0-050, FG-21-09, AND 98-0-047. STUDY 98-0-047 ONLY INCLUDES PATIENTS < 16 YEARS OLD WHO RECEIVED 1 MG/KG/DAY AND >= 16 YEARS OLD WHO RECEIVED 50 MG/DAY DOSE OF FK463.
(2) WITHIN A BODY SYSTEM A PERSON MAY EXPERIENCE MORE THAN ONE ADVERSE EVENT.

Corresponds to Table R6 3 in the applicant's submission dated October 25, 2004.
FK463 = micafungin

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TABLE 13 (continued)

INCIDENCE OF SERIOUS TREATMENT EMERGENT ADVERSE EVENTS OF 50 MG FK463 AND FLUCONAZOLE
ALL TREATED PATIENTS (1)

BODY SYSTEM (2) COSTART TERM	FK463 (N=770)	FLUCONAZOLE 200 MG (N=60)	FLUCONAZOLE 400 MG (N=457)	FLUCONAZOLE TOTAL (N=517)
ILEUS	0	0	1(0.2%)	1(0.2%)
PSEUDOMEMBRANOUS COLITIS	0	0	1(0.2%)	1(0.2%)
RECTAL DISORDER	1(0.1%)	0	1(0.2%)	1(0.2%)
RECTAL HEMORRHAGE	0	0	1(0.2%)	1(0.2%)
ANOREXIA	1(0.1%)	0	0	0
CHOLELITHIASIS	1(0.1%)	0	0	0
ENTERITIS	1(0.1%)	0	0	0
GASTROINTESTINAL CARCINOMA	1(0.1%)	0	0	0
GASTROINTESTINAL DISORDER	3(0.4%)	0	0	0
HEMATEMESIS	1(0.1%)	0	0	0
LIVER DAMAGE	2(0.3%)	0	0	0
RESPIRATORY SYSTEM				
ANY AR	54(7.0%)	0	23(5.0%)	23(4.4%)
DYSPNEA	8(1.0%)	0	8(1.8%)	8(1.5%)
LUNG HEMORRHAGE	2(0.3%)	0	6(1.3%)	6(1.2%)
PNEUMONIA	13(1.7%)	0	6(1.3%)	6(1.2%)
RESPIRATORY FAILURE	21(2.7%)	0	5(1.1%)	5(1.0%)
LUNG DISORDER	0	0	4(0.9%)	4(0.8%)
LUNG EDEMA	3(0.4%)	0	3(0.7%)	3(0.6%)
HYPOXIA	2(0.3%)	0	2(0.4%)	2(0.4%)
RESPIRATORY DISTRESS SYNDROME	5(0.6%)	0	2(0.4%)	2(0.4%)
HEMOPTYSIS	1(0.1%)	0	1(0.2%)	1(0.2%)
HICCUP	0	0	1(0.2%)	1(0.2%)
EMPHYSEMA	1(0.1%)	0	0	0
HYPERVENTILATION	1(0.1%)	0	0	0
INTERSTITIAL PNEUMONIA	1(0.1%)	0	0	0
PULMONARY EMBOLUS	1(0.1%)	0	0	0
RESPIRATORY DISORDER	3(0.4%)	0	0	0
SINUSITIS	2(0.3%)	0	0	0
CARDIOVASCULAR SYSTEM				
ANY AR	50(6.5%)	0	22(4.8%)	22(4.3%)
CONGESTIVE HEART FAILURE	1(0.1%)	0	4(0.9%)	4(0.8%)
HEART ARREST	2(0.3%)	0	3(0.7%)	3(0.6%)
HYPOTENSION	15(1.9%)	0	3(0.7%)	3(0.6%)
ATRIAL FIBRILLATION	9(1.2%)	0	2(0.4%)	2(0.4%)
CARDIOMEGALY	0	0	2(0.4%)	2(0.4%)
CHEST PAIN	1(0.1%)	0	2(0.4%)	2(0.4%)
POSTURAL HYPOTENSION	1(0.1%)	0	2(0.4%)	2(0.4%)
SHOCK	14(1.8%)	0	2(0.4%)	2(0.4%)

(1) STUDIES INCLUDED: 98-0-050, PG-21-09, AND 98-0-047. STUDY 98-0-047 ONLY INCLUDES PATIENTS < 16 YEARS OLD WHO RECEIVED 1 MG/KG/DAY AND >= 16 YEARS OLD WHO RECEIVED 50 MG/DAY DOSE OF FK463.
(2) WITHIN A BODY SYSTEM A PERSON MAY EXPERIENCE MORE THAN ONE ADVERSE EVENT.

Corresponds to Table R6 3 in the applicant's submission dated October 25, 2004.
FK463 = micafungin

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TABLE 13 (continued)

INCIDENCE OF SERIOUS TREATMENT EMERGENT ADVERSE EVENTS OF 50 MG FK463 AND FLUCONAZOLE
ALL TREATED PATIENTS (1)

BODY SYSTEM (2) COSTART TERM	FK463 (N=770)	FLUCONAZOLE 200 MG (N=60)	FLUCONAZOLE 400 MG (N=457)	FLUCONAZOLE TOTAL (N=517)
SUBDURAL HEMATOMA	0	0	2(0.4%)	2(0.4%)
TACHYCARDIA	1(0.1%)	0	2(0.4%)	2(0.4%)
BRADYCARDIA	0	0	1(0.2%)	1(0.2%)
CARDIOMYOPATHY	0	0	1(0.2%)	1(0.2%)
HYPERTENSION	1(0.1%)	0	1(0.2%)	1(0.2%)
PERICARDIAL EFFUSION	2(0.3%)	0	1(0.2%)	1(0.2%)
VASODILATATION	0	0	1(0.2%)	1(0.2%)
ATRIAL FLUTTER	1(0.1%)	0	0	0
DEEP THROMBOPHLEBITIS	2(0.3%)	0	0	0
ELECTROCARDIOGRAM ABNORMAL	1(0.1%)	0	0	0
HEART FAILURE	1(0.1%)	0	0	0
HEMORRHAGE	4(0.5%)	0	0	0
INCREASED CAPILLARY FRAGILITY	1(0.1%)	0	0	0
PALPITATION	1(0.1%)	0	0	0
PERICARDITIS	1(0.1%)	0	0	0
VENTRICULAR TACHYCARDIA	1(0.1%)	0	0	0
UROGENITAL SYSTEM				
ANY AE	15(1.9%)	0	15(3.3%)	15(2.9%)
KIDNEY FAILURE	6(0.8%)	0	6(1.3%)	6(1.2%)
ACUTE KIDNEY FAILURE	4(0.5%)	0	4(0.9%)	4(0.8%)
KIDNEY FUNCTION ABNORMAL	1(0.1%)	0	4(0.9%)	4(0.8%)
OLIGURIA	1(0.1%)	0	1(0.2%)	1(0.2%)
CARCINOMA RENAL	1(0.1%)	0	0	0
HEMATURIA	2(0.3%)	0	0	0
METABOLIC AND NUTRITIONAL DISORDERS				
ANY AE	19(2.5%)	0	13(2.8%)	13(2.5%)
BILIRUBINEMIA	4(0.5%)	0	4(0.9%)	4(0.8%)
DEHYDRATION	3(0.4%)	0	4(0.9%)	4(0.8%)
SGOT INCREASED	0	0	2(0.4%)	2(0.4%)
SGPT INCREASED	0	0	2(0.4%)	2(0.4%)
ACIDOSIS	3(0.4%)	0	1(0.2%)	1(0.2%)
CREATININE INCREASED	2(0.3%)	0	1(0.2%)	1(0.2%)
HYPERVOLEMIA	2(0.3%)	0	1(0.2%)	1(0.2%)
KETOSIS	0	0	1(0.2%)	1(0.2%)
ALKALINE PHOSPHATASE INCREASED	1(0.1%)	0	0	0
BUN INCREASED	1(0.1%)	0	0	0
HYPOKALEMIA	4(0.5%)	0	0	0
HYPONATREMIA	1(0.1%)	0	0	0

(1) STUDIES INCLUDED: 98-0-050, FG-21-09, AND 98-0-047. STUDY 98-0-047 ONLY INCLUDES PATIENTS < 16 YEARS OLD WHO RECEIVED 1 MG/KG/DAY AND >= 16 YEARS OLD WHO RECEIVED 50 MG/DAY DOSE OF FK463.
(2) WITHIN A BODY SYSTEM A PERSON MAY EXPERIENCE MORE THAN ONE ADVERSE EVENT.

Corresponds to Table R6 3 in the applicant's submission dated October 25, 2004.
FK463 = micafungin

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TABLE 13 (continued)

INCIDENCE OF SERIOUS TREATMENT EMERGENT ADVERSE EVENTS OF 50 MG FK463 AND FLUCONAZOLE
ALL TREATED PATIENTS (1)

BODY SYSTEM (2) COSTART TERM	FK463 (N=770)	FLUCONAZOLE 200 MG (N=60)	FLUCONAZOLE 400 MG (N=457)	FLUCONAZOLE TOTAL (N=517)
NERVOUS SYSTEM				
ANY AE	17(2.2%)	3(5.0%)	7(1.5%)	10(1.9%)
CONVULSION	4(0.5%)	0	4(0.9%)	4(0.8%)
GRAND MAL CONVULSION	0	0	2(0.4%)	2(0.4%)
BRAIN ABSCESS	0	0	1(0.2%)	1(0.2%)
CEREBRAL HEMORRHAGE	0	0	1(0.2%)	1(0.2%)
DEMENTIA	0	1(1.7%)	0	1(0.2%)
DIZZINESS	1(0.1%)	0	1(0.2%)	1(0.2%)
MENINGITIS	4(0.5%)	1(1.7%)	0	1(0.2%)
PSYCHOSIS	0	1(1.7%)	0	1(0.2%)
CEREBROVASCULAR ACCIDENT	1(0.1%)	0	0	0
CNS NEOPLASIA BENIGN	1(0.1%)	0	0	0
COMA	1(0.1%)	0	0	0
CONFUSION	1(0.1%)	0	0	0
DELIRIUM	1(0.1%)	0	0	0
ENCEPHALOPATHY	2(0.3%)	0	0	0
HEMIPLEGIA	1(0.1%)	0	0	0
INTRACRANIAL HEMORRHAGE	1(0.1%)	0	0	0
NEUROPATHY	1(0.1%)	0	0	0
THINKING ABNORMAL	1(0.1%)	0	0	0
HEMIC AND LYMPHATIC SYSTEM				
ANY AE	8(1.0%)	1(1.7%)	2(0.4%)	3(0.6%)
LEUKOPENIA	1(0.1%)	1(1.7%)	1(0.2%)	2(0.4%)
ANEMIA	1(0.1%)	0	1(0.2%)	1(0.2%)
COAGULATION DISORDER	2(0.3%)	0	0	0
HEMOLYSIS	1(0.1%)	0	0	0
LEUKEMIA	1(0.1%)	0	0	0
THROMBOCYTOPENIA	3(0.4%)	0	0	0
SKIN AND APPENDAGES				
ANY AE	7(0.9%)	0	3(0.7%)	3(0.6%)
SWEATING	0	0	2(0.4%)	2(0.4%)
RASH	3(0.4%)	0	1(0.2%)	1(0.2%)
HERPES SIMPLEX	1(0.1%)	0	0	0
HERPES ZOSTER	1(0.1%)	0	0	0
MACULOPAPULAR RASH	1(0.1%)	0	0	0
URTICARIA	1(0.1%)	0	0	0
MUSCULOSKELETAL SYSTEM				
ANY AE	0	0	2(0.4%)	2(0.4%)

(1) STUDIES INCLUDED: 98-0-050, FG-21-09, AND 98-0-047. STUDY 98-0-047 ONLY INCLUDES PATIENTS < 16 YEARS OLD WHO RECEIVED 1 MG/KG/DAY AND >= 16 YEARS OLD WHO RECEIVED 50 MG/DAY DOSE OF FK463.
(2) WITHIN A BODY SYSTEM A PERSON MAY EXPERIENCE MORE THAN ONE ADVERSE EVENT.

Corresponds to Table R6 3 in the applicant's submission dated October 25, 2004.
FK463 = micafungin

TABLE 13 (continued)

INCIDENCE OF SERIOUS TREATMENT EMERGENT ADVERSE EVENTS OF 50 MG FK463 AND FLUCONAZOLE
ALL TREATED PATIENTS (1)

BODY SYSTEM (2) COSTART TERM	FK463 (N=770)	FLUCONAZOLE 200 MG (N=60)	FLUCONAZOLE 400 MG (N=457)	FLUCONAZOLE TOTAL (N=517)
MYASTHENIA	0	0	2(0.4%)	2(0.4%)
SPECIAL SENSES				
ANY AE	1(0.1%)	0	0	0
EAR DISORDER	1(0.1%)	0	0	0

(1) STUDIES INCLUDED: 98-0-050, FG-21-09, AND 98-0-047. STUDY 98-0-047 ONLY INCLUDES PATIENTS < 16 YEARS OLD WHO RECEIVED 1 MG/KG/DAY AND >= 16 YEARS OLD WHO RECEIVED 50 MG/DAY DOSE OF FK463.
(2) WITHIN A BODY SYSTEM A PERSON MAY EXPERIENCE MORE THAN ONE ADVERSE EVENT.

Corresponds to Table R6 3 in the applicant's submission dated October 25, 2004.
FK463 = micafungin

7.1.3 Dropouts and Other Significant Adverse Events

Study 98-0-050: A total of 18/425 (4.2%) of micafungin and 33/457 (7.2%) of fluconazole treated patients discontinued study drug due to an adverse event. Of the 11 micafungin patients who discontinued due to an adverse event considered related to study drug, 4 patients discontinued due to hepatic-related events, 4 patients due to events associated with rash or urticaria, and 1 patient due to increased creatinine. The remaining two patients discontinued for the following reasons: heart palpitations, and jaw and joint pain.

Table 14 shows adverse events leading to discontinuation across all three studies compared to fluconazole.

TABLE 14

INCIDENCE OF TREATMENT EMERGENT ADVERSE EVENTS OF 50 MG FK463 AND FLUCONAZOLE, LEADING TO STUDY DRUG DISCONTINUATION
ALL TREATED PATIENTS (1)

BODY SYSTEM (2) COSTART TERM	FK463 (N=770)	FLUCONAZOLE 200 MG (N=60)	FLUCONAZOLE 400 MG (N=457)	FLUCONAZOLE TOTAL (N=517)
ALL SYSTEMS	60(7.8%)	4(6.7%)	33(7.2%)	37(7.2%)
METABOLIC AND NUTRITIONAL DISORDERS				
ANY AE	10(1.3%)	0	11(2.4%)	11(2.1%)
BILIRUBINEMIA	3(0.4%)	0	6(1.3%)	6(1.2%)
SGPT INCREASED	2(0.3%)	0	3(0.7%)	3(0.6%)
SGOT INCREASED	2(0.3%)	0	2(0.4%)	2(0.4%)
CREATININE INCREASED	2(0.3%)	0	1(0.2%)	1(0.2%)
HYPERVOLEMIA	0	0	1(0.2%)	1(0.2%)
KETOSIS	0	0	1(0.2%)	1(0.2%)
ACIDOSIS	1(0.1%)	0	0	0
ALKALINE PHOSPHATASE INCREASED	3(0.4%)	0	0	0
BUN INCREASED	3(0.1%)	0	0	0
DIGESTIVE SYSTEM				
ANY AE	5(0.6%)	0	9(2.0%)	9(1.7%)
LIVER FUNCTION TESTS ABNORMAL	4(0.5%)	0	4(0.9%)	4(0.8%)
DIARRHEA	0	0	1(0.2%)	1(0.2%)
HEPATIC FAILURE	0	0	1(0.2%)	1(0.2%)
HEPATITIS, NONSPECIFIC	0	0	1(0.2%)	1(0.2%)
HEPATOMEGALY	0	0	1(0.2%)	1(0.2%)
LIVER DAMAGE	0	0	1(0.2%)	1(0.2%)
NAUSEA	0	0	1(0.2%)	1(0.2%)
CHOLESTATIC JAUNDICE	1(0.1%)	0	0	0
CARDIOVASCULAR SYSTEM				
ANY AE	12(1.6%)	0	8(1.8%)	8(1.5%)
SHOCK	6(0.8%)	0	2(0.4%)	2(0.4%)
SUBDURAL HEMATOMA	0	0	2(0.4%)	2(0.4%)
HEART ARREST	0	0	1(0.2%)	1(0.2%)
HYPOTENSION	2(0.3%)	0	1(0.2%)	1(0.2%)
TACHYCARDIA	0	0	1(0.2%)	1(0.2%)
VASODILATATION	0	0	1(0.2%)	1(0.2%)
ATRIAL FIBRILLATION	1(0.1%)	0	0	0
HEART FAILURE	1(0.1%)	0	0	0
INCREASED CAPILLARY FRAGILITY	1(0.1%)	0	0	0
PALPITATION	1(0.1%)	0	0	0
NERVOUS SYSTEM				
ANY AE	3(0.4%)	3(5.0%)	4(0.9%)	7(1.4%)
CONVULSION	0	0	1(0.2%)	1(0.2%)

(1) STUDIES INCLUDED: 98-0-050, FG-21-09, AND 98-0-047. STUDY 98-0-047 ONLY INCLUDES PATIENTS < 16 YEARS OLD WHO RECEIVED 1 MG/KG/DAY AND >= 16 YEARS OLD WHO RECEIVED 50 MG/DAY DOSE OF FK463.
(2) WITHIN A BODY SYSTEM A PERSON MAY EXPERIENCE MORE THAN ONE ADVERSE EVENT.

Corresponds to Table R6 4 in the applicant's submission dated October 25, 2004.
FK463 = micafungin

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TABLE 14 (continued)

INCIDENCE OF TREATMENT EMERGENT ADVERSE EVENTS OF 50 MG FK463 AND FLUCONAZOLE, LEADING TO STUDY DRUG DISCONTINUATION
ALL TREATED PATIENTS (1)

BODY SYSTEM (2) COSTART TERM	FK463 (N=770)	FLUCONAZOLE 200 MG (N=60)	FLUCONAZOLE 400 MG (N=457)	FLUCONAZOLE TOTAL (N=517)
DEMENTIA	0	1(1.7%)	0	1(0.2%)
DIZZINESS	0	0	1(0.2%)	1(0.2%)
HEADACHE	0	0	1(0.2%)	1(0.2%)
MENINGITIS	2(0.3%)	1(1.7%)	0	1(0.2%)
PSYCHOSIS	0	1(1.7%)	0	1(0.2%)
SOMNOLENCE	0	0	1(0.2%)	1(0.2%)
INTRACRANIAL HEMORRHAGE	1(0.1%)	0	0	0
RESPIRATORY SYSTEM				
ANY AE	11(1.4%)	0	6(1.3%)	6(1.2%)
LUNG HEMORRHAGE	0	0	3(0.7%)	3(0.6%)
DYSPNEA	1(0.1%)	0	2(0.4%)	2(0.4%)
LUNG DISORDER	0	0	2(0.4%)	2(0.4%)
RESPIRATORY FAILURE	4(0.5%)	0	2(0.4%)	2(0.4%)
PNEUMONIA	4(0.5%)	0	1(0.2%)	1(0.2%)
RESPIRATORY DISTRESS SYNDROME	1(0.1%)	0	1(0.2%)	1(0.2%)
EMPHYSEMA	1(0.1%)	0	0	0
BODY AS A WHOLE				
ANY AE	9(1.2%)	0	2(0.4%)	2(0.4%)
ABDOMINAL PAIN	1(0.1%)	0	1(0.2%)	1(0.2%)
ASTHENIA	0	0	1(0.2%)	1(0.2%)
NECK PAIN	0	0	1(0.2%)	1(0.2%)
PAIN	0	0	1(0.2%)	1(0.2%)
SEPSIS	3(0.4%)	0	1(0.2%)	1(0.2%)
ALLERGIC REACTION	1(0.1%)	0	0	0
ANAPHYLACTOID REACTION	1(0.1%)	0	0	0
CACHEXIA	1(0.1%)	0	0	0
CARCINOMA	1(0.1%)	0	0	0
FEVER	1(0.1%)	0	0	0
PERITONITIS	1(0.1%)	0	0	0
TUBERCULOSIS REACTIVATED	1(0.1%)	0	0	0
HEMIC AND LYMPHATIC SYSTEM				
ANY AE	4(0.5%)	1(1.7%)	1(0.2%)	2(0.4%)
LEUKOPENIA	2(0.3%)	1(1.7%)	1(0.2%)	2(0.4%)
THROMBOCYTOPENIA	2(0.3%)	0	0	0
UROGENITAL SYSTEM				
ANY AE	1(0.1%)	0	2(0.4%)	2(0.4%)
KIDNEY FUNCTION ABNORMAL	0	0	1(0.2%)	1(0.2%)

(1) STUDIES INCLUDED: 98-0-050, FG-21-09, AND 98-0-047. STUDY 98-0-047 ONLY INCLUDES PATIENTS < 16 YEARS OLD WHO RECEIVED 1 MG/KG/DAY AND >= 16 YEARS OLD WHO RECEIVED 50 MG/DAY DOSE OF FK463.
(2) WITHIN A BODY SYSTEM A PERSON MAY EXPERIENCE MORE THAN ONE ADVERSE EVENT.

Corresponds to Table R6 4 in the applicant's submission dated October 25, 2004.
FK463 = micafungin

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TABLE 14 (continued)

INCIDENCE OF TREATMENT EMERGENT ADVERSE EVENTS OF 50 MG FK463 AND FLUCONAZOLE, LEADING TO STUDY DRUG DISCONTINUATION
ALL TREATED PATIENTS (1)

BODY SYSTEM (2) COSTART TERM	FK463 (N=770)	FLUCONAZOLE 200 MG (N=60)	FLUCONAZOLE 400 MG (N=457)	FLUCONAZOLE TOTAL (N=517)
OLIGURIA	0	0	1(0.2%)	1(0.2%)
ACUTE KIDNEY FAILURE	1(0.1%)	0	0	0
SKIN AND APPENDAGES				
ANY AE	7(0.9%)	0	1(0.2%)	1(0.2%)
SWEATING	0	0	1(0.2%)	1(0.2%)
RASH	5(0.6%)	0	0	0
URTICARIA	2(0.3%)	0	0	0
MUSCULOSKELETAL SYSTEM				
ANY AE	1(0.1%)	0	0	0
ARTHRALGIA	1(0.1%)	0	0	0

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(1) STUDIES INCLUDED: 98-0-050, FG-21-09, AND 98-0-047. STUDY 98-0-047 ONLY INCLUDES PATIENTS < 16 YEARS OLD WHO RECEIVED 1 MG/KG/DAY AND >= 16 YEARS OLD WHO RECEIVED 50 MG/DAY DOSE OF FK463.
(2) WITHIN A BODY SYSTEM A PERSON MAY EXPERIENCE MORE THAN ONE ADVERSE EVENT.

Corresponds to Table R6 4 in the applicant's submission dated October 25, 2004.
FK463 = micafungin

Clinical Reviewer's Comment: Clinical narratives for the 4 patients in Study 98-0-050 who discontinued due to hepatic-related events were requested by the Reviewer and submitted by the applicant on January 10, 2005. Below is an abstracted version of the applicant's narratives. The reviewer agrees with the study investigator that the hepatic-related events in all 4 patients were potentially related to micafungin administration.

Patient # 572-522

A 29-year-old Caucasian male diagnosed in —— with chronic myelogenous leukemia active at the time of randomization. The patient was admitted to the hospital on — for an allogeneic matched-sibling peripheral stem cell transplant with an associated high risk of transplant related mortality. Study drug therapy with micafungin was initiated or — (Day 1) at a dose of 50 mg.

The patient developed severe elevated ALT/AST levels on Day 6 that in the Investigator's opinion were possibly related to study drug. The Patient was discontinued from study drug on Day 6 due to elevated ALT/AST levels (ALT on Day 7 was 326 U/L and AST was 142).

The Patient underwent an allogeneic peripheral stem cell transplant on Day 7. Fluconazole therapy was administered from Day 12 to Day 18 for antifungal prophylaxis. The patient developed a suspected fungal infection from Day 19 to Day 36 and was treated with amphotericin B and AmBisome® therapy during this time. The patient achieved neutrophil recovery on Day 23 and was discharged from the hospital on Day 36. The patient did not develop GVHD during the study. The patient's elevated ALT/AST levels had not resolved at the time of study completion (ALT on Day 36 was 351 U/L and AST was 131 U/L). The patient did not develop any additional fungal infection during the study.

Patient # 132-504

A 56-year-old Caucasian male diagnosed in — (estimated) with chronic myelogenous leukemia, active at the time of randomization. The patient was admitted to the hospital on — for an allogeneic matched-sibling bone marrow transplant with an associated high risk of transplant related mortality. Study drug therapy with micafungin was initiated on — (Day 1) at a dose of 50 mg. The Patient underwent an allogeneic bone marrow transplant (BMT) on Day 6. The patient's study drug was held on Day 6 due to the BMT. Study drug was resumed on Day 7 at the same dose of 50 mg.

The Patient developed moderate hyperbilirubinemia on Day 14 that in the Investigator's opinion was possibly related to study drug (total bilirubin of 2.6 mg/dL on Day 14). The patient was discontinued from study drug on Day 16 due to hyperbilirubinemia (total bilirubin on Day 17 was 7.6 mg/dL).

The patient did not receive any additional systemic antifungal therapy. On Day 21, the patient experienced life-threatening diffuse alveolar hemorrhage that in the Investigator's opinion was not related to study drug. On Day 25 the patient developed GVHD that reached an overall maximum Grade II. The Patient was discharged from the hospital on Day 35. The patient was readmitted to the hospital from Day 38 to Day 44 for worsening GVHD. The patient achieved neutrophil recovery on Day 43. The patient's hyperbilirubinemia had not resolved at the end of the study (total bilirubin on Day 44 was 9.0 mg/dL). The patient did not develop a fungal infection during the study.

Patient # 121-013

A 37-year-old Caucasian female diagnosed in — with acute myelogenous leukemia in remission at the time of randomization. The Patient was admitted to the hospital on — for an autologous bone marrow transplant. Significant baseline clinical conditions included elevated alkaline phosphatase and AST levels, anemia, fever and tachycardia. Study

drug therapy with micafungin was initiated on — (Day 1) at a dose of 50 mg. The Patient underwent an autologous bone marrow transplant on Day 8.

The patient developed life-threatening hyperbilirubinemia on Day 10 that in the Investigator's opinion was possibly related to study drug. The patient was discontinued from study drug on Day 15 due to hyperbilirubinemia (total bilirubin on Day 16 was 2.6 mg/dL).

The patient developed a suspected fungal infection from Day 17 to Day 35 and received amphotericin B therapy from Day 17 to Day 35 for empirical antifungal therapy. On Day 26 the patient developed sepsis due to *Enterococcus faecium* that in the Investigator's opinion was not related to study drug. On Day 32 the patient developed progressive neurological deterioration of unknown etiology that in the Investigator's opinion was not related to study drug. On Day 36 the patient developed gastro-intestinal (GI) bleeding and renal failure requiring dialysis that in the Investigator's opinion were not related to study drug.

The patient's condition continued to deteriorate and she expired on Day 37 due to sepsis with the contributing conditions of GI bleed and acute diffuse alveolar damage that in the Investigator's opinion was unlikely related to study drug and not related to a fungal infection. The patient's hyperbilirubinemia had not resolved at the time of death (total bilirubin on Day 37 was 2.8 mg/dL). The patient did not achieve neutrophil recovery during the study and did not develop any additional fungal infections during the study.

Patient # 92-501

A 66-year-old Caucasian male diagnosed in — with non-Hodgkin's lymphoma, in relapse. The patient was admitted to the hospital on — or an allogeneic matched-sibling peripheral stem cell transplant with an associated high risk of transplant related mortality. Study drug therapy with micafungin was initiated on — (Day 1) at a dose of 50 mg. The patient underwent an allogeneic peripheral stem cell transplant on Day 6.

The patient developed moderate hyperbilirubinemia on Day 8 that in the Investigator's opinion was probably related to study drug. The patient was discontinued from study drug on Day 10 due to hyperbilirubinemia.

The patient did not receive any additional antifungal therapy, achieved neutrophil recovery on Day 20, and was discharged from the hospital on Day 21. On Day 36 the patient developed GVHD that reached an overall maximum Grade III. The patient's hyperbilirubinemia had not resolved at the time of study completion. The patient did not develop a fungal infection during the study.

7.1.4 Other Search Strategies

Treatment emergent adverse events for the 50 mg dose (1 mg/kg dose in patients ≤ 40 kg) were also analyzed by age (patients < 6 years, 6-12 years, 13-17 years, and ≥ 18 years) and gender

(males and females). The results based upon age are shown in Tables 15 for micafungin and, for comparison, Table 16 for the 400 mg dose fluconazole. No patient < 18 years of age received a 200 mg dose of fluconazole. A summary of the events reported for 200 mg of fluconazole can be found in Table 18 in Section 7.1.5 (Common Adverse Events). Table 17 shows events by gender for micafungin, 200 mg of fluconazole, and 400 mg of fluconazole.

In the Reviewer's opinion, differences, if any, seen in adverse event rates between pediatric patients and adults or male and female patients treated with micafungin are not considered clinically meaningful and do not warrant reporting by age or gender in the product labeling. In addition, adverse events reported for fluconazole (400 mg dose) in pediatric patients are similar to those reported for micafungin.

Clinical Reviewer's Comment: The safety of micafungin in Study 98-0-050 was previously reviewed in the original submission of NDA 21-506 (see Medical Officer Review). No effect of race was seen on the adverse event profile of micafungin. Therefore, the Reviewer did not request an additional safety analysis of micafungin based on race for this resubmission.

TABLE 15

INCIDENCE OF TREATMENT EMERGENT ADVERSE EVENTS OF 50 MG FK463, BY AGE GROUP
ALL FK463 TREATED PATIENTS (1)

BODY SYSTEM (2) COSTART TERM	AGE <6 (N=41)	6-12 (N=31)	13-17 (N=16)	>=18 (N=682)
ALL SYSTEMS	38(92.7%)	31(100.0%)	15(93.8%)	663(97.2%)
BODY AS A WHOLE				
ANY AE	31(75.6%)	29(93.5%)	12(75.0%)	555(81.4%)
FEVER	9(22.0%)	12(38.7%)	6(37.5%)	269(39.4%)
ABDOMINAL PAIN	4(9.8%)	13(41.9%)	6(37.5%)	195(28.6%)
ASTHENIA	3(7.3%)	5(16.1%)	2(12.5%)	173(25.4%)
INFECTION	13(31.7%)	12(38.7%)	1(6.3%)	160(23.5%)
PROCEDURAL COMPLICATION	10(24.4%)	8(25.8%)	1(6.3%)	141(20.7%)
SEPSIS	6(14.6%)	6(19.4%)	1(6.3%)	124(18.2%)
CHILLS	3(7.3%)	2(6.5%)	3(18.8%)	114(16.7%)
PAIN	5(12.2%)	8(25.8%)	3(18.8%)	101(14.8%)
BACK PAIN	1(2.4%)	4(12.9%)	2(12.5%)	73(10.7%)
ALLERGIC REACTION	5(12.2%)	6(19.4%)	1(6.3%)	49(7.2%)
TRANSFUSION REACTION	1(2.4%)	3(9.7%)	1(6.3%)	40(5.9%)
ABDOMEN ENLARGED	5(12.2%)	5(16.1%)	3(18.8%)	38(5.6%)
FACE EDEMA	1(2.4%)	2(6.5%)	1(6.3%)	36(5.3%)
GRAFT VERSUS HOST DISEASE	6(14.6%)	6(19.4%)	0	30(4.4%)
CACHEXIA	3(7.3%)	1(3.2%)	0	18(2.6%)
FLU SYNDROME	2(4.9%)	0	2(12.5%)	13(1.9%)
MALAISE	0	1(3.2%)	1(6.3%)	13(1.9%)
NECK PAIN	0	1(3.2%)	0	13(1.9%)
ACCIDENTAL INJURY	1(2.4%)	1(3.2%)	0	11(1.6%)
ASCITES	0	1(3.2%)	0	10(1.5%)
LAB TEST ABNORMAL	1(2.4%)	1(3.2%)	0	8(1.2%)
TUBERCULOSIS AGGRAVATED	0	0	0	8(1.2%)
CELLULITIS	0	0	1(6.3%)	7(1.0%)
ABSCESS	1(2.4%)	1(3.2%)	0	4(0.6%)
PELVIC PAIN	0	1(3.2%)	1(6.3%)	4(0.6%)
PERITONITIS	1(2.4%)	0	0	4(0.6%)
DRUG LEVEL INCREASED	0	0	0	3(0.4%)
ANAPHYLACTOID REACTION	0	0	0	2(0.3%)
HERNIA	0	0	0	2(0.3%)
MUCOUS MEMBRANE DISORDER	0	0	0	2(0.3%)
NECK RIGIDITY	0	0	0	2(0.3%)
NEOPLASM BENIGN	0	0	0	2(0.3%)
SARCOMA	0	0	0	2(0.3%)
TUBERCULOSIS REACTIVATED	0	1(3.2%)	0	2(0.3%)
HYPOTHERMIA	0	0	0	1(0.1%)
NECROSIS	0	0	0	1(0.1%)
OVERDOSE	0	0	0	1(0.1%)

(1) STUDIES INCLUDED: 98-0-050, FG-21-09, AND 98-0-047. STUDY 98-0-047 ONLY INCLUDES PATIENTS < 16 YEARS OLD WHO RECEIVED 1 MG/KG/DAY AND >= 16 YEARS OLD WHO RECEIVED 50 MG/DAY DOSE OF FK463.
(2) WITHIN A BODY SYSTEM A PERSON MAY EXPERIENCE MORE THAN ONE ADVERSE EVENT.

FK463 = micafungin; Corresponds to Table R6 8.1 in the applicant's submission dated October 25, 2004.

TABLE 15 (continued)

INCIDENCE OF TREATMENT EMERGENT ADVERSE EVENTS OF 50 MG FK463, BY AGE GROUP
ALL FK463 TREATED PATIENTS (1)

BODY SYSTEM (2) COSTART TERM	AGE <6 (N=41)	6-12 (N=31)	13-17 (N=16)	>=18 (N=682)
PRIMARY GRAFT DYSFUNCTION	0	0	0	1(0.1%)
SURGICAL TREATMENT	0	0	0	1(0.1%)
CARCINOMA	1(2.4%)	0	0	0
DIGESTIVE SYSTEM				
ANY AE	28(68.3%)	27(87.1%)	15(93.8%)	544(79.8%)
DIARRHEA	9(22.0%)	9(29.0%)	7(43.8%)	333(48.8%)
NAUSEA	9(22.0%)	18(58.1%)	10(62.5%)	317(46.5%)
VOMITING	16(39.0%)	19(61.3%)	9(56.3%)	306(44.9%)
MUCOSITIS	12(29.3%)	16(51.6%)	9(56.3%)	301(44.1%)
ANOREXIA	11(26.8%)	13(41.9%)	8(50.0%)	207(30.4%)
CONSTIPATION	4(9.8%)	6(19.4%)	3(18.8%)	148(21.7%)
DYSPEPSIA	2(4.9%)	2(6.5%)	1(6.3%)	123(18.0%)
RECTAL DISORDER	1(2.4%)	4(12.9%)	2(12.5%)	78(11.4%)
DRY MOUTH/NOSE	0	2(6.5%)	1(6.3%)	51(7.5%)
DYSPHAGIA	0	1(3.2%)	0	29(4.3%)
STOMATITIS	0	2(6.5%)	1(6.3%)	28(4.1%)
LIVER FUNCTION TESTS ABNORMAL	3(7.3%)	2(6.5%)	3(18.8%)	27(4.0%)
MELENA	3(7.3%)	3(9.7%)	0	23(3.4%)
GASTROINTESTINAL DISORDER	3(7.3%)	1(3.2%)	0	22(3.2%)
JAUNDICE	1(2.4%)	2(6.5%)	1(6.3%)	21(3.1%)
GASTROENTERITIS	0	0	0	20(2.9%)
COLITIS	0	2(6.5%)	0	19(2.8%)
FLATULENCE	0	0	0	19(2.8%)
ILEUS	0	1(3.2%)	1(6.3%)	19(2.8%)
GASTROINTESTINAL HEMORRHAGE	0	0	0	17(2.5%)
ERUCTATION	0	0	0	15(2.2%)
ESOPHAGITIS	0	1(3.2%)	0	15(2.2%)
GASTRITIS	0	3(9.7%)	0	13(1.9%)
HEMATEMESIS	0	3(9.7%)	3(18.8%)	13(1.9%)
TOOTH DISORDER	0	0	0	13(1.9%)
VENOOCCLUSIVE LIVER DISEASE	1(2.4%)	1(3.2%)	1(6.3%)	12(1.8%)
RECTAL HEMORRHAGE	0	0	2(12.5%)	11(1.6%)
FECAL INCONTINENCE	1(2.4%)	0	0	10(1.5%)
GUM/ORAL HEMORRHAGE	0	1(3.2%)	0	9(1.3%)
LEUKOPLAKIA OF MOUTH	0	0	0	7(1.0%)
MOUTH ULCERATION	0	0	0	7(1.0%)
ENTERITIS	0	0	0	6(0.9%)
GINGIVITIS	1(2.4%)	1(3.2%)	0	5(0.7%)
CHOLELITHIASIS	1(2.4%)	0	0	4(0.6%)
ENTEROCOLITIS	0	0	0	4(0.6%)

(1) STUDIES INCLUDED: 98-0-050, FG-21-09, AND 98-0-047. STUDY 98-0-047 ONLY INCLUDES PATIENTS < 16 YEARS OLD WHO RECEIVED 1 MG/KG/DAY AND >= 16 YEARS OLD WHO RECEIVED 50 MG/DAY DOSE OF FK463.
(2) WITHIN A BODY SYSTEM A PERSON MAY EXPERIENCE MORE THAN ONE ADVERSE EVENT.

Corresponds to Table R6 8.1 in the applicant's submission dated October 25, 2004.
FK463 = micafungin

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TABLE 15 (continued)

INCIDENCE OF TREATMENT EMERGENT ADVERSE EVENTS OF 50 MG FK463, BY AGE GROUP
ALL FK463 TREATED PATIENTS (1)

BODY SYSTEM (2) COSTART TERM	AGE <6 (N=41)	6-12 (N=31)	13-17 (N=16)	>=18 (N=682)
ESOPHAGEAL ULCER	0	0	0	4(0.6%)
HEPATOMEGALY	2(4.9%)	2(6.5%)	1(6.3%)	4(0.6%)
GLOSSITIS	0	0	0	3(0.4%)
SIALADENITIS	0	0	1(6.3%)	3(0.4%)
STOMACH ATONY	0	0	0	3(0.4%)
APHTHOUS STOMATITIS	0	0	0	2(0.3%)
HEPATOSPLENOMEGALY	0	1(3.2%)	0	2(0.3%)
LIVER DAMAGE	0	0	0	2(0.3%)
PAROTID GLAND ENLARGEMENT	0	0	0	2(0.3%)
STOMACH ULCER	0	0	0	2(0.3%)
ABNORMAL STOOLS	0	0	0	1(0.1%)
CHOLESTATIC JAUNDICE	0	0	0	1(0.1%)
DUODENAL ULCER	0	0	0	1(0.1%)
FECAL IMPACTION	0	0	0	1(0.1%)
GASTROINTESTINAL CARCINOMA	0	0	0	1(0.1%)
HEPATITIS, NONSPECIFIC	0	1(3.2%)	0	1(0.1%)
INTESTINAL OBSTRUCTION	0	0	0	1(0.1%)
PANCREAS DISORDER	0	1(3.2%)	0	1(0.1%)
PANCREATITIS	0	0	0	1(0.1%)
PEPTIC ULCER	0	0	0	1(0.1%)
TONGUE DISORDER	0	1(3.2%)	0	1(0.1%)
TONGUE EDEMA	0	0	0	1(0.1%)
TOOTH CARIES	0	0	0	1(0.1%)
DUODENITIS	0	1(3.2%)	0	0
METABOLIC AND NUTRITIONAL DISORDERS				
ANY AE	25(61.0%)	23(74.2%)	11(68.8%)	512(75.1%)
HYPOMAGNESEMIA	6(14.6%)	8(25.8%)	4(25.0%)	248(36.4%)
HYPOKALEMIA	6(14.6%)	11(35.5%)	4(25.0%)	237(34.8%)
PERIPHERAL EDEMA	1(2.4%)	2(6.5%)	1(6.3%)	115(16.9%)
EDEMA	8(19.5%)	6(19.4%)	2(12.5%)	112(16.4%)
HYPOCALCEMIA	2(4.9%)	5(16.1%)	1(6.3%)	94(13.8%)
HYPOPHOSPHATEMIA	1(2.4%)	2(6.5%)	0	81(11.9%)
HYPERGLYCEMIA	4(9.8%)	4(12.9%)	1(6.3%)	71(10.4%)
HYPERVOLEMIA	5(12.2%)	5(16.1%)	2(12.5%)	71(10.4%)
BILIRUBINEMIA	3(7.3%)	5(16.1%)	1(6.3%)	65(9.5%)
HYPONATREMIA	2(4.9%)	4(12.9%)	1(6.3%)	59(8.7%)
SGOT INCREASED	2(4.9%)	3(9.7%)	0	45(6.6%)
CREATININE INCREASED	0	0	1(6.3%)	40(5.9%)
HYPOPROTEINEMIA	4(9.8%)	7(22.6%)	0	39(5.7%)
SGPT INCREASED	3(7.3%)	7(22.6%)	1(6.3%)	38(5.6%)

(1) STUDIES INCLUDED: 98-0-050, FG-21-09, AND 98-0-047. STUDY 98-0-047 ONLY INCLUDES PATIENTS < 16 YEARS OLD WHO RECEIVED 1 MG/KG/DAY AND >= 16 YEARS OLD WHO RECEIVED 50 MG/DAY DOSE OF FK463.
(2) WITHIN A BODY SYSTEM A PERSON MAY EXPERIENCE MORE THAN ONE ADVERSE EVENT.

Corresponds to Table R6 8.1 in the applicant's submission dated October 25, 2004.
FK463 = micafungin

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TABLE 15 (continued)

INCIDENCE OF TREATMENT EMERGENT ADVERSE EVENTS OF 50 MG FK463, BY AGE GROUP
ALL FK463 TREATED PATIENTS (1)

BODY SYSTEM (2) COSTART TERM	AGE <6 (N=41)	6-12 (N=31)	13-17 (N=16)	>=18 (N=682)
ALKALINE PHOSPHATASE INCREASED	1(2.4%)	1(3.2%)	0	32(4.7%)
HYPERKALEMIA	2(4.9%)	1(3.2%)	0	29(4.3%)
BUN INCREASED	1(2.4%)	0	0	22(3.2%)
ACIDOSIS	3(7.3%)	4(12.9%)	0	20(2.9%)
DEHYDRATION	0	0	0	20(2.9%)
HYPOGLYCEMIA	1(2.4%)	1(3.2%)	0	19(2.8%)
LACTIC DEHYDROGENASE INCREASED	0	1(3.2%)	0	15(2.2%)
WEIGHT GAIN	0	0	1(6.3%)	14(2.1%)
WEIGHT LOSS	2(4.9%)	0	0	14(2.1%)
HYPERNATREMIA	1(2.4%)	3(9.7%)	0	11(1.6%)
RESPIRATORY ALKALOSIS	0	1(3.2%)	0	11(1.6%)
HYPERCHLOREMIA	2(4.9%)	1(3.2%)	0	9(1.3%)
HYPERPHOSPHATEMIA	1(2.4%)	1(3.2%)	0	9(1.3%)
HYPOCHLOREMIA	0	0	1(6.3%)	8(1.2%)
HYPERMAGNESEMIA	0	0	0	7(1.0%)
DECREASED BICARBONATE	0	0	0	5(0.7%)
ALKALOSIS	1(2.4%)	0	0	4(0.6%)
HEALING ABNORMAL	1(2.4%)	0	0	4(0.6%)
ELECTROLYTE ABNORMALITY	0	1(3.2%)	0	3(0.4%)
KETOSIS	0	0	1(6.3%)	3(0.4%)
GLYCOSURIA	0	0	1(6.3%)	2(0.3%)
HYPERCALCEMIA	0	0	0	2(0.3%)
HYPOVOLEMIA	0	0	0	2(0.3%)
CREATININE CLEARANCE DECREASED	0	0	0	1(0.1%)
GLOBULIN INCREASED	0	0	0	1(0.1%)
GOUT	0	0	0	1(0.1%)
HYPERLIPEMIA	0	1(3.2%)	0	1(0.1%)
HYPERURICEMIA	0	0	0	1(0.1%)
HYPOCHOLESTEREMIA	0	0	0	1(0.1%)
RESPIRATORY ACIDOSIS	4(9.8%)	0	0	1(0.1%)
HEMIC AND LYMPHATIC SYSTEM				
ANY AR	21(51.2%)	23(74.2%)	12(75.0%)	452(66.3%)
LEUKOPENIA	14(34.1%)	12(38.7%)	9(56.3%)	331(48.5%)
THROMBOCYTOPENIA	13(31.7%)	12(38.7%)	10(62.5%)	303(44.4%)
ANEMIA	12(29.3%)	9(29.0%)	7(43.8%)	166(24.3%)
PETECHIA	3(7.3%)	3(9.7%)	1(6.3%)	37(5.4%)
ECCHYMOSIS	1(2.4%)	2(6.5%)	0	31(4.5%)
COAGULATION DISORDER	0	2(6.5%)	0	16(2.3%)
WBC ABNORMAL	1(2.4%)	1(3.2%)	0	14(2.1%)
LEUKOCYTOSIS	1(2.4%)	1(3.2%)	0	9(1.3%)

(1) STUDIES INCLUDED: 98-0-050, FG-21-09, AND 98-0-047. STUDY 98-0-047 ONLY INCLUDES PATIENTS < 16 YEARS OLD WHO RECEIVED 1 MG/KG/DAY AND >= 16 YEARS OLD WHO RECEIVED 50 MG/DAY DOSE OF FK463.
(2) WITHIN A BODY SYSTEM A PERSON MAY EXPERIENCE MORE THAN ONE ADVERSE EVENT.

Corresponds to Table R6 8.1 in the applicant's submission dated October 25, 2004.
FK463 = micafungin

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TABLE 15 (continued)

INCIDENCE OF TREATMENT EMERGENT ADVERSE EVENTS OF 50 MG FK463, BY AGE GROUP
ALL FK463 TREATED PATIENTS (1)

BODY SYSTEM (2) COSTART TERM	AGE <6 (N=41)	6-12 (N=31)	13-17 (N=16)	>=18 (N=682)
PANCYTOPENIA	0	2(6.5%)	0	9(1.3%)
LYMPHADENOPATHY	0	0	0	7(1.0%)
THROMBOCYTHEMIA	1(2.4%)	1(3.2%)	0	6(0.9%)
PROTHROMBIN DECREASED	4(9.8%)	1(3.2%)	0	5(0.7%)
EOSINOPHILIA	0	0	0	4(0.6%)
SPLENOMEGALY	1(2.4%)	1(3.2%)	0	3(0.4%)
BLEEDING TIME INCREASED	0	0	0	2(0.3%)
CYANOSIS	0	1(3.2%)	0	2(0.3%)
ERYTHROCYTES ABNORMAL	0	0	0	1(0.1%)
FIBRINOGEN INCREASED	0	0	0	1(0.1%)
HEMOLYSIS	0	0	0	1(0.1%)
HEMOLYTIC ANEMIA	0	0	0	1(0.1%)
LEUKEMIA	0	0	0	1(0.1%)
PURPURA	0	1(3.2%)	1(6.3%)	1(0.1%)
RETICULOENDOTHELIAL HYPERPLASIA	0	0	0	1(0.1%)
SPLEEN DISORDER	0	0	0	1(0.1%)
THROMBOPLASTIN DECREASED	0	0	1(6.3%)	1(0.1%)
NERVOUS SYSTEM				
ANY AE	14(34.1%)	18(58.1%)	9(56.3%)	436(63.9%)
HEADACHE	2(4.9%)	8(25.8%)	5(31.3%)	215(31.5%)
INSOMNIA	1(2.4%)	2(6.5%)	3(18.8%)	168(24.6%)
ANXIETY	3(7.3%)	5(16.1%)	3(18.8%)	98(14.4%)
DIZZINESS	0	2(6.5%)	1(6.3%)	64(9.4%)
CONFUSION	0	0	1(6.3%)	50(7.3%)
PARESTHESIA	0	1(3.2%)	3(18.8%)	37(5.4%)
DEPRESSION	1(2.4%)	1(3.2%)	0	33(4.8%)
SOMNOLENCE	1(2.4%)	1(3.2%)	0	33(4.8%)
NERVOUSNESS	6(14.6%)	2(6.5%)	2(12.5%)	29(4.3%)
TREMOR	0	2(6.5%)	1(6.3%)	22(3.2%)
AGITATION	3(7.3%)	3(9.7%)	0	18(2.6%)
ABNORMAL DREAMS	0	0	0	13(1.9%)
HALLUCINATIONS	0	1(3.2%)	0	13(1.9%)
CONVULSION	2(4.9%)	2(6.5%)	0	6(0.9%)
DELIRIUM	0	0	0	6(0.9%)
HYPERTONIA	0	0	0	6(0.9%)
ABNORMAL GAIT	1(2.4%)	0	0	5(0.7%)
HOSTILITY	0	0	0	4(0.6%)
NEURALGIA	0	0	0	4(0.6%)
THINKING ABNORMAL	0	0	0	4(0.6%)
EMOTIONAL LABILITY	0	2(6.5%)	0	3(0.4%)

(1) STUDIES INCLUDED: 98-0-050, FG-21-09, AND 98-0-047. STUDY 98-0-047 ONLY INCLUDES PATIENTS < 16 YEARS OLD WHO RECEIVED 1 MG/KG/DAY AND >= 16 YEARS OLD WHO RECEIVED 50 MG/DAY DOSE OF FK463.
(2) WITHIN A BODY SYSTEM A PERSON MAY EXPERIENCE MORE THAN ONE ADVERSE EVENT.

Corresponds to Table R6 8.1 in the applicant's submission dated October 25, 2004.
FK463 = micafungin

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TABLE 15 (continued)

INCIDENCE OF TREATMENT EMERGENT ADVERSE EVENTS OF 50 MG FK463, BY AGE GROUP
ALL FK463 TREATED PATIENTS (1)

BODY SYSTEM (2) COSTART TERM	AGE <6 (N=41)	6-12 (N=31)	13-17 (N=16)	>=18 (N=682)
ENCEPHALOPATHY	0	0	0	3(0.4%)
EXTRAPYRAMIDAL SYNDROME	0	0	0	3(0.4%)
NEUROPATHY	1(2.4%)	1(3.2%)	0	3(0.4%)
SPEECH DISORDER	0	0	0	3(0.4%)
STUPOR	0	0	0	3(0.4%)
APHASIA	0	0	0	2(0.3%)
COMA	0	2(6.5%)	0	2(0.3%)
DYSTONIA	0	0	0	2(0.3%)
MENINGITIS	0	2(6.5%)	0	2(0.3%)
NEURITIS	0	0	0	2(0.3%)
APATHY	0	0	0	1(0.1%)
CNS DEPRESSION	0	0	0	1(0.1%)
CNS NEOPLASIA BENIGN	0	0	0	1(0.1%)
HYPERESTHESIA	0	0	0	1(0.1%)
INTRACRANIAL HYPERTENSION	0	0	0	1(0.1%)
MOVEMENT DISORDER	0	0	0	1(0.1%)
MYOCLONUS	0	0	0	1(0.1%)
PARANOID REACTION	0	0	0	1(0.1%)
PERSONALITY DISORDER	0	0	0	1(0.1%)
VOCAL CORD PARALYSIS	0	0	0	1(0.1%)
WITHDRAWAL SYNDROME	0	0	0	1(0.1%)
CEREBROVASCULAR ACCIDENT	0	1(3.2%)	0	0
HEMIPLEGIA	0	1(3.2%)	0	0
INTRACRANIAL HEMORRHAGE	1(2.4%)	0	0	0
NYSTAGMUS	1(2.4%)	0	0	0
RESPIRATORY SYSTEM				
ANY AE	23(56.1%)	18(58.1%)	12(75.0%)	393(57.6%)
COUGH INCREASED	3(7.3%)	3(9.7%)	1(6.3%)	121(17.7%)
DYSPNEA	2(4.9%)	0	4(25.0%)	92(13.5%)
LUNG DISORDER	3(7.3%)	3(9.7%)	1(6.3%)	92(13.5%)
RHINITIS	4(9.8%)	0	2(12.5%)	79(11.6%)
EPISTAXIS	2(4.9%)	3(9.7%)	2(12.5%)	55(8.1%)
PHARYNGITIS	1(2.4%)	3(9.7%)	2(12.5%)	55(8.1%)
HICCUP	0	0	1(6.3%)	41(6.0%)
PNEUMONIA	6(14.6%)	3(9.7%)	1(6.3%)	41(6.0%)
ASTHMA	0	0	1(6.3%)	35(5.1%)
HYPOXIA	3(7.3%)	2(6.5%)	0	27(4.0%)
SINUSITIS	0	2(6.5%)	0	21(3.1%)
PLEURAL EFFUSION	0	0	0	20(2.9%)
RESPIRATORY FAILURE	0	1(3.2%)	1(6.3%)	20(2.9%)

(1) STUDIES INCLUDED: 98-0-050, FG-21-09, AND 98-0-047. STUDY 98-0-047 ONLY INCLUDES PATIENTS < 16 YEARS OLD WHO RECEIVED 1 MG/KG/DAY AND >= 16 YEARS OLD WHO RECEIVED 50 MG/DAY DOSE OF FK463.
(2) WITHIN A BODY SYSTEM A PERSON MAY EXPERIENCE MORE THAN ONE ADVERSE EVENT.

Corresponds to Table R6 8.1 in the applicant's submission dated October 25, 2004.
FK463 = micafungin

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TABLE 15 (continued)

INCIDENCE OF TREATMENT EMERGENT ADVERSE EVENTS OF 50 MG FK463, BY AGE GROUP
ALL FK463 TREATED PATIENTS (1)

BODY SYSTEM (2) COSTART TERM	AGE <6 (N=41)	6-12 (N=31)	13-17 (N=16)	>=18 (N=682)
HEMOPTYSIS	0	0	0	18(2.6%)
LUNG EDEMA	0	1(3.2%)	0	15(2.2%)
HYPERVENTILATION	2(4.9%)	4(12.9%)	2(12.5%)	14(2.1%)
RESPIRATORY DISORDER	3(7.3%)	2(6.5%)	0	9(1.3%)
ATELECTASIS	3(7.3%)	1(3.2%)	0	6(0.9%)
APNEA	0	0	0	5(0.7%)
BRONCHITIS	0	0	0	5(0.7%)
PLEURAL DISORDER	0	0	0	3(0.4%)
RESPIRATORY DISTRESS SYNDROME	0	2(6.5%)	0	3(0.4%)
LUNG HEMORRHAGE	1(2.4%)	0	0	2(0.3%)
PULMONARY HYPERTENSION	0	0	0	2(0.3%)
STRIDOR	1(2.4%)	0	0	2(0.3%)
VOICE ALTERATION	0	0	0	2(0.3%)
EMPHYSEMA	0	0	0	1(0.1%)
INTERSTITIAL PNEUMONIA	0	0	0	1(0.1%)
LARYNGITIS	0	0	0	1(0.1%)
PNEUMOTHORAX	0	0	0	1(0.1%)
PULMONARY EMBOLUS	0	0	0	1(0.1%)
PULMONARY TUBERCULOSIS REACTIVATED	0	0	0	1(0.1%)
SPUTUM INCREASED	0	0	0	1(0.1%)
CARDIOVASCULAR SYSTEM				
ANY AE	21(51.2%)	18(58.1%)	7(43.8%)	348(51.0%)
TACHYCARDIA	2(4.9%)	6(19.4%)	4(25.0%)	121(17.7%)
HYPOTENSION	5(12.2%)	4(12.9%)	2(12.5%)	100(14.7%)
HYPERTENSION	12(29.3%)	9(29.0%)	3(18.8%)	87(12.8%)
CHEST PAIN	0	3(9.7%)	0	66(9.7%)
VASODILATATION	1(2.4%)	0	1(6.3%)	65(9.5%)
ATRIAL FIBRILLATION	0	0	0	17(2.5%)
BRADYCARDIA	3(7.3%)	0	1(6.3%)	16(2.3%)
POSTURAL HYPOTENSION	0	0	0	14(2.1%)
SHOCK	1(2.4%)	2(6.5%)	0	13(1.9%)
ARRHYTHMIA	4(9.8%)	2(6.5%)	0	12(1.8%)
SYNCOPE	0	0	0	12(1.8%)
PHLEBITIS	1(2.4%)	1(3.2%)	0	11(1.6%)
HEMORRHAGE	1(2.4%)	0	0	9(1.3%)
CARDIOMEGALY	0	0	0	8(1.2%)
CONGESTIVE HEART FAILURE	0	0	0	7(1.0%)
DEEP THROMBOPHLEBITIS	1(2.4%)	2(6.5%)	0	7(1.0%)
VALVULAR HEART DISEASE	0	1(3.2%)	0	6(0.9%)
PERICARDIAL EFFUSION	0	1(3.2%)	0	5(0.7%)

(1) STUDIES INCLUDED: 98-0-050, FG-21-09, AND 98-0-047. STUDY 98-0-047 ONLY INCLUDES PATIENTS < 16 YEARS OLD WHO RECEIVED 1 MG/KG/DAY AND >= 16 YEARS OLD WHO RECEIVED 50 MG/DAY DOSE OF FK463.
(2) WITHIN A BODY SYSTEM A PERSON MAY EXPERIENCE MORE THAN ONE ADVERSE EVENT.

Corresponds to Table R6 8.1 in the applicant's submission dated October 25, 2004.
FK463 = micafungin

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TABLE 15 (continued)

INCIDENCE OF TREATMENT EMERGENT ADVERSE EVENTS OF 50 MG FK463, BY AGE GROUP
ALL FK463 TREATED PATIENTS (1)

BODY SYSTEM (2) COSTART TERM	AGE <6 (N=41)	6-12 (N=31)	13-17 (N=16)	>=18 (N=682)
PERIPHERAL VASCULAR DISORDER	0	1(3.2%)	0	5(0.7%)
ATRIAL FLUTTER	0	0	0	4(0.6%)
PALLOR	1(2.4%)	0	0	4(0.6%)
PALPITATION	0	0	0	4(0.6%)
THROMBOPHLEBITIS	1(2.4%)	0	0	4(0.6%)
ELECTROCARDIOGRAM ABNORMAL	0	1(3.2%)	0	3(0.4%)
MIGRAINE	0	0	0	3(0.4%)
VENTRICULAR TACHYCARDIA	0	0	1(6.3%)	3(0.4%)
CARDIOVASCULAR DISORDER	1(2.4%)	1(3.2%)	0	2(0.3%)
HEART ARREST	0	0	0	2(0.3%)
SINUS BRADYCARDIA	0	0	0	2(0.3%)
SUPRAVENTRICULAR TACHYCARDIA	0	0	0	2(0.3%)
VENTRICULAR ARRHYTHMIA	0	0	0	2(0.3%)
ANGINA PECTORIS	0	0	0	1(0.1%)
ARTERIOSCLEROSIS	0	0	0	1(0.1%)
AV BLOCK COMPLETE	0	0	0	1(0.1%)
ENDOCARDITIS	0	0	0	1(0.1%)
EXTRASYSTOLES	0	0	0	1(0.1%)
INCREASED CAPILLARY FRAGILITY	0	0	0	1(0.1%)
MYOCARDIAL ISCHEMIA	0	0	0	1(0.1%)
PERICARDITIS	0	0	0	1(0.1%)
VASCULAR DISORDER	0	0	0	1(0.1%)
VENTRICULAR EXTRASYSTOLES	0	0	0	1(0.1%)
HEART FAILURE	1(2.4%)	1(3.2%)	0	0
SKIN AND APPENDAGES				
ANY AE	19(46.3%)	19(61.3%)	9(56.3%)	327(47.9%)
RASH	12(29.3%)	10(32.3%)	5(31.3%)	182(26.7%)
PRURITUS	5(12.2%)	8(25.8%)	6(37.5%)	76(11.1%)
SKIN DISORDER	4(9.8%)	4(12.9%)	1(6.3%)	39(5.7%)
SWEATING	1(2.4%)	0	2(12.5%)	28(4.1%)
FOLLICULITIS	1(2.4%)	1(3.2%)	1(6.3%)	27(4.0%)
DRY SKIN	0	1(3.2%)	1(6.3%)	25(3.7%)
MACULOPAPULAR RASH	0	3(9.7%)	0	22(3.2%)
ALOPECIA	7(17.1%)	2(6.5%)	2(12.5%)	20(2.9%)
HERPES SIMPLEX	0	2(6.5%)	0	17(2.5%)
URTICARIA	5(12.2%)	2(6.5%)	0	16(2.3%)
SKIN ULCER	0	2(6.5%)	0	12(1.8%)
ACNE	0	0	0	8(1.2%)
SKIN DISCOLORATION	1(2.4%)	3(9.7%)	0	8(1.2%)
HERPES ZOSTER	0	1(3.2%)	0	7(1.0%)

(1) STUDIES INCLUDED: 98-0-050, FG-21-09, AND 98-0-047. STUDY 98-0-047 ONLY INCLUDES PATIENTS < 16 YEARS OLD WHO RECEIVED 1 MG/KG/DAY AND >= 16 YEARS OLD WHO RECEIVED 50 MG/DAY DOSE OF FK463.
(2) WITHIN A BODY SYSTEM A PERSON MAY EXPERIENCE MORE THAN ONE ADVERSE EVENT.

Corresponds to Table R6 8.1 in the applicant's submission dated October 25, 2004.
FK463 = micafungin

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TABLE 15 (continued)

INCIDENCE OF TREATMENT EMERGENT ADVERSE EVENTS OF 50 MG FK463, BY AGE GROUP
ALL FK463 TREATED PATIENTS (1)

BODY SYSTEM (2) COSTART TERM	AGE <6 (N=41)	6-12 (N=31)	13-17 (N=16)	>=18 (N=682)
VESICULOBULLOUS RASH	2(4.9%)	1(3.2%)	0	7(1.0%)
EXFOLIATIVE DERMATITIS	0	0	0	5(0.7%)
PETECHIAL RASH	0	1(3.2%)	0	5(0.7%)
ANGIOEDEMA	0	0	0	2(0.3%)
BREAST PAIN	0	0	0	2(0.3%)
CONTACT DERMATITIS	0	0	0	2(0.3%)
NAIL DISORDER	0	0	0	2(0.3%)
PUSTULAR RASH	0	0	1(6.3%)	2(0.3%)
SKIN INFECTION	0	0	0	2(0.3%)
SKIN NODULE	0	0	0	2(0.3%)
SEBORRHEA	0	0	0	1(0.1%)
SUBCUTANEOUS NODULE	0	0	0	1(0.1%)
SUNBURN	0	0	0	1(0.1%)
ECZEMA	1(2.4%)	0	0	0
UROGENITAL SYSTEM				
ANY AE	12(29.3%)	12(38.7%)	8(50.0%)	210(30.8%)
HEMATURIA	1(2.4%)	5(16.1%)	6(37.5%)	61(8.9%)
DYSURIA	1(2.4%)	0	2(12.5%)	40(5.9%)
OLIGURIA	6(14.6%)	5(16.1%)	1(6.3%)	32(4.7%)
URINARY TRACT INFECTION	0	1(3.2%)	2(12.5%)	26(3.8%)
URINARY INCONTINENCE	1(2.4%)	0	0	18(2.6%)
URINARY FREQUENCY	0	1(3.2%)	0	15(2.2%)
CYSTITIS	2(4.9%)	1(3.2%)	1(6.3%)	11(1.6%)
KIDNEY FAILURE	1(2.4%)	1(3.2%)	0	11(1.6%)
VAGINAL HEMORRHAGE	0	0	0	11(1.6%)
VAGINITIS	1(2.4%)	0	0	10(1.5%)
ALBUMINURIA	0	0	0	9(1.3%)
KIDNEY FUNCTION ABNORMAL	0	0	1(6.3%)	9(1.3%)
ACUTE KIDNEY FAILURE	1(2.4%)	1(3.2%)	0	6(0.9%)
URINE ABNORMALITY	0	0	0	6(0.9%)
HEMORRHAGIC CYSTITIS	0	0	0	5(0.7%)
PENIS DISORDER	0	1(3.2%)	0	4(0.6%)
SCROTAL EDEMA	0	1(3.2%)	0	4(0.6%)
URINARY RETENTION	1(2.4%)	1(3.2%)	0	4(0.6%)
URINATION IMPAIRED	0	0	0	4(0.6%)
POLYURIA	0	1(3.2%)	0	3(0.4%)
NOCTURIA	0	0	0	2(0.3%)
URINARY URGENCY	0	1(3.2%)	0	2(0.3%)
ANURIA	0	0	0	1(0.1%)
CARCINOMA RENAL	0	0	0	1(0.1%)

(1) STUDIES INCLUDED: 98-0-050, FG-21-09, AND 98-0-047. STUDY 98-0-047 ONLY INCLUDES PATIENTS < 16 YEARS OLD WHO RECEIVED 1 MG/KG/DAY AND >= 16 YEARS OLD WHO RECEIVED 50 MG/DAY DOSE OF FK463.
(2) WITHIN A BODY SYSTEM A PERSON MAY EXPERIENCE MORE THAN ONE ADVERSE EVENT.

Corresponds to Table R6 8.1 in the applicant's submission dated October 25, 2004.
FK463 = micafungin

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TABLE 15 (continued)

INCIDENCE OF TREATMENT EMERGENT ADVERSE EVENTS OF 50 MG FK463, BY AGE GROUP
ALL FK463 TREATED PATIENTS (1)

BODY SYSTEM (2) COSTART TERM	AGE <6 (N=41)	6-12 (N=31)	13-17 (N=16)	>=18 (N=682)
KIDNEY PAIN	0	0	0	1(0.1%)
MENORRHAGIA	0	0	0	1(0.1%)
METRORRHAGIA	0	0	0	1(0.1%)
OVARIAN DISORDER	0	0	0	1(0.1%)
PROSTATIC DISORDER	0	0	0	1(0.1%)
PYELONEPHRITIS	0	0	0	1(0.1%)
TESTIS DISORDER	0	1(3.2%)	0	1(0.1%)
BALANITIS	1(2.4%)	0	0	0
URETHRAL PAIN	0	1(3.2%)	0	0
MUSCULOSKELETAL SYSTEM				
ANY AE	3(7.3%)	6(19.4%)	6(37.5%)	133(19.5%)
ARTHRALGIA	0	2(6.5%)	3(18.8%)	59(8.7%)
BONE PAIN	1(2.4%)	1(3.2%)	1(6.3%)	30(4.4%)
MYALGIA	0	2(6.5%)	1(6.3%)	23(3.4%)
CRAMPS	0	0	0	21(3.1%)
MYASTHENIA	0	0	1(6.3%)	12(1.8%)
BONE DISORDER	1(2.4%)	0	0	4(0.6%)
JOINT DISORDER	0	0	0	4(0.6%)
ARTHROSIS	0	0	0	3(0.4%)
TWITCHING	0	1(3.2%)	1(6.3%)	3(0.4%)
GENERALIZED SPASM	0	0	0	1(0.1%)
TENDINOUS CONTRACTURE	1(2.4%)	0	0	0
SPECIAL SENSES				
ANY AE	4(9.8%)	9(29.0%)	2(12.5%)	128(18.8%)
ABNORMAL VISION	0	1(3.2%)	0	26(3.8%)
DRY EYES	0	1(3.2%)	0	20(2.9%)
TASTE PERVERSION	0	0	0	20(2.9%)
EAR PAIN	2(4.9%)	3(9.7%)	1(6.3%)	18(2.6%)
EYE HEMORRHAGE	0	1(3.2%)	1(6.3%)	14(2.1%)
CONJUNCTIVITIS	0	1(3.2%)	0	12(1.8%)
EAR DISORDER	0	0	0	9(1.3%)
EYE PAIN	0	3(9.7%)	1(6.3%)	9(1.3%)
IMPAIRED HEARING	0	0	0	6(0.9%)
LACRIMATION DISORDER	0	0	0	6(0.9%)
CONJUNCTIVAL EDEMA	0	0	0	3(0.4%)
MIOSIS	0	0	0	3(0.4%)
OTITIS EXTERNA	1(2.4%)	0	0	3(0.4%)
PHOTOPHOBIA	0	1(3.2%)	0	3(0.4%)
TASTE LOSS	0	0	0	3(0.4%)

(1) STUDIES INCLUDED: 98-0-050, FG-21-09, AND 98-0-047. STUDY 98-0-047 ONLY INCLUDES PATIENTS < 16 YEARS OLD WHO RECEIVED 1 MG/KG/DAY AND >= 16 YEARS OLD WHO RECEIVED 50 MG/DAY DOSE OF FK463.
(2) WITHIN A BODY SYSTEM A PERSON MAY EXPERIENCE MORE THAN ONE ADVERSE EVENT.

Corresponds to Table R6 8.1 in the applicant's submission dated October 25, 2004.
FK463 = micafungin

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TABLE 15 (continued)

INCIDENCE OF TREATMENT EMERGENT ADVERSE EVENTS OF 50 MG FK463, BY AGE GROUP
ALL FK463 TREATED PATIENTS (1)

BODY SYSTEM (2) COSTART TERM	AGE <6 (N=41)	6-12 (N=31)	13-17 (N=16)	>=18 (N=602)
TINNITUS	0	0	0	3(0.4%)
EYE DISORDER	0	0	0	2(0.3%)
RETINAL HEMORRHAGE	0	0	0	2(0.3%)
ANISOCORIA	0	0	0	1(0.1%)
BLEPHARITIS	0	0	0	1(0.1%)
CORNEAL LESION	0	0	0	1(0.1%)
DEAFNESS	0	2(6.5%)	0	1(0.1%)
EXOPHTHALMOS	0	0	0	1(0.1%)
OTITIS MEDIA	0	0	0	1(0.1%)
PAROSMIA	0	0	0	1(0.1%)
RETINAL DISORDER	1(2.4%)	0	0	1(0.1%)
RETINITIS	0	0	0	1(0.1%)
SCLERITIS	0	0	0	1(0.1%)
UVEITIS	0	0	0	1(0.1%)
STRABISMUS	0	1(3.2%)	0	0
INJECTION SITE REACTION				
ANY AR	0	0	0	8(1.2%)
INJECTION SITE INFLAMMATION	0	0	0	7(1.0%)
INJECTION SITE REACTION	0	0	0	1(0.1%)
ENDOCRINE SYSTEM				
ANY AR	2(4.9%)	1(3.2%)	2(12.5%)	1(0.1%)
ADH INAPPROPRIATE	0	0	1(6.3%)	1(0.1%)
ADRENAL CORTEX INSUFFIENCY	1(2.4%)	0	0	0
DIABETES MELLITUS	0	0	1(6.3%)	0
HYPOTHYROIDISM	1(2.4%)	1(3.2%)	0	0

(1) STUDIES INCLUDED: 98-0-050, FG-21-09, AND 98-0-047. STUDY 98-0-047 ONLY INCLUDES PATIENTS < 16 YEARS OLD WHO RECEIVED 1 MG/KG/DAY AND >= 16 YEARS OLD WHO RECEIVED 50 MG/DAY DOSE OF FK463.
(2) WITHIN A BODY SYSTEM A PERSON MAY EXPERIENCE MORE THAN ONE ADVERSE EVENT.

Corresponds to Table R6 8.1 in the applicant's submission dated October 25, 2004.
FK463 = micafungin

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TABLE 16

INCIDENCE OF TREATMENT EMERGENT ADVERSE EVENTS OF FLUCONAZOLE 400 MG, BY AGE GROUP
FLUCONAZOLE 400 MG TREATED PATIENTS (1)

BODY SYSTEM (2) COSTART TERM	AGE <6 (N=17)	AGE 6-12 (N=22)	AGE 13-17 (N=14)	AGE >=18 (N=404)
ALL SYSTEMS	17(100.0%)	22(100.0%)	14(100.0%)	404(100.0%)
DIGESTIVE SYSTEM				
ANY AE	17(100.0%)	21(95.5%)	14(100.0%)	400(99.0%)
DIARRHEA	13(76.5%)	13(59.1%)	6(42.9%)	327(80.9%)
MUCOSITIS	14(82.4%)	18(81.8%)	13(92.9%)	323(80.0%)
NAUSEA	11(64.7%)	9(40.9%)	6(42.9%)	289(71.5%)
VOMITING	13(76.5%)	12(54.5%)	8(57.1%)	275(68.1%)
ANOREXIA	11(64.7%)	16(72.7%)	7(50.0%)	197(48.8%)
DYSPEPSIA	3(17.6%)	1(4.5%)	2(14.3%)	136(33.7%)
CONSTIPATION	3(17.6%)	6(27.3%)	3(21.4%)	131(32.4%)
RECTAL DISORDER	5(29.4%)	5(22.7%)	3(21.4%)	71(17.6%)
DRY MOUTH/NOSE	1(5.9%)	0	0	42(10.4%)
LIVER FUNCTION TESTS ABNORMAL	0	3(13.6%)	1(7.1%)	38(9.4%)
JAUNDICE	1(5.9%)	1(4.5%)	0	31(7.7%)
DYSPHAGIA	0	0	0	28(6.9%)
STOMATITIS	0	2(9.1%)	0	22(5.4%)
ESOPHAGITIS	0	0	0	21(5.2%)
GASTROINTESTINAL DISORDER	0	1(4.5%)	0	15(3.7%)
REGURGITATION	1(5.9%)	0	1(7.1%)	12(3.0%)
VENOOCCLUSIVE LIVER DISEASE	1(5.9%)	2(9.1%)	0	12(3.0%)
FLATULENCE	0	0	0	11(2.7%)
HEMATEMESIS	0	0	1(7.1%)	10(2.5%)
MOUTH ULCERATION	0	0	0	10(2.5%)
GUM/ORAL HEMORRHAGE	0	1(4.5%)	0	9(2.2%)
MELENA	0	1(4.5%)	0	9(2.2%)
COLITIS	0	0	0	8(2.0%)
ENTERITIS	0	0	0	7(1.7%)
GASTROENTERITIS	0	1(4.5%)	0	7(1.7%)
RECTAL HEMORRHAGE	0	0	0	7(1.7%)
HEPATOMEGALY	1(5.9%)	1(4.5%)	0	6(1.5%)
LEUKOPLAKIA OF MOUTH	1(5.9%)	0	0	6(1.5%)
GASTROINTESTINAL HEMORRHAGE	0	0	0	5(1.2%)
TOOTH DISORDER	2(11.8%)	0	0	5(1.2%)
FECAL INCONTINENCE	0	0	0	4(1.0%)
ILEUS	1(5.9%)	0	0	4(1.0%)
GASTRITIS	0	1(4.5%)	0	3(0.7%)
GLOSSITIS	0	0	0	3(0.7%)
BLOODY DIARRHEA	0	0	0	2(0.5%)
ENTEROCOLITIS	0	0	0	2(0.5%)
GINGIVITIS	0	0	0	2(0.5%)

(1) STUDIES INCLUDED: 98-0-050, EC-21-09, AND 98-0-047. STUDY 98-0-047 ONLY INCLUDES PATIENTS < 16 YEARS OLD WHO RECEIVED 1 MG/KG/DAY AND >= 16 YEARS OLD WHO RECEIVED 50 MG/DAY DOSE OF FK463.
(2) WITHIN A BODY SYSTEM A PERSON MAY EXPERIENCE MORE THAN ONE ADVERSE EVENT.

Corresponds to Table R6 8.3 in the applicant's submission dated October 25, 2004.
FK463 = micafungin

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TABLE 16 (continued)

INCIDENCE OF TREATMENT EMERGENT ADVERSE EVENTS OF FLUCONAZOLE 400 MG, BY AGE GROUP
FLUCONAZOLE 400 MG TREATED PATIENTS (1)

BODY SYSTEM (2) COSTART TERM	AGE <6 (N=17)	6-12 (N=22)	13-17 (N=14)	>=18 (N=404)
HEPATIC FAILURE	0	0	0	2(0.5%)
PAROTID GLAND ENLARGEMENT	0	0	0	2(0.5%)
TONGUE DISORDER	0	0	1(7.1%)	2(0.5%)
TONGUE EDEMA	0	0	0	2(0.5%)
ABNORMAL STOOLS	0	0	0	1(0.2%)
CHOLECYSTITIS	0	0	0	1(0.2%)
CHOLELITHIASIS	0	0	0	1(0.2%)
CHOLESTATIC JAUNDICE	0	0	0	1(0.2%)
DUODENITIS	0	0	0	1(0.2%)
ESOPHAGEAL HEMORRHAGE	0	0	0	1(0.2%)
GUM HYPERPLASIA	0	0	0	1(0.2%)
HEPATITIS, NONSPECIFIC	0	0	0	1(0.2%)
INTESTINAL STENOSIS	0	0	0	1(0.2%)
LIVER DAMAGE	0	0	0	1(0.2%)
PSEUDOMEMBRANOUS COLITIS	0	0	0	1(0.2%)
SIALADENITIS	0	0	0	1(0.2%)
STOMACH ATONY	0	0	0	1(0.2%)
STOMACH ULCER HEMORRHAGE	0	0	0	1(0.2%)
HEPATOSPLENOMEGALY	2(11.8%)	0	0	0
PANCREATITIS	0	0	1(7.1%)	0
ULCERATIVE STOMATITIS	0	1(4.5%)	0	0
METABOLIC AND NUTRITIONAL DISORDERS				
ANY AE	13(76.5%)	16(72.7%)	13(92.9%)	389(96.3%)
HYPOMAGNESEMIA	6(35.3%)	10(45.5%)	5(35.7%)	247(61.1%)
HYPOKALEMIA	8(47.1%)	7(31.8%)	2(14.3%)	218(54.0%)
PERIPHERAL EDEMA	0	1(4.5%)	0	112(27.7%)
EDEMA	2(11.8%)	2(9.1%)	1(7.1%)	107(26.5%)
HYPERVOLEMIA	4(23.5%)	7(31.8%)	4(28.6%)	85(21.0%)
HYPERGLYCEMIA	2(11.8%)	6(27.3%)	3(21.4%)	82(20.3%)
HYPOCALCEMIA	5(29.4%)	6(27.3%)	2(14.3%)	77(19.1%)
HILIRUBINEMIA	1(5.9%)	2(9.1%)	2(14.3%)	66(16.3%)
HYPOPHOSPHATEMIA	1(5.9%)	3(13.6%)	1(7.1%)	66(16.3%)
HYPONATREMIA	3(17.6%)	3(13.6%)	1(7.1%)	61(15.1%)
SGPT INCREASED	0	1(4.5%)	0	35(8.7%)
CREATININE INCREASED	0	2(9.1%)	0	33(8.2%)
HYPOPROTEINEMIA	1(5.9%)	7(31.8%)	2(14.3%)	33(8.2%)
HYPERKALEMIA	1(5.9%)	1(4.5%)	2(14.3%)	31(7.7%)
SGOT INCREASED	0	0	0	29(7.2%)
ALKALINE PHOSPHATASE INCREASED	0	0	0	15(3.7%)
LACTIC DEHYDROGENASE INCREASED	0	1(4.5%)	0	15(3.7%)

(1) STUDIES INCLUDED: 98-0-050, MC-21-09, AND 98-0-047. STUDY 98-0-047 ONLY INCLUDES PATIENTS < 16 YEARS OLD WHO RECEIVED 1 MG/KG/DAY AND >= 16 YEARS OLD WHO RECEIVED 50 MG/DAY DOSE OF FK463.
(2) WITHIN A BODY SYSTEM A PERSON MAY EXPERIENCE MORE THAN ONE ADVERSE EVENT.

Corresponds to Table R6 8.3 in the applicant's submission dated October 25, 2004.
FK463 = micafungin

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TABLE 16 (continued)

INCIDENCE OF TREATMENT EMERGENT ADVERSE EVENTS OF FLUCONAZOLE 400 MG, BY AGE GROUP
FLUCONAZOLE 400 MG TREATED PATIENTS (1)

BODY SYSTEM (2) / COSTART TERM	AGE <6 (N=17)	AGE 6-12 (N=22)	AGE 13-17 (N=14)	AGE >=18 (N=404)
BUN INCREASED	0	3[13.6%]	1[7.1%]	14[3.5%]
WEIGHT LOSS	0	0	0	13[3.2%]
DEHYDRATION	0	0	1[7.1%]	12[3.0%]
WEIGHT GAIN	0	0	0	12[3.0%]
ACIDOSIS	1[5.9%]	1[4.5%]	0	11[2.7%]
HYPERPHOSPHATEMIA	0	1[4.5%]	0	8[2.0%]
HYPERMAGNESEMIA	0	0	1[7.1%]	7[1.7%]
CREATININE CLEARANCE DECREASED	0	0	0	5[1.2%]
DECREASED BICARBONATE	0	1[4.5%]	0	4[1.0%]
HEALING ABNORMAL	0	0	1[7.1%]	4[1.0%]
HYPERCHLOREMIA	1[5.9%]	1[4.5%]	0	4[1.0%]
HYPOVOLEMIA	0	0	0	4[1.0%]
RESPIRATORY ALKALOSIS	0	0	0	4[1.0%]
HYPERURICEMIA	1[5.9%]	0	0	3[0.7%]
HYPOCHLOREMIA	0	0	1[7.1%]	3[0.7%]
HYPOGLYCEMIA	0	1[4.5%]	2[14.3%]	3[0.7%]
ALKALOSIS	0	0	0	2[0.5%]
AMYLASE INCREASED	0	0	0	2[0.5%]
HYPERLIPEMIA	0	4[18.2%]	0	2[0.5%]
HYPERNATREMIA	0	1[4.5%]	0	2[0.5%]
THIRST	0	0	0	2[0.5%]
AVITAMINOSIS	0	0	0	1[0.2%]
GLYCOSURIA	0	1[4.5%]	0	1[0.2%]
HYPERCALCEMIA	0	0	0	1[0.2%]
HYPOGLYCEMIC REACTION	0	0	0	1[0.2%]
KETOSIS	0	0	0	1[0.2%]
RESPIRATORY ACIDOSIS	0	1[4.5%]	0	1[0.2%]
GAMMA GLUTAMYL TRANSPEPTIDASE INCREASED	0	1[4.5%]	1[7.1%]	0
HYPERAMMONEMIA	0	1[4.5%]	0	0
BODY AS A WHOLE				
ANY AE	17[100.0%]	22[100.0%]	14[100.0%]	388[96.0%]
FEVER	9[52.9%]	9[40.9%]	7[50.0%]	223[55.2%]
ASTHENIA	1[5.9%]	3[13.6%]	3[21.4%]	178[44.1%]
ABDOMINAL PAIN	4[23.5%]	11[50.0%]	4[28.6%]	151[37.4%]
INFECTION	8[47.1%]	9[40.9%]	5[35.7%]	133[32.9%]
PROCEDURAL COMPLICATION	9[52.9%]	13[59.1%]	6[42.9%]	132[32.7%]
SEPSIS	6[35.3%]	7[31.8%]	4[28.6%]	110[27.2%]
CHILLS	1[5.9%]	5[22.7%]	4[28.6%]	109[27.0%]
PAIN	3[17.6%]	5[22.7%]	1[7.1%]	75[18.6%]
BACK PAIN	0	4[18.2%]	1[7.1%]	57[14.1%]

(1) STUDIES INCLUDED: 98-0-050, EC-21-09, AND 98-0-047. STUDY 98-0-047 ONLY INCLUDES PATIENTS < 16 YEARS OLD WHO RECEIVED 1 MG/KG/DAY AND >= 16 YEARS OLD WHO RECEIVED 50 MG/DAY DOSE OF FK463.
(2) WITHIN A BODY SYSTEM A PERSON MAY EXPERIENCE MORE THAN ONE ADVERSE EVENT.

Corresponds to Table R6 8.3 in the applicant's submission dated October 25, 2004.
FK463 = micafungin

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TABLE 16 (continued)

INCIDENCE OF TREATMENT EMERGENT ADVERSE EVENTS OF FLUCONAZOLE 400 MG, BY AGE GROUP
FLUCONAZOLE 400 MG TREATED PATIENTS (1)

BODY SYSTEM (2) COSTART TERM	AGE <6 (N=17)	6-12 (N=22)	13-17 (N=14)	>=18 (N=404)
ABDOMEN ENLARGED	5(29.4%)	1(4.5%)	0	37(9.2%)
ALLERGIC REACTION	4(23.5%)	5(22.7%)	4(28.6%)	35(8.7%)
FACE EDEMA	3(17.6%)	2(9.1%)	0	31(7.7%)
TRANSFUSION REACTION	1(5.9%)	2(9.1%)	2(14.3%)	25(6.2%)
GRAFT VERSUS HOST DISEASE	6(35.3%)	2(9.1%)	2(14.3%)	23(5.7%)
CACHEXIA	1(5.9%)	2(9.1%)	0	20(5.0%)
FLU SYNDROME	2(11.8%)	1(4.5%)	0	13(3.2%)
NECK PAIN	0	1(4.5%)	0	12(3.0%)
MALAISE	0	1(4.5%)	0	9(2.2%)
ACCIDENTAL INJURY	1(5.9%)	0	0	8(2.0%)
CELLULITIS	1(5.9%)	0	0	8(2.0%)
ASCITES	1(5.9%)	0	0	5(1.2%)
DRUG LEVEL INCREASED	0	0	0	5(1.2%)
LAB TEST ABNORMAL	0	1(4.5%)	0	4(1.0%)
ABSCESS	0	0	0	2(0.5%)
CYST	0	0	0	2(0.5%)
IMMUNOGLOBULIN DECREASED	0	0	0	2(0.5%)
MUCOUS MEMBRANE DISORDER	0	0	0	2(0.5%)
NEOPLASM BENIGN	0	0	0	2(0.5%)
PELVIC PAIN	1(5.9%)	0	0	2(0.5%)
HYPOTHERMIA	0	0	0	1(0.2%)
NECK RIGIDITY	0	0	0	1(0.2%)
PRIMARY GRAFT DYSFUNCTION	0	0	0	1(0.2%)
HEMIC AND LYMPHATIC SYSTEM				
ANY AE	16(94.1%)	19(86.4%)	13(92.9%)	374(92.6%)
LEUKOPENIA	13(76.5%)	14(63.6%)	12(85.7%)	307(76.0%)
THROMBOCYTOPENIA	14(82.4%)	16(72.7%)	9(64.3%)	282(69.8%)
ANEMIA	9(52.9%)	9(40.9%)	7(50.0%)	168(41.6%)
PETECHIA	2(11.8%)	0	0	38(9.4%)
ECCHYMOSIS	2(11.8%)	2(9.1%)	0	24(5.9%)
COAGULATION DISORDER	0	0	0	21(5.2%)
PANCYTOPENIA	0	0	1(7.1%)	10(2.5%)
PROTHROMBIN DECREASED	0	0	1(7.1%)	9(2.2%)
LEUKOCYTOSIS	0	0	1(7.1%)	5(1.2%)
LYMPHADENOPATHY	0	0	0	4(1.0%)
SPLENOMEGALY	1(5.9%)	0	0	4(1.0%)
BLEEDING TIME INCREASED	0	0	0	2(0.5%)
THROMBOPLASTIN DECREASED	0	0	0	2(0.5%)
RBC ABNORMAL	0	0	0	2(0.5%)
PURPURA	0	1(4.5%)	0	0

(1) STUDIES INCLUDED: 98-0-050, FC-21-09, AND 98-0-047. STUDY 98-0-047 ONLY INCLUDES PATIENTS < 16 YEARS OLD WHO RECEIVED 3 MG/KG/DAY AND >= 16 YEARS OLD WHO RECEIVED 50 MG/DAY DOSE OF FK463.
(2) WITHIN A BODY SYSTEM A PERSON MAY EXPERIENCE MORE THAN ONE ADVERSE EVENT.

Corresponds to Table R6 8.3 in the applicant's submission dated October 25, 2004.
FK463 = micafungin

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TABLE 16 (continued)

INCIDENCE OF TREATMENT EMERGENT ADVERSE EVENTS OF FLUCONAZOLE 400 MG, BY AGE GROUP
FLUCONAZOLE 400 MG TREATED PATIENTS (1)

BODY SYSTEM (2) COSTART TERM	AGE <6 (N=17)	6-12 (N=22)	13-17 (N=14)	>=18 (N=404)
NERVOUS SYSTEM				
ANY AE	7(41.2%)	14(63.6%)	10(71.4%)	315(78.0%)
HEADACHE	1(5.9%)	8(36.4%)	3(21.4%)	155(38.4%)
INSOMNIA	0	2(9.1%)	2(14.3%)	144(35.6%)
ANXIETY	1(5.9%)	1(4.5%)	1(7.1%)	89(22.0%)
DIZZINESS	0	3(13.6%)	2(14.3%)	78(19.3%)
DEPRESSION	0	0	3(21.4%)	36(8.9%)
CONFUSION	0	0	1(7.1%)	32(7.9%)
SOMNOLENCE	0	0	2(14.3%)	32(7.9%)
TREMOR	1(5.9%)	1(4.5%)	0	30(7.4%)
PARESTHESIA	0	1(4.5%)	0	24(5.9%)
AGITATION	1(5.9%)	0	0	14(3.5%)
NERVOUSNESS	3(17.6%)	0	0	13(3.2%)
HALLUCINATIONS	0	0	0	11(2.7%)
THINKING ABNORMAL	0	0	0	8(2.0%)
ABNORMAL DREAMS	0	0	0	5(1.2%)
ABNORMAL GAIT	0	0	0	5(1.2%)
DYSTONIA	0	0	0	5(1.2%)
CONVULSION	2(11.8%)	1(4.5%)	0	4(1.0%)
EMOTIONAL LABILITY	0	0	0	4(1.0%)
INCREASED SALIVATION	0	0	0	4(1.0%)
NYSTAGMUS	0	0	0	4(1.0%)
DELIRIUM	0	0	0	3(0.7%)
HYPERTONIA	0	0	0	3(0.7%)
VERTIGO	0	1(4.5%)	0	3(0.7%)
WITHDRAWAL SYNDROME	0	0	0	3(0.7%)
GRAND MAL CONVULSION	0	0	0	2(0.5%)
SPEECH DISORDER	0	0	0	2(0.5%)
ADDICTION	0	0	0	1(0.2%)
AKATHISIA	0	0	0	1(0.2%)
APATHY	0	0	0	1(0.2%)
ATAXIA	0	0	0	1(0.2%)
CEREBROVASCULAR ACCIDENT	0	0	0	1(0.2%)
ENCEPHALITIS	0	0	0	1(0.2%)
ENCEPHALOPATHY	0	0	0	1(0.2%)
EXTRAPYRAMIDAL SYNDROME	0	0	0	1(0.2%)
HYPERKINESIA	0	1(4.5%)	0	1(0.2%)
NEURITIS	0	0	0	1(0.2%)
NEUROPATHY	0	0	0	1(0.2%)
STUPOR	0	0	0	1(0.2%)
BRAIN ABSCESS	1(5.9%)	0	0	0

(1) STUDIES INCLUDED: 98-0-050, FC-21-09, AND 98-0-047. STUDY 98-0-047 ONLY INCLUDES PATIENTS < 16 YEARS OLD WHO RECEIVED 1 MG/KG/DAY AND >= 16 YEARS OLD WHO RECEIVED 50 MG/DAY DOSE OF FK463.
(2) WITHIN A BODY SYSTEM A PERSON MAY EXPERIENCE MORE THAN ONE ADVERSE EVENT.

Corresponds to Table R6 8.3 in the applicant's submission dated October 25, 2004.
FK463 = micafungin

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TABLE 16 (continued)

INCIDENCE OF TREATMENT EMERGENT ADVERSE EVENTS OF FLUCONAZOLE 400 MG. BY AGE GROUP
FLUCONAZOLE 400 MG TREATED PATIENTS (1)

BODY SYSTEM (2) COSTART TERM	AGE <6 (N=17)	6-12 (N=22)	13-17 (N=14)	>=18 (N=404)
CEREBRAL HEMORRHAGE	1(5.9%)	0	0	0
MYOCLONUS	0	1(4.5%)	0	0
RESPIRATORY SYSTEM				
ANY AE	14(82.4%)	13(59.1%)	9(64.3%)	314(77.7%)
COUGH INCREASED	4(23.5%)	3(13.6%)	3(21.4%)	109(27.0%)
LUNG DISORDER	1(5.9%)	1(4.5%)	0	89(22.0%)
RHINITIS	1(5.9%)	3(13.6%)	1(7.1%)	82(20.3%)
DYSPNEA	4(23.5%)	2(9.1%)	3(21.4%)	77(19.1%)
EPISTAXIS	2(11.8%)	4(18.2%)	3(21.4%)	76(18.8%)
PHARYNGITIS	1(5.9%)	2(9.1%)	2(14.3%)	64(15.8%)
HICCUP	0	0	0	57(14.1%)
PNEUMONIA	1(5.9%)	0	0	24(5.9%)
ASTHMA	2(11.8%)	0	0	23(5.7%)
HYPOXIA	2(11.8%)	1(4.5%)	1(7.1%)	23(5.7%)
LUNG EDEMA	1(5.9%)	0	0	17(4.2%)
PLEURAL EFFUSION	0	1(4.5%)	0	17(4.2%)
SINUSITIS	0	0	2(14.3%)	14(3.5%)
HYPERVENTILATION	5(29.4%)	4(18.2%)	0	12(3.0%)
HEMOPTYSIS	0	0	1(7.1%)	9(2.2%)
APNEA	0	0	0	7(1.7%)
ATELECTASIS	0	0	0	7(1.7%)
LUNG HEMORRHAGE	1(5.9%)	0	0	5(1.2%)
RESPIRATORY FAILURE	1(5.9%)	0	0	5(1.2%)
RESPIRATORY DISORDER	2(11.8%)	0	0	4(1.0%)
VOICE ALTERATION	0	0	0	3(0.7%)
ENDMYSEMA	0	0	0	2(0.5%)
HYPOVENTILATION	0	0	0	2(0.5%)
RESPIRATORY DISTRESS SYNDROME	0	0	0	2(0.5%)
LARYNGITIS	0	0	0	1(0.2%)
PLEURAL DISORDER	0	0	0	1(0.2%)
SPUTUM INCREASED	0	0	0	1(0.2%)
STRIDOR	0	0	0	1(0.2%)
CARDIOVASCULAR SYSTEM				
ANY AE	13(76.5%)	19(86.4%)	10(71.4%)	285(70.5%)
TACHYCARDIA	6(35.3%)	3(13.6%)	4(28.6%)	99(24.5%)
HYPERTENSION	8(47.1%)	15(68.2%)	5(35.7%)	89(22.0%)
HYPOTENSION	4(23.5%)	5(22.7%)	3(21.4%)	78(19.3%)
VASODILATATION	2(11.8%)	0	0	71(17.6%)
CHEST PAIN	0	1(4.5%)	1(7.1%)	61(15.1%)

(1) STUDIES INCLUDED: 98-0-050, EC-21-99, AND 98-0-047. STUDY 98-0-047 ONLY INCLUDES PATIENTS < 16 YEARS OLD WHO RECEIVED 1 MG/KG/DAY AND >= 16 YEARS OLD WHO RECEIVED 50 MG/DAY DOSE OF FK463.
(2) WITHIN A BODY SYSTEM A PERSON MAY EXPERIENCE MORE THAN ONE ADVERSE EVENT.

Corresponds to Table R6 8.3 in the applicant's submission dated October 25, 2004.
FK463 = micafungin

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TABLE 16 (continued)

INCIDENCE OF TREATMENT EMERGENT ADVERSE EVENTS OF FLUCONAZOLE 400 MG, BY AGE GROUP
FLUCONAZOLE 400 MG TREATED PATIENTS (1)

BODY SYSTEM (2) COSTART TERM	AGE <6 (N=17)	6-12 (N=22)	13-17 (N=14)	>=18 (N=404)
POSTURAL HYPOTENSION	0	0	2(14.3%)	16(4.0%)
ATRIAL FIBRILLATION	0	0	0	12(3.0%)
BRADYCARDIA	3(17.6%)	2(9.1%)	1(7.1%)	12(3.0%)
SYNCOPE	0	0	0	10(2.5%)
VALVULAR HEART DISEASE	1(5.9%)	0	0	10(2.5%)
CONGESTIVE HEART FAILURE	0	0	0	9(2.2%)
HEMORRHAGE	0	0	0	9(2.2%)
ARRHYTHMIA	2(11.8%)	0	0	8(2.0%)
CARDIOMEGALY	1(5.9%)	0	0	7(1.7%)
SINUS BRADYCARDIA	0	0	0	7(1.7%)
PERICARDIAL EFFUSION	0	0	0	4(1.0%)
THROMBOPHLEBITIS	1(5.9%)	0	0	4(1.0%)
CARDIOVASCULAR DISORDER	1(5.9%)	0	0	3(0.7%)
DEEP THROMBOPHLEBITIS	0	0	0	3(0.7%)
HEART ARREST	1(5.9%)	0	0	3(0.7%)
MIGRAINE	0	0	0	3(0.7%)
PALLOR	0	0	0	3(0.7%)
PALPITATION	0	0	0	3(0.7%)
ATRIAL FLUTTER	0	0	0	2(0.5%)
EXTRASYSTOLES	0	0	0	2(0.5%)
PHLEBITIS	0	0	0	2(0.5%)
SHOCK	2(11.8%)	0	0	2(0.5%)
SUBDURAL HEMATOMA	0	0	0	2(0.5%)
THROMBOSIS	0	0	0	2(0.5%)
CARDIOMYOPATHY	0	0	0	1(0.2%)
ELECTROCARDIOGRAM ABNORMAL	0	0	0	1(0.2%)
EMBOLUS	0	0	0	1(0.2%)
ENDOCARDITIS	0	0	0	1(0.2%)
MYOCARDIAL INFARCT	0	0	0	1(0.2%)
MYOCARDIAL ISCHEMIA	0	0	0	1(0.2%)
PERICARDITIS	0	0	0	1(0.2%)
PERIPHERAL VASCULAR DISORDER	0	0	1(7.1%)	1(0.2%)
T INVERTED	0	0	0	1(0.2%)
VARICOSE VEIN	0	0	0	1(0.2%)
VASCULAR ANOMALY	0	0	0	1(0.2%)
VENTRICULAR EXTRASYSTOLES	0	0	1(7.1%)	1(0.2%)
SKIN AND APPENDAGES				
ANY AE	15(88.2%)	15(68.2%)	10(71.4%)	268(66.3%)
RASH	10(58.8%)	9(40.9%)	4(28.6%)	164(40.6%)
PRURITUS	5(29.4%)	8(36.4%)	2(14.3%)	78(19.3%)

(1) STUDIES INCLUDED: 98-0-050, PG-21-09, AND 98-0-047. STUDY 98-0-047 ONLY INCLUDES PATIENTS < 16 YEARS OLD WHO RECEIVED 1 MG/KG/DAY AND >= 16 YEARS OLD WHO RECEIVED 50 MG/DAY DOSE OF FK463.
(2) WITHIN A BODY SYSTEM A PERSON MAY EXPERIENCE MORE THAN ONE ADVERSE EVENT.

Corresponds to Table R6 8.3 in the applicant's submission dated October 25, 2004.
FK463 = micafungin

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TABLE 16 (continued)

INCIDENCE OF TREATMENT EMERGENT ADVERSE EVENTS OF FLUCONAZOLE 400 MG, BY AGE GROUP
FLUCONAZOLE 400 MG TREATED PATIENTS (1)

BODY SYSTEM (2) COSTART TERM	AGE <6 (N=17)	6-12 (N=22)	13-17 (N=14)	>=18 (N=404)
DRY SKIN	0	2 (9.1%)	3 (21.4%)	27 (6.7%)
SWEATING	2 (11.8%)	0	0	24 (5.9%)
SKIN DISORDER	0	4 (18.2%)	2 (14.3%)	23 (5.7%)
ALOPECIA	5 (29.4%)	5 (22.7%)	1 (7.1%)	18 (4.5%)
MACULOPAPULAR RASH	0	0	0	14 (3.5%)
FOLLICULITIS	0	0	0	12 (3.0%)
HERPES SIMPLEX	0	1 (4.5%)	0	11 (2.7%)
VESICULOBULLOUS RASH	0	0	0	10 (2.5%)
PETECHIAL RASH	0	0	0	9 (2.2%)
URTICARIA	2 (11.8%)	2 (9.1%)	0	8 (2.0%)
SKIN DISCOLORATION	1 (5.9%)	1 (4.5%)	2 (14.3%)	7 (1.7%)
SKIN ULCER	0	0	0	6 (1.5%)
EXFOLIATIVE DERMATITIS	0	0	1 (7.1%)	4 (1.0%)
HERPES ZOSTER	0	0	0	4 (1.0%)
ACNE	0	0	1 (7.1%)	2 (0.5%)
ANGIOEDEMA	0	0	0	2 (0.5%)
CONTACT DERMATITIS	0	0	0	2 (0.5%)
HAIR DISORDER	0	0	0	1 (0.2%)
NAIL DISORDER	0	0	0	1 (0.2%)
PSORIASIS	0	0	0	1 (0.2%)
SKIN NODULE	0	1 (4.5%)	0	0
UROGENITAL SYSTEM				
ANY AE	7 (41.2%)	14 (63.6%)	6 (42.9%)	195 (48.3%)
HEMATURIA	1 (5.9%)	5 (22.7%)	1 (7.1%)	64 (15.8%)
DYSURIA	1 (5.9%)	4 (18.2%)	2 (14.3%)	36 (8.9%)
OLIGURIA	3 (17.6%)	4 (18.2%)	2 (14.3%)	23 (5.7%)
URINARY FREQUENCY	0	0	0	19 (4.7%)
URINARY TRACT INFECTION	0	1 (4.5%)	1 (7.1%)	19 (4.7%)
VAGINAL HEMORRHAGE	0	0	0	19 (4.7%)
KIDNEY FUNCTION ABNORMAL	1 (5.9%)	0	0	18 (4.5%)
ALBUMINURIA	0	0	0	16 (4.0%)
CYSTITIS	1 (5.9%)	1 (4.5%)	0	14 (3.5%)
URINARY INCONTINENCE	0	0	0	13 (3.2%)
KIDNEY FAILURE	0	1 (4.5%)	0	12 (3.0%)
URINARY RETENTION	0	0	0	9 (2.2%)
VAGINITIS	0	0	1 (7.1%)	9 (2.2%)
URINE ABNORMALITY	0	1 (4.5%)	0	8 (2.0%)
ACUTE KIDNEY FAILURE	0	0	0	7 (1.7%)
PENIS DISORDER	0	2 (9.1%)	0	7 (1.7%)
URINARY URGENCY	0	0	0	7 (1.7%)

(1) STUDIES INCLUDED: 98-0-050, EC-21-89, AND 98-0-047. STUDY 98-0-047 ONLY INCLUDES PATIENTS < 16 YEARS OLD WHO RECEIVED 1 MG/KG/DAY AND >= 16 YEARS OLD WHO RECEIVED 50 MG/DAY DOSE OF FK463.
(2) WITHIN A BODY SYSTEM A PERSON MAY EXPERIENCE MORE THAN ONE ADVERSE EVENT.

Corresponds to Table R6 8.3 in the applicant's submission dated October 25, 2004.
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TABLE 16 (continued)

INCIDENCE OF TREATMENT EMERGENT ADVERSE EVENTS OF FLUCONAZOLE 400 MG, BY AGE GROUP
FLUCONAZOLE 400 MG TREATED PATIENTS (1)

BODY SYSTEM (2) COSTART TERM	AGE <6 (N=17)	6-12 (N=22)	13-17 (N=14)	>=18 (N=404)
URINATION IMPAIRED	0	0	0	7(1.7%)
HEMORRHAGIC CYSTITIS	0	2(9.1%)	0	6(1.5%)
SCROTAL EDEMA	0	0	0	6(1.5%)
TESTIS DISORDER	0	0	0	4(1.0%)
POLYURIA	0	0	0	3(0.7%)
LEUKORRHEA	0	0	0	2(0.5%)
NOCTURIA	0	0	0	2(0.5%)
URETHRAL PAIN	0	0	0	2(0.5%)
VULVOVAGINITIS	0	0	0	2(0.5%)
ANURIA	0	0	0	1(0.2%)
DYSMENORRHEA	0	0	0	1(0.2%)
KIDNEY PAIN	0	0	0	1(0.2%)
KIDNEY TUBULAR DISORDER	0	0	0	1(0.2%)
METRORRHAGIA	0	0	1(7.1%)	1(0.2%)
POLYCYSTIC KIDNEY	0	0	0	1(0.2%)
SPECIAL SENSES				
ANY AE	1(5.9%)	8(36.4%)	1(7.1%)	105(26.0%)
ABNORMAL VISION	0	0	0	29(7.2%)
DRY EYES	0	0	0	19(4.7%)
EAR PAIN	0	3(13.6%)	0	14(3.5%)
EYE HEMORRHAGE	0	2(9.1%)	0	14(3.5%)
TASTE PERVERSION	0	0	0	11(2.7%)
CONJUNCTIVITIS	0	2(9.1%)	0	10(2.5%)
EYE PAIN	0	2(9.1%)	0	7(1.7%)
EAR DISORDER	0	0	0	5(1.2%)
DIPLOPIA	0	0	0	4(1.0%)
ANISOCORIA	0	0	0	3(0.7%)
CONJUNCTIVAL EDEMA	0	0	0	2(0.5%)
EYE DISORDER	0	0	0	2(0.5%)
PHOTOPHOBIA	0	0	0	2(0.5%)
EXTRAOCULAR PALSY	0	0	0	1(0.2%)
IMPAIRED HEARING	0	1(4.5%)	0	1(0.2%)
OTITIS MEDIA	1(5.9%)	0	0	1(0.2%)
TINNITUS	0	0	0	1(0.2%)
TASTE LOSS	0	0	1(7.1%)	0
MUSCULOSKELETAL SYSTEM				
ANY AE	2(11.8%)	7(31.8%)	3(21.4%)	102(25.2%)
ARTHRALGIA	1(5.9%)	2(9.1%)	2(14.3%)	52(12.9%)
BONE PAIN	0	2(9.1%)	2(14.3%)	28(6.9%)

(1) STUDIES INCLUDED: 98-0-050, FC-21-09, AND 98-0-047. STUDY 98-0-047 ONLY INCLUDES PATIENTS < 16 YEARS OLD WHO RECEIVED 1 MG/KG/DAY AND >= 16 YEARS OLD WHO RECEIVED 50 MG/DAY DOSE OF FK463.
(2) WITHIN A BODY SYSTEM A PERSON MAY EXPERIENCE MORE THAN ONE ADVERSE EVENT.

Corresponds to Table R6 8.3 in the applicant's submission dated October 25, 2004.
FK463 = micafungin

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TABLE 16 (continued)

INCIDENCE OF TREATMENT EMERGENT ADVERSE EVENTS OF FLUCONAZOLE 400 MG, BY AGE GROUP
FLUCONAZOLE 400 MG TREATED PATIENTS (1)

BODY SYSTEM (2) COSTART TERM	AGE <6 (N=17)	AGE 6-12 (N=22)	AGE 13-17 (N=14)	AGE >=18 (N=404)
MYALGIA	0	3(13.6%)	0	20(5.0%)
CRAMPS	0	0	1(7.1%)	12(3.0%)
MYASTHENIA	0	0	0	9(2.2%)
ARTHROSIS	0	0	1(7.1%)	2(0.5%)
TWITCHING	0	0	0	2(0.5%)
BONE DISORDER	0	0	0	1(0.2%)
JOINT DISORDER	0	0	0	1(0.2%)
GENERALIZED SPASM	1(5.9%)	0	0	0
ENDOCRINE SYSTEM				
ANY AE	0	0	0	3(0.7%)
ADH INAPPROPRIATE	0	0	0	1(0.2%)
ADRENAL CORTEX INSUFFIENCY	0	0	0	1(0.2%)
PARATHYROID DISORDER	0	0	0	1(0.2%)

(1) STUDIES INCLUDED: 98-0-050, FG-21-09, AND 98-0-047. STUDY 98-0-047 ONLY INCLUDES PATIENTS < 16 YEARS OLD WHO RECEIVED 1 MG/KG/DAY AND >= 16 YEARS OLD WHO RECEIVED 50 MG/DAY DOSE OF FK463.
(2) WITHIN A BODY SYSTEM A PERSON MAY EXPERIENCE MORE THAN ONE ADVERSE EVENT.

Corresponds to Table R6 8.3 in the applicant's submission dated October 25, 2004.
FK463 = micafungin

TABLE 17

INCIDENCE OF TREATMENT EMERGENT ADVERSE EVENTS OF 50 MG FK463 AND FLUCONAZOLE, BY GENDER
ALL TREATED PATIENTS (1)

BODY SYSTEM (2) COSTART TERM	FK463 MALE (N=447)	FK463 FEMALE (N=323)	FLUCONAZOLE 200 MG MALE (N=28)	FLUCONAZOLE 200 MG FEMALE (N=32)	FLUCONAZOLE 400 MG MALE (N=274)	FLUCONAZOLE 400 MG FEMALE (N=183)
ALL SYSTEMS	437(97.8%)	310(96.0%)	27(96.4%)	29(90.6%)	274(100.0%)	183(100.0%)
DIGESTIVE SYSTEM						
ANY AE	357(79.9%)	257(79.6%)	15(53.6%)	17(53.1%)	269(98.2%)	183(100.0%)
MUCOSITIS	199(44.5%)	139(43.0%)	0	0	213(77.7%)	155(84.7%)
DIARRHEA	212(47.4%)	146(45.2%)	3(10.7%)	2(6.3%)	219(79.9%)	140(76.5%)
NAUSEA	209(46.8%)	145(44.9%)	4(14.3%)	7(21.9%)	194(70.8%)	121(66.1%)
VOMITING	195(43.6%)	155(48.0%)	5(17.9%)	4(12.5%)	191(69.7%)	117(63.9%)
ANOREXIA	139(31.1%)	100(31.0%)	1(3.6%)	0	139(50.7%)	92(50.3%)
CONSTIPATION	98(21.9%)	63(19.5%)	1(3.6%)	3(9.4%)	86(31.4%)	57(31.1%)
DYSPEPSIA	78(17.4%)	50(15.5%)	1(3.6%)	0	87(31.8%)	55(30.1%)
RECTAL DISORDER	47(10.5%)	38(11.8%)	1(3.6%)	0	43(15.7%)	41(22.4%)
LIVER FUNCTION TESTS ABNORMAL	19(4.3%)	16(5.0%)	2(7.1%)	2(6.3%)	23(8.4%)	19(10.4%)
DRY MOUTH/NOSE	31(6.9%)	23(7.1%)	0	0	30(10.9%)	13(7.1%)
DYSPHAGIA	17(3.8%)	13(4.0%)	1(3.6%)	0	16(5.8%)	12(6.6%)
JAUNDICE	14(3.1%)	11(3.4%)	0	0	21(7.7%)	12(6.6%)
GASTROINTESTINAL DISORDER	13(2.9%)	13(4.0%)	0	0	6(2.2%)	10(5.5%)
VENOOCCLUSIVE LIVER DISEASE	10(2.2%)	5(1.5%)	0	0	6(2.2%)	9(4.9%)
STOMATITIS	16(3.6%)	15(4.6%)	0	0	16(5.8%)	8(4.4%)
GUM/ORAL HEMORRHAGE	4(0.9%)	6(1.9%)	0	0	3(1.1%)	7(3.8%)
ESOPHAGITIS	9(2.0%)	7(2.2%)	1(3.6%)	1(3.1%)	15(5.5%)	6(3.3%)
ERUCTATION	6(1.3%)	9(2.8%)	0	0	9(3.3%)	5(2.7%)
MOUTH ULCERATION	4(0.9%)	3(0.9%)	0	0	5(1.8%)	5(2.7%)
FLATULENCE	12(2.7%)	7(2.2%)	0	1(3.1%)	7(2.6%)	4(2.2%)
GASTRITIS	10(2.2%)	6(1.9%)	0	0	0	4(2.2%)
GASTROENTERITIS	13(2.9%)	7(2.2%)	0	0	4(1.5%)	4(2.2%)
MELENA	16(3.6%)	13(4.0%)	0	0	6(2.2%)	4(2.2%)
HEPATOMEGALY	4(0.9%)	5(1.5%)	1(3.6%)	1(3.1%)	5(1.8%)	3(1.6%)
TONGUE DISORDER	1(0.2%)	1(0.3%)	0	0	0	3(1.6%)
COLITIS	12(2.7%)	9(2.8%)	0	0	6(2.2%)	2(1.1%)
ENTERITIS	4(0.9%)	2(0.6%)	0	0	5(1.8%)	2(1.1%)
ENTEROCOLITIS	3(0.7%)	1(0.3%)	0	0	0	2(1.1%)
FECAL INCONTINENCE	4(0.9%)	7(2.2%)	0	0	2(0.7%)	2(1.1%)
GASTROINTESTINAL HEMORRHAGE	12(2.7%)	5(1.5%)	0	0	3(1.1%)	2(1.1%)
HEMATEMESIS	10(2.2%)	9(2.8%)	0	0	9(3.3%)	2(1.1%)
HEPATIC FAILURE	0	0	0	0	0	2(1.1%)
LEUKOPLAKIA OF MOUTH	5(1.1%)	2(0.6%)	0	0	5(1.8%)	2(1.1%)
RECTAL HEMORRHAGE	5(1.1%)	8(2.5%)	0	0	5(1.8%)	2(1.1%)
TOOTH DISORDER	6(1.3%)	7(2.2%)	0	0	5(1.8%)	2(1.1%)
CHOLESTATIC JAUNDICE	1(0.2%)	0	0	0	0	1(0.5%)
GINGIVITIS	4(0.9%)	3(0.9%)	0	0	1(0.4%)	1(0.5%)

(1) STUDIES INCLUDED: 98-0-050, FC-21-09, AND 98-0-047. STUDY 98-0-047 ONLY INCLUDES PATIENTS < 16 YEARS OLD WHO RECEIVED 1 MG/KG/DAY AND >= 16 YEARS OLD WHO RECEIVED 50 MG/DAY DOSE OF FK463.
(2) WITHIN A BODY SYSTEM A PERSON MAY EXPERIENCE MORE THAN ONE ADVERSE EVENT.

Corresponds to Table R6 9 in the applicant's submission dated October 25, 2004.
FK463 = micafungin

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TABLE 17 (continued)

INCIDENCE OF TREATMENT EMERGENT ADVERSE EVENTS OF 50 MG FK463 AND FLUCONAZOLE, BY GENDER
ALL TREATED PATIENTS [1]

BODY SYSTEM [2] / COSTART TERM	FK463 MALE (N=447)	FK463 FEMALE (N=323)	FLUCONAZOLE 200 MG MALE (N=28)	FLUCONAZOLE 200 MG FEMALE (N=32)	FLUCONAZOLE 400 MG MALE (N=274)	FLUCONAZOLE 400 MG FEMALE (N=183)
CLOSSITIS	3(0.7%)	0	0	0	2(0.7%)	1(0.5%)
ILEUS	8(1.8%)	13(4.0%)	0	0	4(1.5%)	1(0.5%)
INTESTINAL STENOSIS	0	0	0	0	0	1(0.5%)
LIVER DAMAGE	0	2(0.6%)	0	0	0	1(0.5%)
PANCREATITIS	1(0.2%)	0	0	0	0	1(0.5%)
PSEUDOMEMBRANOUS COLITIS	0	0	0	0	0	1(0.5%)
TONGUE EDEMA	1(0.2%)	0	0	0	1(0.4%)	1(0.5%)
ULCERATIVE STOMATITIS	0	0	1(3.6%)	2(6.3%)	0	1(0.5%)
ABNORMAL STOOLS	0	1(0.3%)	0	0	1(0.4%)	0
ACHLORHYDRIA	0	0	1(3.6%)	0	0	0
APHTHOUS STOMATITIS	2(0.4%)	0	1(3.6%)	1(3.1%)	0	0
BLOODY DIARRHEA	0	0	0	0	2(0.7%)	0
CHOLECYSTITIS	0	0	0	0	1(0.4%)	0
CHOLELITHIASIS	3(0.7%)	2(0.6%)	0	0	1(0.4%)	0
DUODENAL ULCER	1(0.2%)	0	0	0	0	0
DUODENITIS	1(0.2%)	0	0	0	1(0.4%)	0
ESOPHAGEAL HEMORRHAGE	0	0	0	0	1(0.4%)	0
ESOPHAGEAL ULCER	1(0.2%)	3(0.9%)	1(3.6%)	1(3.1%)	0	0
FECAL IMPACTION	1(0.2%)	0	0	0	0	0
GASTROINTESTINAL ANOMALY	0	0	0	1(3.1%)	0	0
GASTROINTESTINAL CARCINOMA	0	1(0.3%)	0	0	0	0
GUM HYPERPLASIA	0	0	0	0	1(0.4%)	0
HEPATITIS, NONSPECIFIC	0	2(0.6%)	0	0	1(0.4%)	0
HEPATOSPLENOMEGALY	1(0.2%)	2(0.6%)	0	0	2(0.7%)	0
INTESTINAL OBSTRUCTION	1(0.2%)	0	0	0	0	0
PANCREAS DISORDER	0	2(0.6%)	0	0	0	0
PAROTID GLAND ENLARGEMENT	1(0.2%)	1(0.3%)	0	0	2(0.7%)	0
PEPTIC ULCER	1(0.2%)	0	0	0	0	0
SIALADENITIS	3(0.7%)	1(0.3%)	0	0	1(0.4%)	0
STOMACH ATONY	2(0.4%)	1(0.3%)	0	0	1(0.4%)	0
STOMACH ULCER	1(0.2%)	1(0.3%)	0	1(3.1%)	0	0
STOMACH ULCER HEMORRHAGE	0	0	0	0	1(0.4%)	0
TOOTH CARIES	0	1(0.3%)	0	0	0	0
BODY AS A WHOLE						
ANY AR	367(82.1%)	260(80.5%)	16(57.1%)	17(53.1%)	265(96.7%)	176(96.2%)
FEVER	171(38.3%)	125(38.7%)	10(35.7%)	5(15.6%)	145(52.9%)	103(56.3%)
ABDOMINAL PAIN	120(26.8%)	98(30.3%)	2(7.1%)	3(9.4%)	97(35.4%)	73(39.9%)
ASTHENIA	106(23.7%)	77(23.8%)	1(3.6%)	0	116(42.3%)	69(37.7%)
PROCEDURAL COMPLICATION	97(21.7%)	63(19.5%)	0	0	94(34.3%)	66(36.1%)
INFECTION	119(26.6%)	67(20.7%)	1(3.6%)	4(12.5%)	97(35.4%)	58(31.7%)

(1) STUDIES INCLUDED: 98-0-050, PC-21-09, AND 98-0-047. STUDY 98-0-047 ONLY INCLUDES PATIENTS < 16 YEARS OLD WHO RECEIVED 1 MG/KG/DAY AND >= 16 YEARS OLD WHO RECEIVED 50 MG/DAY DOSE OF FK463.
(2) WITHIN A BODY SYSTEM A PERSON MAY EXPERIENCE MORE THAN ONE ADVERSE EVENT.

Corresponds to Table R6 9 in the applicant's submission dated October 25, 2004.
FK463 = micafungin

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TABLE 17 (continued)

INCIDENCE OF TREATMENT EMERGENT ADVERSE EVENTS OF 50 MG FK463 AND FLUCONAZOLE, BY GENDER
ALL TREATED PATIENTS (1)

BODY SYSTEM (2) COSTART TERM	FK463 MALE (N=447)	FK463 FEMALE (N=323)	FLUCONAZOLE 200 MG MALE (N=28)	FLUCONAZOLE 200 MG FEMALE (N=32)	FLUCONAZOLE 400 MG MALE (N=274)	FLUCONAZOLE 400 MG FEMALE (N=183)
SEPSIS	78(17.4%)	59(18.3%)	0	0	80(29.2%)	47(25.7%)
CHILLS	80(17.9%)	42(13.0%)	0	0	80(29.2%)	39(21.3%)
PAIN	74(16.6%)	43(13.3%)	1(3.6%)	2(6.3%)	48(17.5%)	36(19.7%)
BACK PAIN	43(9.6%)	37(11.5%)	1(3.6%)	2(6.3%)	31(11.3%)	31(16.9%)
ALLERGIC REACTION	39(8.7%)	22(6.8%)	1(3.6%)	0	27(9.9%)	21(11.5%)
ABDOMEN ENLARGED	23(5.1%)	28(8.7%)	0	0	25(9.1%)	18(9.8%)
FACE EDEMA	21(4.7%)	19(5.9%)	0	0	19(6.9%)	17(9.3%)
TRANSFUSION REACTION	35(7.8%)	10(3.1%)	0	0	17(6.2%)	13(7.1%)
CACHEXIA	11(2.5%)	11(3.4%)	1(3.6%)	0	13(4.7%)	10(5.5%)
FLU SYNDROME	11(2.5%)	6(1.9%)	1(3.6%)	0	9(3.3%)	7(3.8%)
GRAFT VERSUS HOST DISEASE	23(5.1%)	19(5.9%)	0	0	27(9.9%)	6(3.3%)
MALAISE	10(2.2%)	5(1.5%)	0	1(3.1%)	4(1.5%)	6(3.3%)
NECK PAIN	9(2.0%)	5(1.5%)	1(3.6%)	2(6.3%)	7(2.6%)	6(3.3%)
CELLULITIS	5(1.1%)	3(0.9%)	0	0	5(1.8%)	4(2.2%)
ACCIDENTAL INJURY	10(2.2%)	3(0.9%)	1(3.6%)	0	6(2.2%)	3(1.6%)
LAB TEST ABNORMAL	4(0.9%)	6(1.9%)	0	0	3(1.1%)	2(1.1%)
MUCOUS MEMBRANE DISORDER	0	2(0.6%)	0	0	0	2(1.1%)
DRUG LEVEL INCREASED	3(0.7%)	0	0	0	4(1.5%)	1(0.5%)
NEOPLASM BENIGN	1(0.2%)	1(0.3%)	0	0	1(0.4%)	1(0.5%)
PELVIC PAIN	3(0.7%)	3(0.9%)	0	0	2(0.7%)	1(0.5%)
PRIMARY GRAFT DYSFUNCTION	1(0.2%)	0	0	0	0	1(0.5%)
ABSCESS	3(0.7%)	3(0.9%)	0	0	2(0.7%)	0
ANAPHYLACTOID REACTION	1(0.2%)	1(0.3%)	0	0	0	0
ASCITES	5(1.1%)	6(1.9%)	0	0	6(2.2%)	0
CARCINOMA	0	1(0.3%)	0	0	0	0
CYST	0	0	0	0	2(0.7%)	0
HERNIA	2(0.4%)	0	0	0	0	0
HYDROCEPHALUS	0	0	1(3.6%)	0	0	0
HYPOTHERMIA	0	1(0.3%)	1(3.6%)	0	1(0.4%)	0
IMMUNOGLOBULINS DECREASED	0	0	0	0	2(0.7%)	0
NECK RIGIDITY	1(0.2%)	1(0.3%)	1(3.6%)	0	1(0.4%)	0
NECROSIS	0	1(0.3%)	0	0	0	0
OVERDOSE	1(0.2%)	0	0	0	0	0
PERITONITIS	3(0.7%)	2(0.6%)	0	0	0	0
SARCOMA	2(0.4%)	0	0	0	0	0
SURGICAL TREATMENT	0	1(0.3%)	0	0	0	0
TUBERCULOSIS AGGRAVATED	3(0.7%)	5(1.5%)	2(7.1%)	2(6.3%)	0	0
TUBERCULOSIS REACTIVATED	2(0.4%)	1(0.3%)	0	0	0	0
METABOLIC AND NUTRITIONAL DISORDERS						
ANY AR	337(75.4%)	234(72.4%)	11(39.3%)	6(18.8%)	256(93.4%)	175(95.6%)

(1) STUDIES INCLUDED: 98-0-050, PC-21-09, AND 98-0-047. STUDY 98-0-047 ONLY INCLUDES PATIENTS < 16 YEARS OLD WHO RECEIVED 1 MG/KG/DAY AND >= 16 YEARS OLD WHO RECEIVED 50 MG/DAY DOSE OF FK463.
(2) WITHIN A BODY SYSTEM A PERSON MAY EXPERIENCE MORE THAN ONE ADVERSE EVENT.

Corresponds to Table R6 9 in the applicant's submission dated October 25, 2004.
FK463 = micafungin

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TABLE 17 (continued)

INCIDENCE OF TREATMENT EMERGENT ADVERSE EVENTS OF 50 MG FK463 AND FLUCONAZOLE, BY GENDER
ALL TREATED PATIENTS (1)

BODY SYSTEM (2) COSTART TERM	FK463 MALE (N=447)	FK463 FEMALE (N=323)	FLUCONAZOLE 200 MG MALE (N=28)	FLUCONAZOLE 200 MG FEMALE (N=32)	FLUCONAZOLE 400 MG MALE (N=274)	FLUCONAZOLE 400 MG FEMALE (N=183)
HYPOKALEMIA	153(34.2%)	105(32.5%)	1(3.6%)	1(3.1%)	129(47.1%)	106(57.9%)
HYPOMAGNESEMIA	166(37.1%)	100(31.0%)	0	0	164(59.9%)	104(56.8%)
PERIPHERAL EDEMA	65(14.5%)	54(16.7%)	0	0	63(23.0%)	50(27.3%)
EDEMA	68(15.2%)	60(18.6%)	0	0	65(23.7%)	47(25.7%)
HYPOCALCEMIA	64(14.3%)	38(11.8%)	2(7.1%)	0	47(17.2%)	43(23.5%)
HYPOPHOSPHATEMIA	52(11.6%)	32(9.9%)	0	0	32(11.7%)	39(21.3%)
HYPERGLYCEMIA	50(11.2%)	30(9.3%)	1(3.6%)	0	58(21.2%)	35(19.1%)
HYPERVOLEMIA	48(10.7%)	35(10.8%)	0	0	65(23.7%)	35(19.1%)
HYPONATREMIA	31(6.9%)	35(10.8%)	2(7.1%)	1(3.1%)	35(12.8%)	33(18.0%)
BILIRUBINEMIA	43(9.6%)	31(9.6%)	0	0	50(18.2%)	21(11.5%)
HYPOPROTEINEMIA	30(6.7%)	20(6.2%)	3(10.7%)	0	22(8.0%)	21(11.5%)
HYPERKALEMIA	24(5.4%)	8(2.5%)	2(7.1%)	1(3.1%)	22(8.0%)	13(7.1%)
SGPT INCREASED	23(5.1%)	26(8.0%)	0	0	25(9.1%)	11(6.0%)
ACIDOSIS	14(3.1%)	13(4.0%)	0	0	3(1.1%)	10(5.5%)
SGOT INCREASED	24(5.4%)	26(8.0%)	1(3.6%)	0	19(6.9%)	10(5.5%)
LACTIC DEHYDROGENASE INCREASED	6(1.3%)	10(3.1%)	1(3.6%)	1(3.1%)	9(3.3%)	7(3.8%)
ALKALINE PHOSPHATASE INCREASED	14(3.1%)	20(6.2%)	2(7.1%)	1(3.1%)	9(3.3%)	6(3.3%)
BUN INCREASED	9(2.0%)	14(4.3%)	0	0	12(4.4%)	6(3.3%)
CREATININE INCREASED	33(7.4%)	8(2.5%)	0	0	29(10.6%)	6(3.3%)
HYPERMAGNESEMIA	3(0.7%)	4(1.2%)	0	0	2(0.7%)	6(3.3%)
WEIGHT GAIN	12(2.7%)	3(0.9%)	0	0	7(2.6%)	5(2.7%)
DECREASED BICARBONATE	3(0.7%)	2(0.6%)	0	0	1(0.4%)	4(2.2%)
DEHYDRATION	15(3.4%)	5(1.5%)	1(3.6%)	1(3.1%)	9(3.3%)	4(2.2%)
HYPERPHOSPHATEMIA	5(1.1%)	6(1.9%)	0	0	5(1.8%)	4(2.2%)
CREATININE CLEARANCE DECREASED	1(0.2%)	0	0	0	2(0.7%)	3(1.6%)
HEALING ABNORMAL	3(0.7%)	2(0.6%)	0	0	2(0.7%)	3(1.6%)
HYPERCHLOREMIA	6(1.3%)	6(1.9%)	0	0	3(1.1%)	3(1.6%)
HYPERURICEMIA	1(0.2%)	0	0	0	1(0.4%)	3(1.6%)
HYPOCHLOREMIA	4(0.9%)	5(1.5%)	0	0	1(0.4%)	3(1.6%)
HYPOGLYCEMIA	12(2.7%)	9(2.8%)	0	1(3.1%)	3(1.1%)	3(1.6%)
WEIGHT LOSS	11(2.5%)	5(1.5%)	0	0	10(3.6%)	3(1.6%)
HYPERLIPEMIA	0	2(0.6%)	0	0	4(1.5%)	2(1.1%)
HYPERNATREMIA	8(1.8%)	7(2.2%)	1(3.6%)	0	1(0.4%)	2(1.1%)
RESPIRATORY ALKALOSIS	6(1.3%)	6(1.9%)	0	0	2(0.7%)	2(1.1%)
AMYLASE INCREASED	0	0	0	0	1(0.4%)	1(0.5%)
GAMMA GLUTAMYL TRANSPEPTIDASE INCREASED	0	0	0	0	1(0.4%)	1(0.5%)
HYPOGLYCEMIC REACTION	0	0	0	0	0	1(0.5%)
HYPOVOLEMIA	1(0.2%)	1(0.3%)	0	0	3(1.1%)	1(0.5%)
KETOSIS	4(0.9%)	0	0	0	0	1(0.5%)
RESPIRATORY ACIDOSIS	2(0.4%)	3(0.9%)	0	0	1(0.4%)	1(0.5%)

(1) STUDIES INCLUDED: 98-0-050, FG-21-09, AND 98-0-047. STUDY 98-0-047 ONLY INCLUDES PATIENTS < 16 YEARS OLD WHO RECEIVED 1 MG/KG/DAY AND >= 16 YEARS OLD WHO RECEIVED 50 MG/DAY DOSE OF FK463.
(2) WITHIN A BODY SYSTEM A PERSON MAY EXPERIENCE MORE THAN ONE ADVERSE EVENT.

Corresponds to Table R6 9 in the applicant's submission dated October 25, 2004.
FK463 = micafungin

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TABLE 17 (continued)

INCIDENCE OF TREATMENT EMERGENT ADVERSE EVENTS OF 50 MG FK463 AND FLUCONAZOLE, BY GENDER
ALL TREATED PATIENTS (1)

BODY SYSTEM (2) / COSTART TERM	FK463 MALE (N=447)	FK463 FEMALE (N=323)	FLUCONAZOLE 200 MG MALE (N=28)	FLUCONAZOLE 200 MG FEMALE (N=32)	FLUCONAZOLE 400 MG MALE (N=274)	FLUCONAZOLE 400 MG FEMALE (N=193)
ALKALOSIS	2(0.4%)	3(0.9%)	0	0	2(0.7%)	0
AVITAMINOSIS	0	0	0	0	1(0.4%)	0
ELECTROLYTE ABNORMALITY	2(0.4%)	2(0.6%)	0	0	0	0
GLOBULIN INCREASED	1(0.2%)	0	0	0	0	0
GLYCOSURIA	3(0.7%)	0	0	0	2(0.7%)	0
GOUT	1(0.2%)	0	0	0	0	0
HYPERAMMONEMIA	0	0	0	0	1(0.4%)	0
HYPERCALCEMIA	0	2(0.6%)	0	0	1(0.4%)	0
HYPOCHOLESTREMIA	0	1(0.3%)	0	0	0	0
THIRST	0	0	0	0	2(0.7%)	0
HEMIC AND LYMPHATIC SYSTEM						
ANY AE	297(66.4%)	211(65.3%)	9(32.1%)	4(12.5%)	252(92.0%)	170(92.9%)
LEUKOPENIA	221(49.4%)	145(44.9%)	6(21.4%)	2(6.3%)	207(75.5%)	139(76.0%)
THROMBOCYTOPENIA	202(45.2%)	136(42.1%)	1(3.6%)	1(3.1%)	188(68.6%)	133(72.7%)
ANEMIA	110(24.6%)	84(26.0%)	3(10.7%)	0	116(42.3%)	77(42.1%)
ECCHYMOSIS	18(4.0%)	16(5.0%)	0	0	9(3.3%)	19(10.4%)
PETECHIA	26(5.8%)	18(5.6%)	0	0	22(8.0%)	18(9.8%)
COAGULATION DISORDER	7(1.6%)	11(3.4%)	0	0	13(4.7%)	8(4.4%)
PANCYTOPENIA	7(1.6%)	4(1.2%)	0	0	6(2.2%)	5(2.7%)
PROTHROMBIN DECREASED	4(0.9%)	6(1.9%)	0	0	7(2.6%)	3(1.6%)
LEUKOCYTOSIS	6(1.3%)	5(1.5%)	0	0	4(1.5%)	2(1.1%)
THROMBOPLASTIN DECREASED	1(0.2%)	1(0.3%)	0	0	0	2(1.1%)
LYMPHADENOPATHY	0	7(2.2%)	1(3.6%)	0	3(1.1%)	1(0.5%)
PURPURA	1(0.2%)	2(0.6%)	0	0	0	1(0.5%)
SPLENOMEGALY	4(0.9%)	1(0.3%)	0	0	4(1.5%)	1(0.5%)
WBC ABNORMAL	9(2.0%)	7(2.2%)	0	0	1(0.4%)	1(0.5%)
BLEEDING TIME INCREASED	0	2(0.6%)	0	0	2(0.7%)	0
CYANOSIS	1(0.2%)	2(0.6%)	0	0	0	0
EOSINOPHILIA	0	4(1.2%)	1(3.6%)	1(3.1%)	0	0
ERYTHROCYTES ABNORMAL	0	1(0.3%)	0	0	0	0
FIBRINOGEN INCREASED	1(0.2%)	0	0	0	0	0
HEMOLYSIS	0	1(0.3%)	0	0	0	0
HEMOLYTIC ANEMIA	1(0.2%)	0	0	0	0	0
HYPOCHROMIC ANEMIA	0	0	1(3.6%)	0	0	0
LEUKEMIA	0	1(0.3%)	0	0	0	0
RETICULOENDOTHELIAL HYPERPLASIA	0	1(0.3%)	0	0	0	0
SPLEEN DISORDER	1(0.2%)	0	0	0	0	0
THROMBOCYTHEMIA	2(0.4%)	5(1.5%)	0	0	0	0
CARDIOVASCULAR SYSTEM						

(1) STUDIES INCLUDED: 98-0-050, PC-21-09, AND 98-0-047. STUDY 98-0-047 ONLY INCLUDES PATIENTS < 16 YEARS OLD WHO RECEIVED 1 MG/KG/DAY AND >= 16 YEARS OLD WHO RECEIVED 50 MG/DAY DOSE OF FK463.
(2) WITHIN A BODY SYSTEM A PERSON MAY EXPERIENCE MORE THAN ONE ADVERSE EVENT.

Corresponds to Table R6 9 in the applicant's submission dated October 25, 2004.
FK463 = micafungin

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TABLE 17 (continued)

INCIDENCE OF TREATMENT EMERGENT ADVERSE EVENTS OF 50 MG FK463 AND FLUCONAZOLE, BY GENDER
ALL TREATED PATIENTS (1)

BODY SYSTEM (2) COSTART TERM	FK463 MALE (N=447)	FK463 FEMALE (N=323)	FLUCONAZOLE 200 MG MALE (N=28)	FLUCONAZOLE 200 MG FEMALE (N=32)	FLUCONAZOLE 400 MG MALE (N=274)	FLUCONAZOLE 400 MG FEMALE (N=193)
ANY AE	223(49.9%)	171(52.9%)	2(7.1%)	4(12.5%)	179(65.3%)	140(80.9%)
TACHYCARDIA	68(15.2%)	65(20.1%)	0	0	60(21.9%)	52(28.4%)
HYPERTENSION	65(14.5%)	46(14.2%)	0	1(3.1%)	72(26.3%)	45(24.6%)
HYPOTENSION	54(12.1%)	57(17.6%)	2(7.1%)	0	49(17.9%)	41(22.4%)
CHEST PAIN	40(8.9%)	29(9.0%)	0	3(9.4%)	27(9.9%)	36(19.7%)
VASODILATATION	41(9.2%)	26(8.0%)	0	0	37(13.5%)	36(19.7%)
BRADYCARDIA	13(2.9%)	7(2.2%)	1(3.6%)	0	10(3.6%)	8(4.4%)
HEMORRHAGE	6(1.3%)	4(1.2%)	1(3.6%)	0	2(0.7%)	7(3.8%)
ATRIAL FIBRILLATION	11(2.5%)	6(1.9%)	0	0	6(2.2%)	6(3.3%)
CARDIOMEGALY	2(0.4%)	6(1.9%)	0	0	2(0.7%)	6(3.3%)
VALVULAR HEART DISEASE	2(0.4%)	5(1.5%)	0	0	5(1.8%)	6(3.3%)
CONGESTIVE HEART FAILURE	1(0.2%)	6(1.9%)	0	0	4(1.5%)	5(2.7%)
POSTURAL HYPOTENSION	6(1.3%)	8(2.5%)	0	0	13(4.7%)	5(2.7%)
ARRHYTHMIA	8(1.8%)	10(3.1%)	0	0	6(2.2%)	4(2.2%)
HEART ARREST	2(0.4%)	0	0	0	0	4(2.2%)
SINUS BRADYCARDIA	0	2(0.6%)	0	0	3(1.1%)	4(2.2%)
SYNCOPE	6(1.3%)	6(1.9%)	0	0	6(2.2%)	4(2.2%)
THROMBOPHLEBITIS	1(0.2%)	4(1.2%)	0	0	1(0.4%)	4(2.2%)
SHOCK	7(1.6%)	9(2.8%)	0	0	1(0.4%)	3(1.6%)
CARDIOVASCULAR DISORDER	0	4(1.2%)	0	0	2(0.7%)	2(1.1%)
DEEP THROMBOPHLEBITIS	5(1.1%)	5(1.5%)	0	0	1(0.4%)	2(1.1%)
MIGRAINE	0	3(0.9%)	0	0	1(0.4%)	2(1.1%)
PERICARDIAL EFFUSION	4(0.9%)	2(0.6%)	0	0	2(0.7%)	2(1.1%)
ATRIAL FLUTTER	4(0.9%)	0	0	0	1(0.4%)	1(0.5%)
EMBOLUS	0	0	0	0	0	1(0.5%)
ENDOCARDITIS	1(0.2%)	0	0	0	0	1(0.5%)
EXTRASYSTOLES	1(0.2%)	0	0	0	1(0.4%)	1(0.5%)
MYOCARDIAL INFARCT	0	0	0	0	0	1(0.5%)
MYOCARDIAL ISCHEMIA	1(0.2%)	0	0	0	0	1(0.5%)
PALLOR	4(0.9%)	1(0.3%)	1(3.6%)	0	2(0.7%)	1(0.5%)
PALPITATION	3(0.7%)	1(0.3%)	0	1(3.1%)	2(0.7%)	1(0.5%)
PERICARDITIS	0	1(0.3%)	0	0	0	1(0.5%)
PERIPHERAL VASCULAR DISORDER	2(0.4%)	4(1.2%)	0	0	1(0.4%)	1(0.5%)
SUBDURAL HEMATOMA	0	0	0	0	1(0.4%)	1(0.5%)
THROMBOSIS	0	0	0	0	1(0.4%)	1(0.5%)
VARICOSE VEIN	0	0	0	0	0	1(0.5%)
VASCULAR ANOMALY	0	0	0	0	0	1(0.5%)
ANGINA PECTORIS	1(0.2%)	0	0	0	0	0
ARTERIOSCLEROSIS	0	1(0.3%)	0	0	0	0
AV BLOCK COMPLETE	0	1(0.3%)	0	0	0	0
CARDIOMYOPATHY	0	0	0	0	1(0.4%)	0

(1) STUDIES INCLUDED: 98-0-050, MC-21-09, AND 98-0-047. STUDY 98-0-047 ONLY INCLUDES PATIENTS < 16 YEARS OLD WHO RECEIVED 1 MG/KG/DAY AND >= 16 YEARS OLD WHO RECEIVED 50 MG/DAY DOSE OF FK463.
(2) WITHIN A BODY SYSTEM A PERSON MAY EXPERIENCE MORE THAN ONE ADVERSE EVENT.

Corresponds to Table R6 9 in the applicant's submission dated October 25, 2004.
FK463 = micafungin

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TABLE 17 (continued)

INCIDENCE OF TREATMENT EMERGENT ADVERSE EVENTS OF 50 MG FK463 AND FLUCONAZOLE, BY GENDER
ALL TREATED PATIENTS (1)

BODY SYSTEM (2) COSTART TERM	FK463 MALE (N=447)	FK463 FEMALE (N=323)	FLUCONAZOLE 200 MG MALE (N=28)	FLUCONAZOLE 200 MG FEMALE (N=32)	FLUCONAZOLE 400 MG MALE (N=274)	FLUCONAZOLE 400 MG FEMALE (N=183)
ELECTROCARDIOGRAM ABNORMAL	2(0.4%)	2(0.6%)	0	0	1(0.4%)	0
HEART FAILURE	0	2(0.6%)	0	0	0	0
INCREASED CAPILLARY FRAGILITY	1(0.2%)	0	0	0	0	0
PHLEBITIS	9(2.0%)	4(1.2%)	0	0	2(0.7%)	0
SUPRAVENTRICULAR TACHYCARDIA	1(0.2%)	1(0.3%)	0	0	0	0
T INVERTED	0	0	0	0	1(0.4%)	0
VASCULAR DISORDER	1(0.2%)	0	0	0	0	0
VENTRICULAR ARRHYTHMIA	1(0.2%)	1(0.3%)	0	0	0	0
VENTRICULAR EXTRASYSTOLES	0	1(0.3%)	0	0	2(0.7%)	0
VENTRICULAR TACHYCARDIA	1(0.2%)	3(0.9%)	0	0	0	0
NERVOUS SYSTEM						
ANY AE	283(63.3%)	194(60.1%)	8(28.6%)	12(37.5%)	204(74.5%)	142(77.6%)
HEADACHE	133(29.8%)	97(30.0%)	3(10.7%)	3(9.4%)	97(35.4%)	70(38.3%)
INSOMNIA	112(25.1%)	62(19.2%)	0	3(9.4%)	94(34.3%)	54(29.5%)
ANXIETY	60(13.4%)	49(15.2%)	0	1(3.1%)	50(18.2%)	42(23.0%)
DIZZINESS	37(8.3%)	30(9.3%)	3(10.7%)	3(9.4%)	47(17.2%)	36(19.7%)
CONFUSION	27(6.0%)	24(7.4%)	0	0	18(6.6%)	15(8.2%)
DEPRESSION	17(3.8%)	18(5.6%)	1(3.6%)	1(3.1%)	24(8.8%)	15(8.2%)
SOMNOLENCE	21(4.7%)	14(4.3%)	2(7.1%)	2(6.3%)	19(6.9%)	15(8.2%)
TREMOR	14(3.1%)	11(3.4%)	0	0	21(7.7%)	11(6.0%)
AGITATION	17(3.8%)	7(2.2%)	0	0	6(2.2%)	9(4.9%)
NERVOUSNESS	17(3.8%)	22(6.8%)	0	0	9(3.3%)	7(3.8%)
PARESTHESIA	21(4.7%)	20(6.2%)	0	1(3.1%)	18(6.6%)	7(3.8%)
HALLUCINATIONS	9(2.0%)	5(1.5%)	0	0	7(2.6%)	4(2.2%)
CONVULSION	4(0.9%)	6(1.9%)	1(3.6%)	0	4(1.5%)	3(1.6%)
THINKING ABNORMAL	2(0.4%)	2(0.6%)	0	0	5(1.8%)	3(1.6%)
ABNORMAL DREAMS	6(1.3%)	7(2.2%)	0	0	3(1.1%)	2(1.1%)
ABNORMAL GAIT	0	6(1.9%)	0	0	3(1.1%)	2(1.1%)
GRAND MAL CONVULSION	0	0	0	0	0	2(1.1%)
VERTIGO	0	0	0	0	2(0.7%)	2(1.1%)
ATAXIA	0	0	0	0	0	1(0.5%)
BRAIN ABSCESS	0	0	0	0	0	1(0.5%)
CEREBRAL HEMORRHAGE	0	0	0	0	0	1(0.5%)
CEREBROVASCULAR ACCIDENT	1(0.2%)	0	0	0	0	1(0.5%)
DYSTONIA	0	2(0.6%)	0	0	4(1.5%)	1(0.5%)
EMOTIONAL LABILITY	3(0.7%)	2(0.6%)	0	0	3(1.1%)	1(0.5%)
ENCEPHALOPATHY	3(0.7%)	0	0	0	0	1(0.5%)
HYPERTONIA	3(0.7%)	3(0.9%)	0	0	2(0.7%)	1(0.5%)
INCREASED SALIVATION	0	0	0	0	3(1.1%)	1(0.5%)
NEUROPATHY	2(0.4%)	3(0.9%)	0	0	0	1(0.5%)

(1) STUDIES INCLUDED: 98-0-050, PC-21-09, AND 98-0-047. STUDY 98-0-047 ONLY INCLUDES PATIENTS < 16 YEARS OLD WHO RECEIVED 1 MG/KG/DAY AND >= 16 YEARS OLD WHO RECEIVED 50 MG/DAY DOSE OF FK463.
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Corresponds to Table R6 9 in the applicant's submission dated October 25, 2004.
FK463 = micafungin

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TABLE 17 (continued)

INCIDENCE OF TREATMENT EMERGENT ADVERSE EVENTS OF 50 MG FK463 AND FLUCONAZOLE, BY GENDER
ALL TREATED PATIENTS (1)

BODY SYSTEM (2) COSTART TERM	FK463 MALE (N=447)	FK463 FEMALE (N=323)	FLUCONAZOLE 200 MG MALE (N=28)	FLUCONAZOLE 200 MG FEMALE (N=32)	FLUCONAZOLE 400 MG MALE (N=274)	FLUCONAZOLE 400 MG FEMALE (N=183)
NYSTAGMUS	1 (0.2%)	0	0	0	3 (1.1%)	1 (0.5%)
ADDICTION	0	0	0	0	1 (0.4%)	0
AKATHISIA	0	0	0	0	1 (0.4%)	0
APATHY	0	1 (0.3%)	0	0	1 (0.4%)	0
APHASIA	1 (0.2%)	1 (0.3%)	0	0	0	0
CNS DEPRESSION	0	1 (0.3%)	0	0	0	0
CNS NEOPLASIA BENIGN	0	1 (0.3%)	0	0	0	0
COMA	2 (0.4%)	2 (0.6%)	1 (3.6%)	0	0	0
DELIRIUM	4 (0.9%)	2 (0.6%)	0	0	3 (1.1%)	0
DEMENTIA	0	0	1 (3.6%)	0	0	0
ENCEPHALITIS	0	0	0	0	1 (0.4%)	0
EXTRAPYRAMIDAL SYNDROME	2 (0.4%)	1 (0.3%)	0	0	1 (0.4%)	0
HEMIPLEGIA	0	1 (0.3%)	0	0	0	0
HOSTILITY	4 (0.9%)	0	0	0	0	0
HYPERESTHESIA	0	1 (0.3%)	0	0	0	0
HYPERKINESIA	0	0	0	0	2 (0.7%)	0
INTRACRANIAL HEMORRHAGE	0	1 (0.3%)	0	0	0	0
INTRACRANIAL HYPERTENSION	1 (0.2%)	0	0	0	0	0
MENINGITIS	2 (0.4%)	2 (0.6%)	2 (7.1%)	0	0	0
MOVEMENT DISORDER	1 (0.2%)	0	0	0	0	0
MYOCLONUS	0	1 (0.3%)	0	0	1 (0.4%)	0
NEURALGIA	4 (0.9%)	0	0	0	0	0
NEURITIS	1 (0.2%)	1 (0.3%)	0	0	1 (0.4%)	0
PARANOID REACTION	0	1 (0.3%)	0	0	0	0
PERSONALITY DISORDER	1 (0.2%)	0	0	0	0	0
PSYCHOSIS	0	0	0	1 (3.1%)	0	0
SPEECH DISORDER	2 (0.4%)	1 (0.3%)	0	0	2 (0.7%)	0
STUPOR	3 (0.7%)	0	0	0	1 (0.4%)	0
VOCAL CORD PARALYSIS	1 (0.2%)	0	0	0	0	0
WITHDRAWAL SYNDROME	1 (0.2%)	0	0	0	3 (1.1%)	0
RESPIRATORY SYSTEM						
ANY AE	263 (58.8%)	183 (56.7%)	8 (28.6%)	6 (18.8%)	216 (78.8%)	134 (73.2%)
COUGH INCREASED	75 (16.8%)	53 (16.4%)	2 (7.1%)	0	77 (28.1%)	42 (23.0%)
EPISTAXIS	37 (8.3%)	25 (7.7%)	1 (3.6%)	0	46 (16.8%)	39 (21.3%)
DYSPNEA	51 (11.4%)	47 (14.6%)	0	1 (3.1%)	49 (17.9%)	37 (20.2%)
LUNG DISORDER	55 (12.3%)	44 (13.6%)	0	0	57 (20.8%)	34 (18.6%)
PHARYNGITIS	29 (6.5%)	32 (9.9%)	1 (3.6%)	1 (3.1%)	39 (14.2%)	30 (16.4%)
RHINITIS	56 (12.5%)	29 (9.0%)	1 (3.6%)	1 (3.1%)	57 (20.8%)	30 (16.4%)
PNEUMONIA	27 (6.0%)	24 (7.4%)	3 (10.7%)	2 (6.3%)	15 (5.5%)	10 (5.5%)
SINUSITIS	16 (3.6%)	7 (2.2%)	0	1 (3.1%)	6 (2.2%)	10 (5.5%)

(1) STUDIES INCLUDED: 98-0-050, MC-21-99, AND 98-0-047. STUDY 98-0-047 ONLY INCLUDES PATIENTS < 16 YEARS OLD WHO RECEIVED 1 MG/KG/DAY AND >= 16 YEARS OLD WHO RECEIVED 50 MG/DAY DOSE OF FK463.
(2) WITHIN A BODY SYSTEM A PERSON MAY EXPERIENCE MORE THAN ONE ADVERSE EVENT.

Corresponds to Table R6 9 in the applicant's submission dated October 25, 2004.
FK463 = micafungin

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TABLE 17 (continued)

INCIDENCE OF TREATMENT EMERGENT ADVERSE EVENTS OF 50 MG FK463 AND FLUCONAZOLE, BY GENDER
ALL TREATED PATIENTS (1)

BODY SYSTEM (2) COSTART TERM	FK463 MALE (N=447)	FK463 FEMALE (N=323)	FLUCONAZOLE 200 MG MALE (N=28)	FLUCONAZOLE 200 MG FEMALE (N=32)	FLUCONAZOLE 400 MG MALE (N=274)	FLUCONAZOLE 400 MG FEMALE (N=193)
HYPOXIA	15(3.4%)	17(5.3%)	0	0	18(6.6%)	9(4.9%)
HICCUP	37(8.3%)	5(1.5%)	1(3.6%)	0	49(17.9%)	8(4.1%)
LUNG EDEMA	4(0.9%)	12(3.7%)	0	0	10(3.6%)	8(4.1%)
ASTHMA	22(4.9%)	14(4.3%)	1(3.6%)	0	18(6.6%)	7(3.6%)
HYPERVENTILATION	9(2.0%)	13(4.0%)	0	1(3.1%)	14(5.1%)	7(3.6%)
PLEURAL EFFUSION	11(2.5%)	9(2.8%)	0	0	12(4.4%)	6(3.1%)
HEMOPTYSIS	9(2.0%)	9(2.8%)	1(3.6%)	0	5(1.8%)	5(2.7%)
LUNG HEMORRHAGE	1(0.2%)	2(0.6%)	0	0	2(0.7%)	4(2.1%)
RESPIRATORY DISORDER	7(1.6%)	7(2.2%)	0	0	2(0.7%)	4(2.1%)
APNEA	2(0.4%)	3(0.9%)	0	0	4(1.5%)	3(1.6%)
ATELECTASIS	3(0.7%)	7(2.2%)	0	0	4(1.5%)	3(1.6%)
RESPIRATORY FAILURE	12(2.7%)	10(3.1%)	0	0	3(1.1%)	3(1.6%)
RESPIRATORY DISTRESS SYNDROME	2(0.4%)	3(0.9%)	0	0	0	2(1.1%)
EMPHYSEMA	1(0.2%)	0	0	0	1(0.4%)	1(0.5%)
HYPOVENTILATION	0	0	0	0	1(0.4%)	1(0.5%)
LARYNGITIS	0	1(0.3%)	0	0	0	1(0.5%)
PLEURAL DISORDER	1(0.2%)	2(0.6%)	1(3.6%)	0	0	1(0.5%)
VOICE ALTERATION	1(0.2%)	1(0.3%)	0	0	2(0.7%)	1(0.5%)
BRONCHIECTASIS	0	0	1(3.6%)	0	0	0
BRONCHITIS	2(0.4%)	3(0.9%)	1(3.6%)	1(3.1%)	0	0
INTERSTITIAL PNEUMONIA	1(0.2%)	0	0	0	0	0
PNEUMOTHORAX	1(0.2%)	0	0	0	0	0
PULMONARY EMBOLUS	0	1(0.3%)	0	0	0	0
PULMONARY HYPERTENSION	0	2(0.6%)	0	0	0	0
PULMONARY TUBERCULOSIS	1(0.2%)	0	0	0	0	0
REACTIVATED						
SPUTUM INCREASED	1(0.2%)	0	0	0	1(0.4%)	0
STRIDOR	2(0.4%)	1(0.3%)	0	0	1(0.4%)	0
SKIN AND APPENDAGES						
ANY AE	225(50.3%)	149(46.1%)	7(25.0%)	6(18.8%)	192(70.1%)	116(63.4%)
RASH	135(30.2%)	74(22.9%)	0	0	119(43.4%)	68(37.2%)
PRURITUS	54(12.1%)	41(12.7%)	1(3.6%)	0	44(16.1%)	49(26.8%)
DRY SKIN	17(3.8%)	10(3.1%)	1(3.6%)	0	18(6.6%)	14(7.7%)
SKIN DISORDER	30(6.7%)	18(5.6%)	1(3.6%)	1(3.1%)	16(5.8%)	13(7.1%)
ALOPECIA	13(2.9%)	18(5.6%)	0	0	18(6.6%)	11(6.0%)
SWEATING	22(4.9%)	9(2.8%)	1(3.6%)	1(3.1%)	17(6.2%)	9(4.9%)
VESICULOBULLOUS RASH	6(1.3%)	4(1.2%)	0	0	4(1.5%)	6(3.1%)
SKIN DISCOLORATION	4(0.9%)	8(2.5%)	1(3.6%)	0	6(2.2%)	5(2.7%)
HERPES SIMPLEX	6(1.3%)	13(4.0%)	1(3.6%)	3(9.4%)	8(2.9%)	4(2.1%)
MACULOPAPULAR RASH	14(3.1%)	11(3.4%)	1(3.6%)	0	10(3.6%)	4(2.1%)

(1) STUDIES INCLUDED: 98-0-050, FC-21-03, AND 98-0-047. STUDY 98-0-047 ONLY INCLUDES PATIENTS < 16 YEARS OLD WHO RECEIVED 1 MG/KG/DAY AND >= 16 YEARS OLD WHO RECEIVED 50 MG/DAY DOSE OF FK463.
(2) WITHIN A BODY SYSTEM A PERSON MAY EXPERIENCE MORE THAN ONE ADVERSE EVENT.

Corresponds to Table R6 9 in the applicant's submission dated October 25, 2004.
FK463 = micafungin

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TABLE 17 (continued)

INCIDENCE OF TREATMENT EMERGENT ADVERSE EVENTS OF 50 MG FK463 AND FLUCONAZOLE, BY GENDER
ALL TREATED PATIENTS (1)

BODY SYSTEM (2) COSTART TERM	FK463 MALE (N=447)	FK463 FEMALE (N=323)	FLUCONAZOLE 200 MG MALE (N=28)	FLUCONAZOLE 200 MG FEMALE (N=32)	FLUCONAZOLE 400 MG MALE (N=274)	FLUCONAZOLE 400 MG FEMALE (N=183)
URTICARIA	20(4.5%)	3(0.9%)	0	1(3.1%)	9(3.3%)	3(1.6%)
CONTACT DERMATITIS	0	2(0.6%)	0	0	0	2(1.1%)
HERPES ZOSTER	4(0.9%)	4(1.2%)	0	0	2(0.7%)	2(1.1%)
PETECHIAL RASH	4(0.9%)	2(0.6%)	0	0	7(2.6%)	2(1.1%)
ACNE	7(1.6%)	1(0.3%)	0	0	2(0.7%)	1(0.5%)
EXFOLIATIVE DERMATITIS	4(0.9%)	1(0.3%)	0	0	4(1.5%)	1(0.5%)
FOLLICULITIS	26(5.8%)	4(1.2%)	0	0	11(4.0%)	1(0.5%)
HAIR DISORDER	0	0	0	0	0	1(0.5%)
PSORIASIS	0	0	0	0	0	1(0.5%)
SKIN ULCER	4(0.9%)	10(3.1%)	1(3.6%)	0	5(1.8%)	1(0.5%)
ANGIONEMMA	1(0.2%)	1(0.3%)	0	0	2(0.7%)	0
BREAST PAIN	0	2(0.6%)	0	0	0	0
ECZEMA	1(0.2%)	0	0	1(3.1%)	0	0
NAIL DISORDER	2(0.4%)	0	0	0	1(0.4%)	0
PUSTULAR RASH	1(0.2%)	2(0.6%)	0	0	0	0
SEBORRHEA	1(0.2%)	0	0	0	0	0
SKIN INFECTION	0	2(0.6%)	0	0	0	0
SKIN NODULE	2(0.4%)	0	0	0	1(0.4%)	0
SUBCUTANEOUS NODULE	1(0.2%)	0	0	0	0	0
SUNBURN	1(0.2%)	0	0	0	0	0
UROGENITAL SYSTEM						
ANY AE	140(31.3%)	102(31.6%)	2(7.1%)	5(15.6%)	122(44.5%)	100(54.6%)
HEMATURIA	42(9.4%)	31(9.6%)	0	0	44(16.1%)	27(14.8%)
DYSURIA	26(5.8%)	17(5.3%)	0	0	24(8.8%)	19(10.4%)
VAGINAL HEMORRHAGE	0	11(3.4%)	0	0	0	19(10.4%)
OLIGURIA	31(6.9%)	13(4.0%)	0	0	18(6.6%)	14(7.7%)
URINARY TRACT INFECTION	12(2.7%)	17(5.3%)	0	2(6.3%)	8(2.9%)	13(7.1%)
VAGINITIS	0	11(3.4%)	0	1(3.1%)	0	10(5.5%)
KIDNEY FUNCTION ABNORMAL	7(1.6%)	3(0.9%)	0	0	10(3.6%)	9(4.9%)
KIDNEY FAILURE	10(2.2%)	3(0.9%)	0	0	6(2.2%)	7(3.8%)
URINARY INCONTINENCE	10(2.2%)	9(2.8%)	0	0	7(2.6%)	6(3.3%)
ACUTE KIDNEY FAILURE	3(0.7%)	5(1.5%)	0	0	2(0.7%)	5(2.7%)
CYSTITIS	7(1.6%)	8(2.5%)	0	0	11(4.0%)	5(2.7%)
HEMORRHAGIC CYSTITIS	3(0.7%)	2(0.6%)	0	0	3(1.1%)	5(2.7%)
URINARY FREQUENCY	10(2.2%)	6(1.9%)	1(3.6%)	1(3.1%)	14(5.1%)	5(2.7%)
URINARY RETENTION	5(1.1%)	1(0.3%)	0	0	5(1.8%)	4(2.2%)
URINE ABNORMALITY	4(0.9%)	2(0.6%)	1(3.6%)	1(3.1%)	5(1.8%)	4(2.2%)
ALBUMINURIA	7(1.6%)	2(0.6%)	0	0	14(5.1%)	2(1.1%)
LEUKORRHEA	0	0	0	0	0	2(1.1%)
METRORRHAGIA	0	1(0.3%)	0	0	0	2(1.1%)

(1) STUDIES INCLUDED: 98-0-050, FG-21-89, AND 98-0-047. STUDY 98-0-047 ONLY INCLUDES PATIENTS < 16 YEARS OLD WHO RECEIVED 1 MG/KG/DAY AND >= 16 YEARS OLD WHO RECEIVED 50 MG/DAY DOSE OF FK463.
(2) WITHIN A BODY SYSTEM A PERSON MAY EXPERIENCE MORE THAN ONE ADVERSE EVENT.

Corresponds to Table R6 9 in the applicant's submission dated October 25, 2004.
FK463 = micafungin

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TABLE 17 (continued)

INCIDENCE OF TREATMENT EMERGENT ADVERSE EVENTS OF 50 MG FK463 AND FLUCONAZOLE, BY GENDER
ALL TREATED PATIENTS [1]

BODY SYSTEM (2) COSTART TERM	FK463 MALE (N=447)	FK463 FEMALE (N=323)	FLUCONAZOLE 200 MG MALE (N=28)	FLUCONAZOLE 200 MG FEMALE (N=32)	FLUCONAZOLE 400 MG MALE (N=274)	FLUCONAZOLE 400 MG FEMALE (N=183)
URETHRAL PAIN	0	1(0.3%)	0	0	0	2(1.1%)
URINARY URGENCY	1(0.2%)	2(0.6%)	0	0	5(1.8%)	2(1.1%)
URINATION IMPAIRED	1(0.2%)	3(0.9%)	0	0	5(1.8%)	2(1.1%)
VULVOVAGINITIS	0	0	0	0	0	2(1.1%)
ANURIA	0	1(0.3%)	0	0	0	1(0.5%)
DYSMENORRHEA	0	0	0	0	0	1(0.5%)
KIDNEY PAIN	1(0.2%)	0	0	0	0	1(0.5%)
KIDNEY TUBULAR DISORDER	0	0	0	0	0	1(0.5%)
POLYCYSTIC KIDNEY	0	0	0	0	0	1(0.5%)
POLYURIA	2(0.4%)	2(0.6%)	1(3.6%)	0	2(0.7%)	1(0.5%)
BALANITIS	1(0.2%)	0	0	0	0	0
CARCINOMA RENAL	1(0.2%)	0	0	0	0	0
MENORRHAGIA	0	1(0.3%)	0	0	0	0
NOCTURIA	1(0.2%)	1(0.3%)	0	0	2(0.7%)	0
OVARIAN DISORDER	0	1(0.3%)	0	0	0	0
PENIS DISORDER	5(1.1%)	0	0	0	9(3.3%)	0
PROSTATIC DISORDER	1(0.2%)	0	0	0	0	0
PYELONEPHRITIS	1(0.2%)	0	0	0	0	0
SALPINGITIS	0	0	0	1(3.1%)	0	0
SCROTAL EDEMA	5(1.1%)	0	0	0	6(2.2%)	0
TESTIS DISORDER	2(0.4%)	0	0	0	4(1.5%)	0
SPECIAL SENSES						
ANY AE	81(18.1%)	62(19.2%)	1(3.6%)	2(6.3%)	67(24.5%)	48(26.2%)
ABNORMAL VISION	12(2.7%)	15(4.6%)	0	0	18(6.6%)	11(6.0%)
EYE HEMORRHAGE	10(2.2%)	6(1.9%)	0	0	8(2.9%)	8(4.4%)
EAR PAIN	12(2.7%)	12(3.7%)	0	1(3.1%)	10(3.6%)	7(3.8%)
DRY EYES	13(2.9%)	8(2.5%)	0	0	13(4.7%)	6(3.3%)
CONJUNCTIVITIS	10(2.2%)	3(0.9%)	1(3.6%)	1(3.1%)	8(2.9%)	4(2.2%)
EAR DISORDER	4(0.9%)	5(1.5%)	0	0	2(0.7%)	3(1.6%)
CONJUNCTIVAL EDEMA	2(0.4%)	1(0.3%)	0	0	0	2(1.1%)
DIPLOPIA	0	0	0	0	2(0.7%)	2(1.1%)
IMPAIRED HEARING	3(0.7%)	3(0.9%)	0	0	0	2(1.1%)
TASTE PERVERSION	13(2.9%)	7(2.2%)	0	0	9(3.3%)	2(1.1%)
ANISOCORIA	0	1(0.3%)	0	0	2(0.7%)	1(0.5%)
EXTRAOCULAR PALSY	0	0	0	0	0	1(0.5%)
EYE DISORDER	2(0.4%)	0	0	0	1(0.4%)	1(0.5%)
EYE PAIN	7(1.6%)	6(1.9%)	0	0	8(2.9%)	1(0.5%)
OTITIS MEDIA	0	1(0.3%)	0	0	1(0.4%)	1(0.5%)
PHOTOPHOBIA	3(0.7%)	1(0.3%)	0	0	1(0.4%)	1(0.5%)
TINNITUS	1(0.2%)	2(0.6%)	0	0	0	1(0.5%)

(1) STUDIES INCLUDED: 98-0-050, FC-21-09, AND 98-0-047. STUDY 98-0-047 ONLY INCLUDES PATIENTS < 16 YEARS OLD WHO RECEIVED 1 MG/KG/DAY AND >= 16 YEARS OLD WHO RECEIVED 50 MG/DAY DOSE OF FK463.
(2) WITHIN A BODY SYSTEM A PERSON MAY EXPERIENCE MORE THAN ONE ADVERSE EVENT.

Corresponds to Table R6 9 in the applicant's submission dated October 25, 2004.
FK463 = micafungin

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TABLE 17 (continued)

INCIDENCE OF TREATMENT EMERGENT ADVERSE EVENTS OF 50 MG FK463 AND FLUCONAZOLE, BY GENDER
ALL TREATED PATIENTS (1)

BODY SYSTEM (2) COSTART TERM	FK463 MALE (N=447)	FK463 FEMALE (N=323)	FLUCONAZOLE 200 MG MALE (N=28)	FLUCONAZOLE 200 MG FEMALE (N=32)	FLUCONAZOLE 400 MG MALE (N=274)	FLUCONAZOLE 400 MG FEMALE (N=183)
BLEPHARITIS	1(0.2%)	0	0	0	0	0
CORNEAL LESION	0	1(0.3%)	0	0	0	0
DEAFNESS	2(0.4%)	1(0.3%)	0	0	0	0
EXOPHTHALMOS	0	1(0.3%)	0	0	0	0
LACRIMATION DISORDER	2(0.4%)	4(1.2%)	0	0	0	0
MIOSIS	1(0.2%)	2(0.6%)	0	0	0	0
OTITIS EXTERNA	2(0.4%)	2(0.6%)	0	0	0	0
PAROSMIA	1(0.2%)	0	0	0	0	0
RETINAL DISORDER	1(0.2%)	1(0.3%)	0	0	0	0
RETINAL HEMORRHAGE	1(0.2%)	1(0.3%)	0	0	0	0
RETINITIS	0	1(0.3%)	0	0	0	0
SCLERITIS	1(0.2%)	0	0	0	0	0
STRABISMUS	1(0.2%)	0	0	0	0	0
TASTE LOSS	3(0.7%)	0	0	0	1(0.4%)	0
UVEITIS	1(0.2%)	0	0	0	0	0
MUSCULOSKELETAL SYSTEM						
ANY AE	91(20.4%)	57(17.6%)	2(7.1%)	0	72(26.3%)	42(23.0%)
ARTHRALGIA	39(8.7%)	25(7.7%)	0	0	38(13.9%)	19(10.4%)
BONE PAIN	23(5.1%)	10(3.1%)	0	0	17(6.2%)	15(8.2%)
MYALGIA	15(3.4%)	11(3.4%)	1(3.6%)	0	16(5.8%)	7(3.8%)
CRAMPS	14(3.1%)	7(2.2%)	0	0	8(2.9%)	5(2.7%)
MYASTHENIA	6(1.3%)	7(2.2%)	0	0	4(1.5%)	5(2.7%)
ARTHROSIS	3(0.7%)	0	0	0	3(1.1%)	0
BONE DISORDER	3(0.7%)	2(0.6%)	0	0	1(0.4%)	0
GENERALIZED SPASM	1(0.2%)	0	0	0	1(0.4%)	0
JOINT DISORDER	1(0.2%)	3(0.9%)	0	0	1(0.4%)	0
MUSCLE ATROPHY	0	0	1(3.6%)	0	0	0
TENDINOUS CONTRACTURE	0	1(0.3%)	0	0	0	0
TWITCHING	4(0.9%)	1(0.3%)	0	0	2(0.7%)	0
ENDOCRINE SYSTEM						
ANY AE	4(0.9%)	2(0.6%)	0	0	1(0.4%)	2(1.1%)
ADH INAPPROPRIATE	2(0.4%)	0	0	0	0	1(0.5%)
ADRENAL CORTEX INSUFFIENCY	0	1(0.3%)	0	0	0	1(0.5%)
DIABETES MELLITUS	0	1(0.3%)	0	0	0	0
HYPOTHYROIDISM	2(0.4%)	0	0	0	0	0
PARATHYROID DISORDER	0	0	0	0	1(0.4%)	0
INJECTION SITE REACTION						
ANY AE	4(0.9%)	4(1.2%)	6(21.4%)	6(18.8%)	0	0

(1) STUDIES INCLUDED: 98-0-050, FG-21-89, AND 98-0-047. STUDY 98-0-047 ONLY INCLUDES PATIENTS < 16 YEARS OLD WHO RECEIVED 1 MG/KG/DAY AND >= 16 YEARS OLD WHO RECEIVED 50 MG/DAY DOSE OF FK463.
(2) WITHIN A BODY SYSTEM A PERSON MAY EXPERIENCE MORE THAN ONE ADVERSE EVENT.

Corresponds to Table R6 9 in the applicant's submission dated October 25, 2004.
FK463 = micafungin

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TABLE 17 (continued)

INCIDENCE OF TREATMENT EMERGENT ADVERSE EVENTS OF 50 MG FK463 AND FLUCONAZOLE, BY GENDER
ALL TREATED PATIENTS (1)

BODY SYSTEM (2)	FK463		FLUCONAZOLE 200 MG		FLUCONAZOLE 400 MG	
COSTART TERM	MALE (N=447)	FEMALE (N=323)	MALE (N=29)	FEMALE (N=32)	MALE (N=274)	FEMALE (N=183)
INJECTION SITE INFLAMMATION	3(0.7%)	4(1.2%)	5(17.2%)	5(15.6%)	0	0
INJECTION SITE REACTION	1(0.2%)	0	1(3.4%)	1(3.1%)	0	0

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(1) STUDIES INCLUDED: 98-0-050, FC-21-89, AND 98-0-047. STUDY 98-0-047 ONLY INCLUDES PATIENTS < 16 YEARS OLD WHO RECEIVED 1 MG/KG/DAY AND >= 16 YEARS OLD WHO RECEIVED 50 MG/DAY DOSE OF FK463.
(2) WITHIN A BODY SYSTEM A PERSON MAY EXPERIENCE MORE THAN ONE ADVERSE EVENT.

Corresponds to Table R6 9 in the applicant's submission dated October 25, 2004.
FK463 = micafungin

7.1.5 Common Adverse Events

Table 18 shows all adverse events across all three studies compared to fluconazole.

Clinical Reviewer's Comment: Certain adverse events, such as those related to infection, appear to be more common in the micafungin treated patients than in those who received fluconazole. This discrepancy may be explained by the fact that Study 98-0-047 was conducted in patients with invasive candidiasis and was a single arm study of micafungin. There was no fluconazole comparator group.

Study 98-0-050: All patients who received micafungin (425) and all patients who received fluconazole (457) experienced at least one adverse event during the study. The more common adverse events that occurred in either group included mucositis (77.9% micafungin 80.5% fluconazole), leucopenia (77.9%, 75.7%), diarrhea (74.1%, 78.6%), thrombocytopenia (74.8%, 70.2%), nausea (70.6%, 68.9%), and vomiting; (66.4%, 67.4%).

TABLE 18

INCIDENCE OF TREATMENT EMERGENT ADVERSE EVENTS OF 50 MG FK463 AND FLUCONAZOLE
ALL TREATED PATIENTS (1)

BODY SYSTEM (2) COSTART TERM	FK463 (N=770)	FLUCONAZOLE 200 MG (N=60)	FLUCONAZOLE 400 MG (N=457)	FLUCONAZOLE TOTAL (N=517)
ALL SYSTEMS	747(97.0%)	56(93.3%)	457(100.0%)	513(99.2%)
DIGESTIVE SYSTEM				
ANY AE	614(79.7%)	32(53.3%)	452(98.9%)	484(93.6%)
MUCOSITIS	338(43.9%)	0	368(80.5%)	368(71.2%)
DIARRHEA	358(46.5%)	5(8.3%)	359(78.6%)	364(70.4%)
NAUSEA	354(46.0%)	11(18.3%)	315(68.9%)	326(63.1%)
VOMITING	350(45.5%)	9(15.0%)	308(67.4%)	317(61.3%)
ANOREXIA	239(31.0%)	1(1.7%)	231(50.5%)	232(44.9%)
CONSTIPATION	161(20.9%)	4(6.7%)	143(31.3%)	147(28.4%)
DYSPEPSIA	128(16.6%)	1(1.7%)	142(31.1%)	143(27.7%)
RECTAL DISORDER	85(11.0%)	1(1.7%)	84(18.4%)	85(16.4%)
LIVER FUNCTION TESTS ABNORMAL	35(4.5%)	4(6.7%)	42(9.2%)	46(8.9%)
DRY MOUTH/NOSE	54(7.0%)	0	43(9.4%)	43(8.3%)
JAUNDICE	25(3.2%)	0	33(7.2%)	33(6.4%)
DYSPHAGIA	30(3.9%)	1(1.7%)	28(6.1%)	29(5.6%)
STOMATITIS	31(4.0%)	0	24(5.3%)	24(4.6%)
ESOPHAGITIS	16(2.1%)	2(3.3%)	21(4.6%)	23(4.4%)
GASTROINTESTINAL DISORDER	26(3.4%)	0	16(3.5%)	16(3.1%)
VENOOCCLUSIVE LIVER DISEASE	15(1.9%)	0	15(3.3%)	15(2.9%)
ERUCTATION	15(1.9%)	0	14(3.1%)	14(2.7%)
FLATULENCE	19(2.5%)	1(1.7%)	11(2.4%)	12(2.3%)
HEMATEMESIS	19(2.5%)	0	11(2.4%)	11(2.1%)
GUM/ORAL HEMORRHAGE	10(1.3%)	0	10(2.2%)	10(1.9%)
HEPATOMEGALY	9(1.2%)	2(3.3%)	8(1.8%)	10(1.9%)
MELENA	29(3.8%)	0	10(2.2%)	10(1.9%)
MOUTH ULCERATION	7(0.9%)	0	10(2.2%)	10(1.9%)
COLITIS	21(2.7%)	0	8(1.8%)	8(1.5%)
GASTROENTERITIS	20(2.6%)	0	8(1.8%)	8(1.5%)
ENTERITIS	6(0.8%)	0	7(1.5%)	7(1.4%)
LEUKOPLAKIA OF MOUTH	7(0.9%)	0	7(1.5%)	7(1.4%)
RECTAL HEMORRHAGE	13(1.7%)	0	7(1.5%)	7(1.4%)
TOOTH DISORDER	13(1.7%)	0	7(1.5%)	7(1.4%)
GASTROINTESTINAL HEMORRHAGE	17(2.2%)	0	5(1.1%)	5(1.0%)
ILEUS	21(2.7%)	0	5(1.1%)	5(1.0%)
FECAL INCONTINENCE	11(1.4%)	0	4(0.9%)	4(0.8%)
GASTRITIS	16(2.1%)	0	4(0.9%)	4(0.8%)
ULCERATIVE STOMATITIS	0	3(5.0%)	1(0.2%)	4(0.8%)
GLOSSITIS	3(0.4%)	0	3(0.7%)	3(0.6%)
TONGUE DISORDER	2(0.3%)	0	3(0.7%)	3(0.6%)
APHTHOUS STOMATITIS	2(0.3%)	2(3.3%)	0	2(0.4%)

(1) STUDIES INCLUDED: 98-0-050, FG-21-09, AND 98-0-047. STUDY 98-0-047 ONLY INCLUDES PATIENTS < 16 YEARS OLD WHO RECEIVED 1 MG/KG/DAY AND >= 16 YEARS OLD WHO RECEIVED 50 MG/DAY DOSE OF FK463.
(2) WITHIN A BODY SYSTEM A PERSON MAY EXPERIENCE MORE THAN ONE ADVERSE EVENT.

Corresponds to Table R6 1 in the applicant's submission dated October 25, 2004.
FK463 = micafungin

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TABLE 18 (continued)

INCIDENCE OF TREATMENT EMERGENT ADVERSE EVENTS OF 50 MG FK463 AND FLUCONAZOLE
ALL TREATED PATIENTS (1)

BODY SYSTEM (2) COSTART TERM	FK463 (N=770)	FLUCONAZOLE 200 MG (N=60)	FLUCONAZOLE 400 MG (N=457)	FLUCONAZOLE TOTAL (N=517)
BLOODY DIARRHEA	0	0	2(0.4%)	2(0.4%)
ENTEROCOLITIS	4(0.5%)	0	2(0.4%)	2(0.4%)
ESOPHAGEAL ULCER	4(0.5%)	2(3.3%)	0	2(0.4%)
GINGIVITIS	7(0.9%)	0	2(0.4%)	2(0.4%)
HEPATIC FAILURE	0	0	2(0.4%)	2(0.4%)
HEPATOSPLENOMEGALY	3(0.4%)	0	2(0.4%)	2(0.4%)
PAROTID GLAND ENLARGEMENT	2(0.3%)	0	2(0.4%)	2(0.4%)
TONGUE EDEMA	1(0.1%)	0	2(0.4%)	2(0.4%)
ABNORMAL STOOLS	1(0.1%)	0	1(0.2%)	1(0.2%)
ACHLORHYDRIA	0	1(1.7%)	0	1(0.2%)
CHOLECYSTITIS	0	0	1(0.2%)	1(0.2%)
CHOLELITHIASIS	5(0.6%)	0	1(0.2%)	1(0.2%)
CHOLESTATIC JAUNDICE	1(0.1%)	0	1(0.2%)	1(0.2%)
DUODENITIS	1(0.1%)	0	1(0.2%)	1(0.2%)
ESOPHAGEAL HEMORRHAGE	0	0	1(0.2%)	1(0.2%)
GASTROINTESTINAL ANOMALY	0	1(1.7%)	0	1(0.2%)
GUM HYPERPLASIA	0	0	1(0.2%)	1(0.2%)
HEPATITIS, NONSPECIFIC	2(0.3%)	0	1(0.2%)	1(0.2%)
INTESTINAL STENOSIS	0	0	1(0.2%)	1(0.2%)
LIVER DAMAGE	2(0.3%)	0	1(0.2%)	1(0.2%)
PANCREATITIS	1(0.1%)	0	1(0.2%)	1(0.2%)
PSEUDOMEMBRANOUS COLITIS	0	0	1(0.2%)	1(0.2%)
SIALADENITIS	4(0.5%)	0	1(0.2%)	1(0.2%)
STOMACH ATONY	3(0.4%)	0	1(0.2%)	1(0.2%)
STOMACH ULCER	2(0.3%)	1(1.7%)	0	1(0.2%)
STOMACH ULCER HEMORRHAGE	0	0	1(0.2%)	1(0.2%)
DUODENAL ULCER	1(0.1%)	0	0	0
FECAL IMPACTION	1(0.1%)	0	0	0
GASTROINTESTINAL CARCINOMA	1(0.1%)	0	0	0
INTESTINAL OBSTRUCTION	1(0.1%)	0	0	0
PANCREAS DISORDER	2(0.3%)	0	0	0
PEPTIC ULCER	1(0.1%)	0	0	0
TOOTH CARIES	1(0.1%)	0	0	0
BODY AS A WHOLE				
ANY AE	627(81.4%)	33(55.0%)	441(96.5%)	474(91.7%)
FEVER	296(38.4%)	15(25.0%)	248(54.3%)	263(50.9%)
ASTHENIA	183(23.8%)	1(1.7%)	185(40.5%)	186(36.0%)
ABDOMINAL PAIN	218(28.3%)	5(8.3%)	170(37.2%)	175(33.8%)
INFECTION	186(24.2%)	5(8.3%)	155(33.9%)	160(30.9%)
PROCEDURAL COMPLICATION	160(20.8%)	0	160(35.0%)	160(30.9%)

(1) STUDIES INCLUDED: 98-0-050, FG-21-09, AND 98-0-047. STUDY 98-0-047 ONLY INCLUDES PATIENTS < 16 YEARS OLD WHO RECEIVED 1 MG/KG/DAY AND >= 16 YEARS OLD WHO RECEIVED 50 MG/DAY DOSE OF FK463.
(2) WITHIN A BODY SYSTEM A PERSON MAY EXPERIENCE MORE THAN ONE ADVERSE EVENT.

Corresponds to Table R6 1 in the applicant's submission dated October 25, 2004.
FK463 = micafungin

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TABLE 18 (continued)

INCIDENCE OF TREATMENT EMERGENT ADVERSE EVENTS OF 50 MG FK463 AND FLUCONAZOLE
ALL TREATED PATIENTS (1)

BODY SYSTEM (2) COSTART TERM	FK463 (N=770)	FLUCONAZOLE 200 MG (N=60)	FLUCONAZOLE 400 MG (N=457)	FLUCONAZOLE TOTAL (N=517)
SEPSIS	137(17.8%)	0	127(27.8%)	127(24.6%)
CHILLS	122(15.8%)	0	119(26.0%)	119(23.0%)
PAIN	117(15.2%)	3(5.0%)	84(18.4%)	87(16.8%)
BACK PAIN	80(10.4%)	3(5.0%)	62(13.6%)	65(12.6%)
ALLERGIC REACTION	61(7.9%)	1(1.7%)	49(10.5%)	49(9.5%)
ABDOMEN ENLARGED	51(6.6%)	0	43(9.4%)	43(8.3%)
FACE EDEMA	40(5.2%)	0	36(7.9%)	36(7.0%)
GRAFT VERSUS HOST DISEASE	42(5.5%)	0	33(7.2%)	33(6.4%)
TRANSFUSION REACTION	45(5.8%)	0	30(6.6%)	30(5.8%)
CACHEXIA	22(2.9%)	1(1.7%)	23(5.0%)	24(4.6%)
FLU SYNDROME	17(2.2%)	1(1.7%)	16(3.5%)	17(3.3%)
NECK PAIN	14(1.8%)	2(3.3%)	13(2.8%)	16(3.1%)
MALAISE	15(1.9%)	1(1.7%)	10(2.2%)	11(2.1%)
ACCIDENTAL INJURY	13(1.7%)	1(1.7%)	9(2.0%)	10(1.9%)
CELLULITIS	8(1.0%)	0	9(2.0%)	9(1.7%)
ASCITES	11(1.4%)	0	6(1.3%)	6(1.2%)
DRUG LEVEL INCREASED	3(0.4%)	0	5(1.1%)	5(1.0%)
LAB TEST ABNORMAL	10(1.3%)	0	5(1.1%)	5(1.0%)
TUBERCULOSIS AGGRAVATED	8(1.0%)	4(6.7%)	0	4(0.8%)
PELVIC PAIN	6(0.8%)	0	3(0.7%)	3(0.6%)
ABSCESS	6(0.8%)	0	2(0.4%)	2(0.4%)
CYST	0	0	2(0.4%)	2(0.4%)
HYPOTHERMIA	1(0.1%)	1(1.7%)	1(0.2%)	2(0.4%)
IMMUNOGLOBULINS DECREASED	0	0	2(0.4%)	2(0.4%)
MUCOUS MEMBRANE DISORDER	2(0.3%)	0	2(0.4%)	2(0.4%)
NECK RIGIDITY	2(0.3%)	1(1.7%)	1(0.2%)	2(0.4%)
NEOPLASM BENIGN	2(0.3%)	0	2(0.4%)	2(0.4%)
HYDROCEPHALUS	0	1(1.7%)	0	1(0.2%)
PRIMARY GRAFT DYSFUNCTION	1(0.1%)	0	1(0.2%)	1(0.2%)
ANAPHYLACTOID REACTION	2(0.3%)	0	0	0
CARCINOMA	1(0.1%)	0	0	0
HERNIA	2(0.3%)	0	0	0
NECROSIS	1(0.1%)	0	0	0
OVERDOSE	1(0.1%)	0	0	0
PERITONITIS	5(0.6%)	0	0	0
SARCOMA	2(0.3%)	0	0	0
SURGICAL TREATMENT	1(0.1%)	0	0	0
TUBERCULOSIS REACTIVATED	3(0.4%)	0	0	0
METABOLIC AND NUTRITIONAL DISORDERS				
ANY AE	571(74.2%)	17(28.3%)	431(94.3%)	448(86.7%)

(1) STUDIES INCLUDED: 98-0-050, FG-21-09, AND 98-0-047. STUDY 98-0-047 ONLY INCLUDES PATIENTS < 16 YEARS OLD WHO RECEIVED 1 MG/KG/DAY AND >= 16 YEARS OLD WHO RECEIVED 50 MG/DAY DOSE OF FK463.
(2) WITHIN A BODY SYSTEM A PERSON MAY EXPERIENCE MORE THAN ONE ADVERSE EVENT.

Corresponds to Table R6 1 in the applicant's submission dated October 25, 2004.
FK463 = micafungin

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TABLE 18 (continued)

INCIDENCE OF TREATMENT EMERGENT ADVERSE EVENTS OF 50 MG FK463 AND FLUCONAZOLE
ALL TREATED PATIENTS (1)

BODY SYSTEM (2) COSTART TERM	FK463 (N=770)	FLUCONAZOLE 200 MG (N=60)	FLUCONAZOLE 400 MG (N=457)	FLUCONAZOLE TOTAL (N=517)
HYPOMAGNESEMIA	266(34.5%)	0	269(58.6%)	268(51.8%)
HYPOKALEMIA	258(33.5%)	2(3.3%)	235(51.4%)	237(45.8%)
PERIPHERAL EDEMA	119(15.5%)	0	113(24.7%)	113(21.9%)
EDEMA	128(16.6%)	0	112(24.5%)	112(21.7%)
HYPERVOLEMIA	83(10.8%)	0	100(21.9%)	100(19.3%)
HYPERGLYCEMIA	80(10.4%)	1(1.7%)	93(20.4%)	94(18.2%)
HYPOCALCEMIA	102(13.2%)	2(3.3%)	90(19.7%)	92(17.8%)
BILIRUBINEMIA	74(9.6%)	0	71(15.5%)	71(13.7%)
HYPONATREMIA	66(8.6%)	3(5.0%)	68(14.9%)	71(13.7%)
HYPOPHOSPHATEMIA	84(10.9%)	0	71(15.5%)	71(13.7%)
HYPOPROTEINEMIA	50(6.5%)	3(5.0%)	43(9.4%)	46(8.9%)
HYPERKALEMIA	32(4.2%)	3(5.0%)	35(7.7%)	38(7.4%)
SGPT INCREASED	49(6.4%)	0	36(7.9%)	36(7.0%)
CREATININE INCREASED	41(5.3%)	0	35(7.7%)	35(6.8%)
SGOT INCREASED	50(6.5%)	1(1.7%)	29(6.3%)	30(5.8%)
ALKALINE PHOSPHATASE INCREASED	34(4.4%)	3(5.0%)	15(3.3%)	18(3.5%)
BUN INCREASED	23(3.0%)	0	18(3.9%)	18(3.5%)
LACTIC DEHYDROGENASE INCREASED	16(2.1%)	2(3.3%)	16(3.5%)	18(3.5%)
DEHYDRATION	20(2.6%)	2(3.3%)	13(2.8%)	15(2.9%)
ACIDOSIS	27(3.5%)	0	13(2.8%)	13(2.5%)
WEIGHT LOSS	16(2.1%)	0	13(2.8%)	13(2.5%)
WEIGHT GAIN	15(1.9%)	0	12(2.6%)	12(2.3%)
HYPERPHOSPHATEMIA	11(1.4%)	0	9(2.0%)	9(1.7%)
HYPERMAGNESEMIA	7(0.9%)	0	8(1.8%)	8(1.5%)
HYPOGLYCEMIA	21(2.7%)	1(1.7%)	6(1.3%)	7(1.4%)
HYPERCHLOREMIA	12(1.6%)	0	6(1.3%)	6(1.2%)
HYPERLIPEMIA	2(0.3%)	0	6(1.3%)	6(1.2%)
CREATININE CLEARANCE DECREASED	1(0.1%)	0	5(1.1%)	5(1.0%)
DECREASED BICARBONATE	5(0.6%)	0	5(1.1%)	5(1.0%)
HEALING ABNORMAL	5(0.6%)	0	5(1.1%)	5(1.0%)
HYPERNATREMIA	15(1.9%)	1(1.7%)	3(0.7%)	4(0.8%)
HYPERURICEMIA	1(0.1%)	0	4(0.9%)	4(0.8%)
HYPOCHLOREMIA	9(1.2%)	0	4(0.9%)	4(0.8%)
HYPOVOLEMIA	2(0.3%)	0	4(0.9%)	4(0.8%)
RESPIRATORY ALKALOSIS	12(1.6%)	0	4(0.9%)	4(0.8%)
ALKALOSIS	5(0.6%)	0	2(0.4%)	2(0.4%)
AMYLASE INCREASED	0	0	2(0.4%)	2(0.4%)
GAMMA GLUTAMYL TRANSPEPTIDASE INCREASED	0	0	2(0.4%)	2(0.4%)
GLYCOSURIA	3(0.4%)	0	2(0.4%)	2(0.4%)
RESPIRATORY ACIDOSIS	5(0.6%)	0	2(0.4%)	2(0.4%)
THIRST	0	0	2(0.4%)	2(0.4%)

(1) STUDIES INCLUDED: 98-0-050, FG-21-09, AND 98-0-047. STUDY 98-0-047 ONLY INCLUDES PATIENTS < 16 YEARS OLD WHO RECEIVED 1 MG/KG/DAY AND >= 16 YEARS OLD WHO RECEIVED 50 MG/DAY DOSE OF FK463.
(2) WITHIN A BODY SYSTEM A PERSON MAY EXPERIENCE MORE THAN ONE ADVERSE EVENT.

Corresponds to Table R6 1 in the applicant's submission dated October 25, 2004.
FK463 = micafungin

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TABLE 18 (continued)

INCIDENCE OF TREATMENT EMERGENT ADVERSE EVENTS OF 50 MG FK463 AND FLUCONAZOLE
ALL TREATED PATIENTS (1)

BODY SYSTEM (2) COSTART TERM	FK463 (N=770)	FLUCONAZOLE 200 MG (N=60)	FLUCONAZOLE 400 MG (N=457)	FLUCONAZOLE TOTAL (N=517)
AVITAMINOSIS	0	0	1(0.2%)	1(0.2%)
HYPERAMMONEMIA	0	0	1(0.2%)	1(0.2%)
HYPERCALCEMIA	2(0.3%)	0	1(0.2%)	1(0.2%)
HYPOGLYCEMIC REACTION	0	0	1(0.2%)	1(0.2%)
KETOSIS	4(0.5%)	0	1(0.2%)	1(0.2%)
ELECTROLYTE ABNORMALITY	4(0.5%)	0	0	0
GLOBULIN INCREASED	1(0.1%)	0	0	0
GOUT	1(0.1%)	0	0	0
HYPOCHOLESTEREMIA	1(0.1%)	0	0	0
HEMIC AND LYMPHATIC SYSTEM				
ANY AR	508(66.0%)	13(21.7%)	422(92.3%)	435(84.1%)
LEUKOPENIA	366(47.5%)	8(13.3%)	346(75.7%)	354(68.5%)
THROMBOCYTOPENIA	338(43.9%)	2(3.3%)	321(70.2%)	323(62.5%)
ANEMIA	194(25.2%)	3(5.0%)	193(42.2%)	196(37.9%)
PETECHIA	44(5.7%)	0	40(8.8%)	40(7.7%)
ECCHYMOSIS	34(4.4%)	0	28(6.1%)	28(5.4%)
COAGULATION DISORDER	18(2.3%)	0	21(4.6%)	21(4.1%)
PANCYTOPENIA	11(1.4%)	0	11(2.4%)	11(2.1%)
PROTHROMBIN DECREASED	10(1.3%)	0	10(2.2%)	10(1.9%)
LEUKOCYTOSIS	11(1.4%)	0	6(1.3%)	6(1.2%)
LYMPHADENOPATHY	7(0.9%)	1(1.7%)	4(0.9%)	5(1.0%)
SPLENOMEGALY	5(0.6%)	0	5(1.1%)	5(1.0%)
BLEEDING TIME INCREASED	2(0.3%)	0	2(0.4%)	2(0.4%)
EOSINOPHILIA	4(0.5%)	2(3.3%)	0	2(0.4%)
THROMBOPLASTIN DECREASED	2(0.3%)	0	2(0.4%)	2(0.4%)
WBC ABNORMAL	16(2.1%)	0	2(0.4%)	2(0.4%)
HYPOCHROMIC ANEMIA	0	1(1.7%)	0	1(0.2%)
PURPURA	3(0.4%)	0	1(0.2%)	1(0.2%)
CYANOSIS	3(0.4%)	0	0	0
ERYTHROCYTES ABNORMAL	1(0.1%)	0	0	0
FIBRINOGEN INCREASED	1(0.1%)	0	0	0
HEMOLYSIS	1(0.1%)	0	0	0
HEMOLYTIC ANEMIA	1(0.1%)	0	0	0
LEUKEMIA	1(0.1%)	0	0	0
RETICULOENDOTHELIAL HYPERPLASIA	1(0.1%)	0	0	0
SPLEEN DISORDER	1(0.1%)	0	0	0
THROMBOCYTHEMIA	8(1.0%)	0	0	0
NERVOUS SYSTEM				
ANY AR	477(61.9%)	20(33.3%)	346(75.7%)	366(70.8%)

(1) STUDIES INCLUDED: 98-0-050, FG-21-09, AND 98-0-047. STUDY 98-0-047 ONLY INCLUDES PATIENTS < 16 YEARS OLD WHO RECEIVED 1 MG/KG/DAY AND >= 16 YEARS OLD WHO RECEIVED 50 MG/DAY DOSE OF FK463.
(2) WITHIN A BODY SYSTEM A PERSON MAY EXPERIENCE MORE THAN ONE ADVERSE EVENT.

Corresponds to Table R6 1 in the applicant's submission dated October 25, 2004.
FK463 = micafungin

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TABLE 18 (continued)

INCIDENCE OF TREATMENT EMERGENT ADVERSE EVENTS OF 50 MG FK463 AND FLUCONAZOLE
ALL TREATED PATIENTS (1)

BODY SYSTEM (2) COSTART TERM	FK463 (N=770)	FLUCONAZOLE 200 MG (N=60)	FLUCONAZOLE 400 MG (N=457)	FLUCONAZOLE TOTAL (N=517)
HEADACHE	230(29.9%)	6(10.0%)	167(36.5%)	173(33.5%)
INSOMNIA	174(22.6%)	3(5.0%)	148(32.4%)	151(29.2%)
ANXIETY	109(14.2%)	1(1.7%)	92(20.1%)	93(18.0%)
DIZZINESS	67(8.7%)	6(10.0%)	83(18.2%)	89(17.2%)
DEPRESSION	35(4.5%)	2(3.3%)	39(8.5%)	41(7.9%)
SOMNOLENCE	35(4.5%)	4(6.7%)	34(7.4%)	38(7.4%)
CONFUSION	51(6.6%)	0	33(7.2%)	33(6.4%)
TREMOR	25(3.2%)	0	32(7.0%)	32(6.2%)
PARESTHESIA	41(5.3%)	1(1.7%)	25(5.5%)	26(5.0%)
NERVOUSNESS	39(5.1%)	0	16(3.5%)	16(3.1%)
AGITATION	24(3.1%)	0	15(3.3%)	15(2.9%)
HALLUCINATIONS	14(1.8%)	0	11(2.4%)	11(2.1%)
CONVULSION	10(1.3%)	1(1.7%)	7(1.5%)	8(1.5%)
THINKING ABNORMAL	4(0.5%)	0	8(1.8%)	8(1.5%)
ABNORMAL DREAMS	13(1.7%)	0	5(1.1%)	5(1.0%)
ABNORMAL GAIT	6(0.8%)	0	5(1.1%)	5(1.0%)
DYSTONIA	2(0.3%)	0	5(1.1%)	5(1.0%)
EMOTIONAL LABILITY	5(0.6%)	0	4(0.9%)	4(0.8%)
INCREASED SALIVATION	0	0	4(0.9%)	4(0.8%)
NYSTAGMUS	1(0.1%)	0	4(0.9%)	4(0.8%)
VERTIGO	0	0	4(0.9%)	4(0.8%)
DELIRIUM	6(0.8%)	0	3(0.7%)	3(0.6%)
HYPERTONIA	6(0.8%)	0	3(0.7%)	3(0.6%)
WITHDRAWAL SYNDROME	1(0.1%)	0	3(0.7%)	3(0.6%)
GRAND MAL CONVULSION	0	0	2(0.4%)	2(0.4%)
HYPERKINESIA	0	0	2(0.4%)	2(0.4%)
MENINGITIS	4(0.5%)	2(3.3%)	0	2(0.4%)
SPEECH DISORDER	3(0.4%)	0	2(0.4%)	2(0.4%)
ADDICTION	0	0	1(0.2%)	1(0.2%)
AKATHISIA	0	0	1(0.2%)	1(0.2%)
APATHY	1(0.1%)	0	1(0.2%)	1(0.2%)
ATAXIA	0	0	1(0.2%)	1(0.2%)
BRAIN ABSCESS	0	0	1(0.2%)	1(0.2%)
CEREBRAL HEMORRHAGE	0	0	1(0.2%)	1(0.2%)
CEREBROVASCULAR ACCIDENT	1(0.1%)	0	1(0.2%)	1(0.2%)
COMA	4(0.5%)	1(1.7%)	0	1(0.2%)
DEMENTIA	0	1(1.7%)	0	1(0.2%)
ENCEPHALITIS	0	0	1(0.2%)	1(0.2%)
ENCEPHALOPATHY	3(0.4%)	0	1(0.2%)	1(0.2%)
EXTRAPYRAMIDAL SYNDROME	3(0.4%)	0	1(0.2%)	1(0.2%)
MYOCLONUS	1(0.1%)	0	1(0.2%)	1(0.2%)

(1) STUDIES INCLUDED: 98-0-050, FG-21-09, AND 98-0-047. STUDY 98-0-047 ONLY INCLUDES PATIENTS < 16 YEARS OLD WHO RECEIVED 1 MG/KG/DAY AND >= 16 YEARS OLD WHO RECEIVED 50 MG/DAY DOSE OF FK463.
(2) WITHIN A BODY SYSTEM A PERSON MAY EXPERIENCE MORE THAN ONE ADVERSE EVENT.

Corresponds to Table R6 1 in the applicant's submission dated October 25, 2004.
FK463 = micafungin

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TABLE 18 (continued)

INCIDENCE OF TREATMENT EMERGENT ADVERSE EVENTS OF 50 MG FK463 AND FLUCONAZOLE
ALL TREATED PATIENTS (1)

BODY SYSTEM (2) COSTART TERM	FK463 (N=770)	FLUCONAZOLE 200 MG (N=60)	FLUCONAZOLE 400 MG (N=457)	FLUCONAZOLE TOTAL (N=517)
NEURITIS	2(0.3%)	0	1(0.2%)	1(0.2%)
NEUROPATHY	5(0.6%)	0	1(0.2%)	1(0.2%)
PSYCHOSIS	0	1(1.7%)	0	1(0.2%)
STUPOR	3(0.4%)	0	1(0.2%)	1(0.2%)
APHASIA	2(0.3%)	0	0	0
CNS DEPRESSION	1(0.1%)	0	0	0
CNS NEOPLASIA BENIGN	1(0.1%)	0	0	0
HEMIPLEGIA	1(0.1%)	0	0	0
HOSTILITY	4(0.5%)	0	0	0
HYPERESTHESIA	1(0.1%)	0	0	0
INTRACRANIAL HEMORRHAGE	1(0.1%)	0	0	0
INTRACRANIAL HYPERTENSION	1(0.1%)	0	0	0
MOVEMENT DISORDER	1(0.1%)	0	0	0
NEURALGIA	4(0.5%)	0	0	0
PARANOID REACTION	1(0.1%)	0	0	0
PERSONALITY DISORDER	1(0.1%)	0	0	0
VOCAL CORD PARALYSIS	1(0.1%)	0	0	0
RESPIRATORY SYSTEM				
ANY AE	446(57.9%)	14(23.3%)	350(76.6%)	364(70.4%)
COUGH INCREASED	128(16.6%)	2(3.3%)	119(26.0%)	121(23.4%)
LUNG DISORDER	99(12.9%)	0	91(19.9%)	91(17.6%)
RHINITIS	85(11.0%)	2(3.3%)	87(19.0%)	89(17.2%)
DYSPNEA	98(12.7%)	1(1.7%)	86(18.8%)	87(16.8%)
EPISTAXIS	62(8.1%)	1(1.7%)	85(18.6%)	86(16.6%)
PHARYNGITIS	61(7.9%)	2(3.3%)	69(15.1%)	71(13.7%)
HICCUP	42(5.5%)	1(1.7%)	57(12.5%)	58(11.2%)
PNEUMONIA	51(6.6%)	5(8.3%)	25(5.5%)	30(5.8%)
HYPOXIA	32(4.2%)	0	27(5.9%)	27(5.2%)
ASTHMA	36(4.7%)	1(1.7%)	25(5.5%)	26(5.0%)
HYPERVENTILATION	22(2.9%)	1(1.7%)	21(4.6%)	22(4.3%)
LUNG EDEMA	16(2.1%)	0	18(3.9%)	18(3.5%)
PLEURAL EFFUSION	20(2.6%)	0	18(3.9%)	18(3.5%)
SINUSITIS	23(3.0%)	1(1.7%)	16(3.5%)	17(3.3%)
HEMOPTYSIS	18(2.3%)	1(1.7%)	10(2.2%)	11(2.1%)
APNEA	5(0.6%)	0	7(1.5%)	7(1.4%)
ATELECTASIS	10(1.3%)	0	7(1.5%)	7(1.4%)
LUNG HEMORRHAGE	3(0.4%)	0	6(1.3%)	6(1.2%)
RESPIRATORY DISORDER	14(1.8%)	0	6(1.3%)	6(1.2%)
RESPIRATORY FAILURE	22(2.9%)	0	6(1.3%)	6(1.2%)
VOICE ALTERATION	2(0.3%)	0	3(0.7%)	3(0.6%)

(1) STUDIES INCLUDED: 98-0-050, FG-21-09, AND 98-0-047. STUDY 98-0-047 ONLY INCLUDES PATIENTS < 16 YEARS OLD WHO RECEIVED 1 MG/KG/DAY AND >= 16 YEARS OLD WHO RECEIVED 50 MG/DAY DOSE OF FK463.
(2) WITHIN A BODY SYSTEM A PERSON MAY EXPERIENCE MORE THAN ONE ADVERSE EVENT.

Corresponds to Table R6 1 in the applicant's submission dated October 25, 2004.
FK463 = micafungin

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TABLE 18 (continued)

INCIDENCE OF TREATMENT EMERGENT ADVERSE EVENTS OF 50 MG FK463 AND FLUCONAZOLE
ALL TREATED PATIENTS (1)

BODY SYSTEM (2) COSTART TERM	FK463 (N=770)	FLUCONAZOLE 200 MG (N=60)	FLUCONAZOLE 400 MG (N=457)	FLUCONAZOLE TOTAL (N=517)
BRONCHITIS	5(0.6%)	2(3.3%)	0	2(0.4%)
EMPHYSEMA	1(0.1%)	0	2(0.4%)	2(0.4%)
HYPOVENTILATION	0	0	2(0.4%)	2(0.4%)
PLEURAL DISORDER	3(0.4%)	1(1.7%)	1(0.2%)	2(0.4%)
RESPIRATORY DISTRESS SYNDROME	5(0.6%)	0	2(0.4%)	2(0.4%)
BRONCHIECTASIS	0	1(1.7%)	0	1(0.2%)
LARYNGITIS	1(0.1%)	0	1(0.2%)	1(0.2%)
SPUTUM INCREASED	1(0.1%)	0	1(0.2%)	1(0.2%)
STRIDOR	3(0.4%)	0	1(0.2%)	1(0.2%)
INTERSTITIAL PNEUMONIA	1(0.1%)	0	0	0
PNEUMOTHORAX	1(0.1%)	0	0	0
PULMONARY EMBOLUS	1(0.1%)	0	0	0
PULMONARY HYPERTENSION	2(0.3%)	0	0	0
PULMONARY TUBERCULOSIS REACTIVATED	1(0.1%)	0	0	0
CARDIOVASCULAR SYSTEM				
ANY AE	394(51.2%)	6(10.0%)	327(71.6%)	333(64.4%)
HYPERTENSION	111(14.4%)	1(1.7%)	117(25.6%)	118(22.8%)
TACHYCARDIA	133(17.3%)	0	112(24.5%)	112(21.7%)
HYPOTENSION	111(14.4%)	2(3.3%)	90(19.7%)	92(17.8%)
VASODILATATION	67(8.7%)	0	73(16.0%)	73(14.1%)
CHEST PAIN	69(9.0%)	3(5.0%)	63(13.8%)	66(12.8%)
BRADYCARDIA	20(2.6%)	1(1.7%)	18(3.9%)	19(3.7%)
POSTURAL HYPOTENSION	14(1.8%)	0	18(3.9%)	18(3.5%)
ATRIAL FIBRILLATION	17(2.2%)	0	12(2.6%)	12(2.3%)
VALVULAR HEART DISEASE	7(0.9%)	0	11(2.4%)	11(2.1%)
ARRHYTHMIA	18(2.3%)	0	10(2.2%)	10(1.9%)
HEMORRHAGE	10(1.3%)	1(1.7%)	9(2.0%)	10(1.9%)
SYNCOPE	12(1.6%)	0	10(2.2%)	10(1.9%)
CONGESTIVE HEART FAILURE	7(0.9%)	0	9(2.0%)	9(1.7%)
CARDIOMEGALY	8(1.0%)	0	8(1.8%)	8(1.5%)
SINUS BRADYCARDIA	2(0.3%)	0	7(1.5%)	7(1.4%)
THROMBOPHLEBITIS	5(0.6%)	0	5(1.1%)	5(1.0%)
CARDIOVASCULAR DISORDER	4(0.5%)	0	4(0.9%)	4(0.8%)
HEART ARREST	2(0.3%)	0	4(0.9%)	4(0.8%)
PALLOR	5(0.6%)	1(1.7%)	3(0.7%)	4(0.8%)
PALPITATION	4(0.5%)	1(1.7%)	3(0.7%)	4(0.8%)
PERICARDIAL EFFUSION	6(0.8%)	0	4(0.9%)	4(0.8%)
SHOCK	16(2.1%)	0	4(0.9%)	4(0.8%)
DEEP THROMBOPHLEBITIS	10(1.3%)	0	3(0.7%)	3(0.6%)
MIGRAINE	3(0.4%)	0	3(0.7%)	3(0.6%)

(1) STUDIES INCLUDED: 98-0-050, FG-21-09, AND 98-0-047. STUDY 98-0-047 ONLY INCLUDES PATIENTS < 16 YEARS OLD WHO RECEIVED 1 MG/KG/DAY AND >= 16 YEARS OLD WHO RECEIVED 50 MG/DAY DOSE OF FK463.
(2) WITHIN A BODY SYSTEM A PERSON MAY EXPERIENCE MORE THAN ONE ADVERSE EVENT.

Corresponds to Table R6 1 in the applicant's submission dated October 25, 2004.
FK463 = micafungin

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TABLE 18 (continued)

INCIDENCE OF TREATMENT EMERGENT ADVERSE EVENTS OF 50 MG FK463 AND FLUCONAZOLE
ALL TREATED PATIENTS (1)

BODY SYSTEM (2) COSTART TERM	FK463 (N=770)	FLUCONAZOLE 200 MG (N=60)	FLUCONAZOLE 400 MG (N=457)	FLUCONAZOLE TOTAL (N=517)
ATRIAL FLUTTER	4(0.5%)	0	2(0.4%)	2(0.4%)
EXTRASYSTOLES	1(0.1%)	0	2(0.4%)	2(0.4%)
PERIPHERAL VASCULAR DISORDER	6(0.8%)	0	2(0.4%)	2(0.4%)
PHLEBITIS	13(1.7%)	0	2(0.4%)	2(0.4%)
SUBDURAL HEMATOMA	0	0	2(0.4%)	2(0.4%)
THROMBOSIS	0	0	2(0.4%)	2(0.4%)
VENTRICULAR EXTRASYSTOLES	1(0.1%)	0	2(0.4%)	2(0.4%)
CARDIOMYOPATHY	0	0	1(0.2%)	1(0.2%)
ELECTROCARDIOGRAM ABNORMAL	4(0.5%)	0	1(0.2%)	1(0.2%)
EMBOLUS	0	0	1(0.2%)	1(0.2%)
ENDOCARDITIS	1(0.1%)	0	1(0.2%)	1(0.2%)
MYOCARDIAL INFARCT	0	0	1(0.2%)	1(0.2%)
MYOCARDIAL ISCHEMIA	1(0.1%)	0	1(0.2%)	1(0.2%)
PERICARDITIS	1(0.1%)	0	1(0.2%)	1(0.2%)
T INVERTED	0	0	1(0.2%)	1(0.2%)
VARICOSE VEIN	0	0	1(0.2%)	1(0.2%)
VASCULAR ANOMALY	0	0	1(0.2%)	1(0.2%)
ANGINA PECTORIS	1(0.1%)	0	0	0
ARTERIOSCLEROSIS	1(0.1%)	0	0	0
AV BLOCK COMPLETE	1(0.1%)	0	0	0
HEART FAILURE	2(0.3%)	0	0	0
INCREASED CAPILLARY FRAGILITY	1(0.1%)	0	0	0
SUPRAVENTRICULAR TACHYCARDIA	2(0.3%)	0	0	0
VASCULAR DISORDER	1(0.1%)	0	0	0
VENTRICULAR ARRHYTHMIA	2(0.3%)	0	0	0
VENTRICULAR TACHYCARDIA	4(0.5%)	0	0	0
SKIN AND APPENDAGES				
ANY AE	374(48.6%)	13(21.7%)	308(67.4%)	321(62.1%)
RASH	209(27.1%)	0	187(40.9%)	187(36.2%)
PRURITUS	95(12.3%)	1(1.7%)	93(20.4%)	94(18.2%)
DRY SKIN	27(3.5%)	1(1.7%)	32(7.0%)	33(6.4%)
SKIN DISORDER	48(6.2%)	2(3.3%)	29(6.3%)	31(6.0%)
ALOPECIA	31(4.0%)	0	29(6.3%)	29(5.6%)
SWEATING	31(4.0%)	2(3.3%)	26(5.7%)	28(5.4%)
HERPES SIMPLEX	19(2.5%)	4(6.7%)	12(2.6%)	16(3.1%)
MACULOPAPULAR RASH	25(3.2%)	1(1.7%)	14(3.1%)	15(2.9%)
URTICARIA	23(3.0%)	1(1.7%)	12(2.6%)	13(2.5%)
FOLLICULITIS	30(3.9%)	0	12(2.6%)	12(2.3%)
SKIN DISCOLORATION	12(1.6%)	1(1.7%)	11(2.4%)	12(2.3%)
VESICULOBULLOUS RASH	10(1.3%)	0	10(2.2%)	10(1.9%)

(1) STUDIES INCLUDED: 98-0-050, FG-21-09, AND 98-0-047. STUDY 98-0-047 ONLY INCLUDES PATIENTS < 16 YEARS OLD WHO RECEIVED 1 MG/KG/DAY AND >= 16 YEARS OLD WHO RECEIVED 50 MG/DAY DOSE OF FK463.
(2) WITHIN A BODY SYSTEM A PERSON MAY EXPERIENCE MORE THAN ONE ADVERSE EVENT.

Corresponds to Table R6 1 in the applicant's submission dated October 25, 2004.
FK463 = micafungin

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TABLE 18 (continued)

INCIDENCE OF TREATMENT EMERGENT ADVERSE EVENTS OF 50 MG FK463 AND FLUCONAZOLE
ALL TREATED PATIENTS (1)

BODY SYSTEM (2) COSTART TERM	FK463 (N=770)	FLUCONAZOLE 200 MG (N=60)	FLUCONAZOLE 400 MG (N=457)	FLUCONAZOLE TOTAL (N=517)
PETECHIAL RASH	6(0.8%)	0	9(2.0%)	9(1.7%)
SKIN ULCER	14(1.8%)	1(1.7%)	6(1.3%)	7(1.4%)
EXFOLIATIVE DERMATITIS	5(0.6%)	0	5(1.1%)	5(1.0%)
HERPES ZOSTER	8(1.0%)	0	4(0.9%)	4(0.8%)
ACNE	8(1.0%)	0	3(0.7%)	3(0.6%)
ANGIOEDEMA	2(0.3%)	0	2(0.4%)	2(0.4%)
CONTACT DERMATITIS	2(0.3%)	0	2(0.4%)	2(0.4%)
ECZEMA	1(0.1%)	1(1.7%)	0	1(0.2%)
HAIR DISORDER	0	0	1(0.2%)	1(0.2%)
NAIL DISORDER	2(0.3%)	0	1(0.2%)	1(0.2%)
PSORIASIS	0	0	1(0.2%)	1(0.2%)
SKIN NODULE	2(0.3%)	0	1(0.2%)	1(0.2%)
BREAST PAIN	2(0.3%)	0	0	0
PUSTULAR RASH	3(0.4%)	0	0	0
SEBORRHEA	1(0.1%)	0	0	0
SKIN INFECTION	2(0.3%)	0	0	0
SUBCUTANEOUS NODULE	1(0.1%)	0	0	0
SUNBURN	1(0.1%)	0	0	0
UROGENITAL SYSTEM				
ANY AR	242(31.4%)	7(11.7%)	222(48.6%)	229(44.3%)
HEMATURIA	73(9.5%)	0	71(15.5%)	71(13.7%)
DYSURIA	43(5.6%)	0	43(9.4%)	43(8.3%)
OLIGURIA	44(5.7%)	0	32(7.0%)	32(6.2%)
URINARY TRACT INFECTION	29(3.8%)	2(3.3%)	21(4.6%)	23(4.4%)
URINARY FREQUENCY	16(2.1%)	2(3.3%)	19(4.2%)	21(4.1%)
KIDNEY FUNCTION ABNORMAL	10(1.3%)	0	19(4.2%)	19(3.7%)
VAGINAL HEMORRHAGE	11(1.4%)	0	19(4.2%)	19(3.7%)
ALBUMINURIA	9(1.2%)	0	16(3.5%)	16(3.1%)
CYSTITIS	15(1.9%)	0	16(3.5%)	16(3.1%)
KIDNEY FAILURE	13(1.7%)	0	13(2.8%)	13(2.5%)
URINARY INCONTINENCE	19(2.5%)	0	13(2.8%)	13(2.5%)
URINE ABNORMALITY	6(0.8%)	2(3.3%)	9(2.0%)	11(2.1%)
VAGINITIS	11(1.4%)	1(1.7%)	10(2.2%)	11(2.1%)
PENIS DISORDER	5(0.6%)	0	9(2.0%)	9(1.7%)
URINARY RETENTION	6(0.8%)	0	9(2.0%)	9(1.7%)
HEMORRHAGIC CYSTITIS	5(0.6%)	0	8(1.8%)	8(1.5%)
ACUTE KIDNEY FAILURE	8(1.0%)	0	7(1.5%)	7(1.4%)
URINARY URGENCY	3(0.4%)	0	7(1.5%)	7(1.4%)
URINATION IMPAIRED	4(0.5%)	0	7(1.5%)	7(1.4%)
SCROTAL EDEMA	5(0.6%)	0	6(1.3%)	6(1.2%)

(1) STUDIES INCLUDED: 98-0-050, FG-21-09, AND 98-0-047. STUDY 98-0-047 ONLY INCLUDES PATIENTS < 16 YEARS OLD WHO RECEIVED 1 MG/KG/DAY AND >= 16 YEARS OLD WHO RECEIVED 50 MG/DAY DOSE OF FK463.
(2) WITHIN A BODY SYSTEM A PERSON MAY EXPERIENCE MORE THAN ONE ADVERSE EVENT.

Corresponds to Table R6 1 in the applicant's submission dated October 25, 2004.
FK463 = micafungin

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TABLE 18 (continued)

INCIDENCE OF TREATMENT EMERGENT ADVERSE EVENTS OF 50 MG FK463 AND FLUCONAZOLE
ALL TREATED PATIENTS (1)

BODY SYSTEM (2) COSTART TERM	FK463 (N=770)	FLUCONAZOLE 200 MG (N=60)	FLUCONAZOLE 400 MG (N=457)	FLUCONAZOLE TOTAL (N=517)
POLYURIA	4(0.5%)	1(1.7%)	3(0.7%)	4(0.8%)
TESTIS DISORDER	2(0.3%)	0	4(0.9%)	4(0.8%)
LEUKORRHEA	0	0	2(0.4%)	2(0.4%)
METRORRHAGIA	1(0.1%)	0	2(0.4%)	2(0.4%)
NOCTURIA	2(0.3%)	0	2(0.4%)	2(0.4%)
URETHRAL PAIN	1(0.1%)	0	2(0.4%)	2(0.4%)
VULVOVAGINITIS	0	0	2(0.4%)	2(0.4%)
ANURIA	1(0.1%)	0	1(0.2%)	1(0.2%)
DYSMENORRHEA	0	0	1(0.2%)	1(0.2%)
KIDNEY PAIN	1(0.1%)	0	1(0.2%)	1(0.2%)
KIDNEY TUBULAR DISORDER	0	0	1(0.2%)	1(0.2%)
POLYCYSTIC KIDNEY	0	0	1(0.2%)	1(0.2%)
SALPINGITIS	0	1(1.7%)	0	1(0.2%)
BALANITIS	1(0.1%)	0	0	0
CARCINOMA RENAL	1(0.1%)	0	0	0
MENORRHAGIA	1(0.1%)	0	0	0
OVARIAN DISORDER	1(0.1%)	0	0	0
PROSTATIC DISORDER	1(0.1%)	0	0	0
PYELONEPHRITIS	1(0.1%)	0	0	0
SPECIAL SENSES				
ANY AE	143(18.6%)	3(5.0%)	115(25.2%)	118(22.8%)
ABNORMAL VISION	27(3.5%)	0	29(6.3%)	29(5.6%)
DRY EYES	21(2.7%)	0	19(4.2%)	19(3.7%)
EAR PAIN	24(3.1%)	1(1.7%)	17(3.7%)	18(3.5%)
EYE HEMORRHAGE	16(2.1%)	0	16(3.5%)	16(3.1%)
CONJUNCTIVITIS	13(1.7%)	2(3.3%)	12(2.6%)	14(2.7%)
TASTE PERVERSION	20(2.6%)	0	11(2.4%)	11(2.1%)
EYE PAIN	13(1.7%)	0	9(2.0%)	9(1.7%)
EAR DISORDER	9(1.2%)	0	5(1.1%)	5(1.0%)
DIPLOPIA	0	0	4(0.9%)	4(0.8%)
ANISOCORIA	1(0.1%)	0	3(0.7%)	3(0.6%)
CONJUNCTIVAL EDEMA	3(0.4%)	0	2(0.4%)	2(0.4%)
EYE DISORDER	2(0.3%)	0	2(0.4%)	2(0.4%)
IMPAIRED HEARING	6(0.8%)	0	2(0.4%)	2(0.4%)
OTITIS MEDIA	1(0.1%)	0	2(0.4%)	2(0.4%)
PHOTOPHOBIA	4(0.5%)	0	2(0.4%)	2(0.4%)
EXTRAOCULAR PALSY	0	0	1(0.2%)	1(0.2%)
TASTE LOSS	3(0.4%)	0	1(0.2%)	1(0.2%)
TINNITUS	3(0.4%)	0	1(0.2%)	1(0.2%)
BLEPHARITIS	1(0.1%)	0	0	0

(1) STUDIES INCLUDED: 98-0-050, FG-21-09, AND 98-0-047. STUDY 98-0-047 ONLY INCLUDES PATIENTS < 16 YEARS OLD WHO RECEIVED 1 MG/KG/DAY AND >= 16 YEARS OLD WHO RECEIVED 50 MG/DAY DOSE OF FK463.
(2) WITHIN A BODY SYSTEM A PERSON MAY EXPERIENCE MORE THAN ONE ADVERSE EVENT.

Corresponds to Table R6 1 in the applicant's submission dated October 25, 2004.
FK463 = micafungin

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TABLE 18 (continued)

INCIDENCE OF TREATMENT EMERGENT ADVERSE EVENTS OF 50 MG FK463 AND FLUCONAZOLE
ALL TREATED PATIENTS (1)

BODY SYSTEM (2) COSTART TERM	FK463 (N=770)	FLUCONAZOLE 200 MG (N=60)	FLUCONAZOLE 400 MG (N=457)	FLUCONAZOLE TOTAL (N=517)
CORNEAL LESION	1(0.1%)	0	0	0
DEAFNESS	3(0.4%)	0	0	0
EXOPHTHALMOS	1(0.1%)	0	0	0
LACRIMATION DISORDER	6(0.8%)	0	0	0
MIOSIS	3(0.4%)	0	0	0
OTITIS EXTERNA	4(0.5%)	0	0	0
PAROSMIA	1(0.1%)	0	0	0
RETINAL DISORDER	2(0.3%)	0	0	0
RETINAL HEMORRHAGE	2(0.3%)	0	0	0
RETINITIS	1(0.1%)	0	0	0
SCLERITIS	1(0.1%)	0	0	0
STRABISMUS	1(0.1%)	0	0	0
UVEITIS	1(0.1%)	0	0	0
MUSCULOSKELETAL SYSTEM				
ANY AE	148(19.2%)	2(3.3%)	114(24.9%)	116(22.4%)
ARTHRALGIA	64(8.3%)	0	57(12.5%)	57(11.0%)
BONE PAIN	33(4.3%)	0	32(7.0%)	32(6.2%)
MYALGIA	26(3.4%)	1(1.7%)	23(5.0%)	24(4.6%)
CRAMPS	21(2.7%)	0	13(2.8%)	13(2.5%)
MYASTHENIA	13(1.7%)	0	9(2.0%)	9(1.7%)
ARTHROSIS	3(0.4%)	0	3(0.7%)	3(0.6%)
TWITCHING	5(0.6%)	0	2(0.4%)	2(0.4%)
BONE DISORDER	5(0.6%)	0	1(0.2%)	1(0.2%)
GENERALIZED SPASM	1(0.1%)	0	1(0.2%)	1(0.2%)
JOINT DISORDER	4(0.5%)	0	1(0.2%)	1(0.2%)
MUSCLE ATROPHY	0	1(1.7%)	0	1(0.2%)
TENDINOUS CONTRACTURE	1(0.1%)	0	0	0
INJECTION SITE REACTION				
ANY AE	8(1.0%)	12(20.0%)	0	12(2.3%)
INJECTION SITE INFLAMMATION	7(0.9%)	10(16.7%)	0	10(1.9%)
INJECTION SITE REACTION	1(0.1%)	2(3.3%)	0	2(0.4%)
ENDOCRINE SYSTEM				
ANY AE	6(0.8%)	0	3(0.7%)	3(0.6%)
ADH INAPPROPRIATE	2(0.3%)	0	1(0.2%)	1(0.2%)
ADRENAL CORTEX INSUFFIENCY	1(0.1%)	0	1(0.2%)	1(0.2%)
PARATHYROID DISORDER	0	0	1(0.2%)	1(0.2%)
DIABETES MELLITUS	1(0.1%)	0	0	0
HYPOTHYROIDISM	2(0.3%)	0	0	0

(1) STUDIES INCLUDED: 98-0-050, FG-21-09, AND 98-0-047. STUDY 98-0-047 ONLY INCLUDES PATIENTS < 16 YEARS OLD WHO RECEIVED 1 MG/KG/DAY AND >= 16 YEARS OLD WHO RECEIVED 50 MG/DAY DOSE OF FK463.
(2) WITHIN A BODY SYSTEM A PERSON MAY EXPERIENCE MORE THAN ONE ADVERSE EVENT.

Corresponds to Table R6 1 in the applicant's submission dated October 25, 2004.
FK463 = micafungin

7.1.6 Treatment-Related Adverse Events

The incidence of adverse events determined to be related to study drug are shown in Table 19.

Study 98-0-050: Common drug-related adverse events (>1% in the micafungin group) included bilirubinemia (3.3% micafungin, 3.1% fluconazole), nausea (2.4% micafungin, 2.6% fluconazole), diarrhea (2.1% and 3.3%), hypokalemia (1.9%, 1.8%), rash (1.9%, 1.3%), vomiting (1.6%, 1.1%), hypophosphatemia (1.6%, 0.9%), abdominal pain (1.4% and 1.5%), leukopenia (1.2%, 0.9%), and hypomagnesemia (1.2%, 1.3%).

TABLE 19

INCIDENCE OF TREATMENT EMERGENT, RELATED ADVERSE EVENTS OF 50 MG FK463 AND FLUCONAZOLE
ALL TREATED PATIENTS (1)

BODY SYSTEM (2) COSTART TERM	FK463 (N=770)	FLUCONAZOLE 200 MG (N=60)	FLUCONAZOLE 400 MG (N=457)	FLUCONAZOLE TOTAL (N=517)
ALL SYSTEMS	204(26.5%)	26(43.3%)	83(18.2%)	109(21.1%)
DIGESTIVE SYSTEM				
ANY AE	59(7.7%)	9(15.0%)	42(9.2%)	51(9.9%)
DIARRHEA	15(1.9%)	2(3.3%)	15(3.3%)	17(3.3%)
NAUSEA	21(2.7%)	4(6.7%)	12(2.6%)	16(3.1%)
LIVER FUNCTION TESTS ABNORMAL	9(1.2%)	2(3.3%)	10(2.2%)	12(2.3%)
VOMITING	21(2.7%)	2(3.3%)	5(1.1%)	7(1.4%)
ANOREXIA	5(0.6%)	0	3(0.7%)	3(0.6%)
CONSTIPATION	3(0.4%)	0	3(0.7%)	3(0.6%)
MUCOSITIS	1(0.1%)	0	3(0.7%)	3(0.6%)
DYSPEPSIA	3(0.4%)	0	2(0.4%)	2(0.4%)
HEPATOMEGALY	2(0.3%)	0	2(0.4%)	2(0.4%)
RECTAL DISORDER	1(0.1%)	0	2(0.4%)	2(0.4%)
APHTHOUS STOMATITIS	1(0.1%)	1(1.7%)	0	1(0.2%)
ESOPHAGITIS	0	1(1.7%)	0	1(0.2%)
GASTROINTESTINAL ANOMALY	0	1(1.7%)	0	1(0.2%)
GASTROINTESTINAL DISORDER	0	0	1(0.2%)	1(0.2%)
GUM/ORAL HEMORRHAGE	0	0	1(0.2%)	1(0.2%)
HEPATIC FAILURE	0	0	1(0.2%)	1(0.2%)
HEPATITIS, NONSPECIFIC	0	0	1(0.2%)	1(0.2%)
JAUNDICE	2(0.3%)	0	1(0.2%)	1(0.2%)
LEUKOPLAKIA OF MOUTH	0	0	1(0.2%)	1(0.2%)
LIVER DAMAGE	0	0	1(0.2%)	1(0.2%)
TONGUE DISORDER	0	0	1(0.2%)	1(0.2%)
DRY MOUTH/NOSE	1(0.1%)	0	0	0
DYSPHAGIA	1(0.1%)	0	0	0
FLATULENCE	2(0.3%)	0	0	0
GASTRITIS	1(0.1%)	0	0	0
HEMATEMESIS	1(0.1%)	0	0	0
SIALADENITIS	1(0.1%)	0	0	0
STOMATITIS	1(0.1%)	0	0	0
METABOLIC AND NUTRITIONAL DISORDERS				
ANY AE	86(11.2%)	4(6.7%)	33(7.2%)	37(7.2%)
BILIRUBINEMIA	16(2.1%)	0	14(3.1%)	14(2.7%)
SGOT INCREASED	22(2.9%)	0	9(2.0%)	9(1.7%)
SGPT INCREASED	17(2.2%)	0	9(2.0%)	9(1.7%)
HYPOKALEMIA	15(1.9%)	0	8(1.8%)	8(1.5%)
HYPOCALCEMIA	19(2.5%)	2(3.3%)	4(0.9%)	6(1.2%)
HYPOMAGNESEMIA	22(2.9%)	0	6(1.3%)	6(1.2%)

(1) STUDIES INCLUDED: 98-0-050, FG-21-09, AND 98-0-047. STUDY 98-0-047 ONLY INCLUDES PATIENTS < 16 YEARS OLD WHO RECEIVED 1 MG/KG/DAY (BETWEEN .8 AND 1.2 MG/KG/DAY), AND >= 16 YEARS OLD WHO RECEIVED 50 MG/DAY DOSE OF FK463.
(2) WITHIN A BODY SYSTEM A PERSON MAY EXPERIENCE MORE THAN ONE ADVERSE EVENT.

Corresponds to Table for Item 18 in the applicant's submission dated January 10, 2005.
FK463 = micafungin

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TABLE 19 (continued)

INCIDENCE OF TREATMENT EMERGENT, RELATED ADVERSE EVENTS OF 50 MG FK463 AND FLUCONAZOLE
ALL TREATED PATIENTS (1)

BODY SYSTEM (2) COSTART TERM	FK463 (N=770)	FLUCONAZOLE 200 MG (N=60)	FLUCONAZOLE 400 MG (N=457)	FLUCONAZOLE TOTAL (N=517)
CREATININE INCREASED	4(0.5%)	0	4(0.9%)	4(0.8%)
HYPOPHOSPHATEMIA	7(0.9%)	0	4(0.9%)	4(0.8%)
ALKALINE PHOSPHATASE INCREASED	14(1.8%)	0	2(0.4%)	2(0.4%)
HYPERVOLEMIA	2(0.3%)	0	2(0.4%)	2(0.4%)
HYPONATREMIA	4(0.5%)	0	2(0.4%)	2(0.4%)
HYPOPROTEINEMIA	6(0.8%)	2(3.3%)	0	2(0.4%)
LACTIC DEHYDROGENASE INCREASED	1(0.1%)	1(1.7%)	1(0.2%)	2(0.4%)
CREATININE CLEARANCE DECREASED	0	0	1(0.2%)	1(0.2%)
EDEMA	4(0.5%)	0	1(0.2%)	1(0.2%)
GAMMA GLUTAMYL TRANSPEPTIDASE INCREASED	0	0	1(0.2%)	1(0.2%)
HYPERGLYCEMIA	1(0.1%)	0	1(0.2%)	1(0.2%)
HYPERKALEMIA	1(0.1%)	1(1.7%)	0	1(0.2%)
HYPOGLYCEMIA	0	0	1(0.2%)	1(0.2%)
PERIPHERAL EDEMA	4(0.5%)	0	1(0.2%)	1(0.2%)
WEIGHT LOSS	0	0	1(0.2%)	1(0.2%)
ACIDOSIS	2(0.3%)	0	0	0
BUN INCREASED	1(0.1%)	0	0	0
DECREASED BICARBONATE	1(0.1%)	0	0	0
GLOBULIN INCREASED	1(0.1%)	0	0	0
HYPERCHLOREMIA	4(0.5%)	0	0	0
HYPOCHLOREMIA	1(0.1%)	0	0	0
BODY AS A WHOLE				
ANY AE	46(6.0%)	4(6.7%)	27(5.9%)	31(6.0%)
ABDOMINAL PAIN	13(1.7%)	1(1.7%)	7(1.5%)	8(1.5%)
INFECTION	2(0.3%)	0	7(1.5%)	7(1.4%)
CHILLS	4(0.5%)	0	6(1.3%)	6(1.2%)
ASTHENIA	6(0.8%)	0	5(1.1%)	5(1.0%)
FEVER	19(2.5%)	2(3.3%)	2(0.4%)	4(0.8%)
DRUG LEVEL INCREASED	1(0.1%)	0	3(0.7%)	3(0.6%)
ALLERGIC REACTION	1(0.1%)	0	2(0.4%)	2(0.4%)
PAIN	2(0.3%)	0	2(0.4%)	2(0.4%)
BACK PAIN	4(0.5%)	1(1.7%)	0	1(0.2%)
LAB TEST ABNORMAL	1(0.1%)	0	1(0.2%)	1(0.2%)
NECK PAIN	1(0.1%)	0	1(0.2%)	1(0.2%)
PROCEDURAL COMPLICATION	2(0.3%)	0	1(0.2%)	1(0.2%)
SEPSIS	1(0.1%)	0	1(0.2%)	1(0.2%)
ABDOMEN ENLARGED	1(0.1%)	0	0	0
ANAPHYLACTOID REACTION	1(0.1%)	0	0	0
MALAISE	1(0.1%)	0	0	0

(1) STUDIES INCLUDED: 98-0-050, FG-21-09, AND 98-0-047. STUDY 98-0-047 ONLY INCLUDES PATIENTS < 16 YEARS OLD WHO RECEIVED 1 MG/KG/DAY (BETWEEN .8 AND 1.2 MG/KG/DAY), AND >= 16 YEARS OLD WHO RECEIVED 50 MG/DAY DOSE OF FK463.
(2) WITHIN A BODY SYSTEM A PERSON MAY EXPERIENCE MORE THAN ONE ADVERSE EVENT.

Corresponds to Table for Item 18 in the applicant's submission dated January 10, 2005.
FK463 = micafungin

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TABLE 19 (continued)

INCIDENCE OF TREATMENT EMERGENT, RELATED ADVERSE EVENTS OF 50 MG FK463 AND FLUCONAZOLE
ALL TREATED PATIENTS (1)

BODY SYSTEM (2) COSTART TERM	FK463 (N=770)	FLUCONAZOLE 200 MG (N=60)	FLUCONAZOLE 400 MG (N=457)	FLUCONAZOLE TOTAL (N=517)
NERVOUS SYSTEM				
ANY AE	22(2.9%)	5(8.3%)	12(2.6%)	17(3.3%)
DIZZINESS	0	3(5.0%)	5(1.1%)	8(1.5%)
HEADACHE	12(1.6%)	0	4(0.9%)	4(0.8%)
SOMNOLENCE	3(0.4%)	2(3.3%)	1(0.2%)	3(0.6%)
CONFUSION	1(0.1%)	0	1(0.2%)	1(0.2%)
DEPRESSION	0	0	1(0.2%)	1(0.2%)
AGITATION	1(0.1%)	0	0	0
ANXIETY	2(0.3%)	0	0	0
HALLUCINATIONS	1(0.1%)	0	0	0
HOSTILITY	1(0.1%)	0	0	0
INSOMNIA	2(0.3%)	0	0	0
MENINGITIS	1(0.1%)	0	0	0
PARESTHESIA	1(0.1%)	0	0	0
THINKING ABNORMAL	1(0.1%)	0	0	0
TREMOR	2(0.3%)	0	0	0
HEMIC AND LYMPHATIC SYSTEM				
ANY AE	43(5.6%)	8(13.3%)	8(1.8%)	16(3.1%)
LEUKOPENIA	23(3.0%)	6(10.0%)	4(0.9%)	10(1.9%)
ANEMIA	10(1.3%)	2(3.3%)	3(0.7%)	5(1.0%)
THROMBOCYTOPENIA	8(1.0%)	0	5(1.1%)	5(1.0%)
EOSINOPHILIA	2(0.3%)	2(3.3%)	0	2(0.4%)
BLEEDING TIME INCREASED	1(0.1%)	0	1(0.2%)	1(0.2%)
PETECHIA	0	0	1(0.2%)	1(0.2%)
COAGULATION DISORDER	1(0.1%)	0	0	0
ECCHYMOSIS	1(0.1%)	0	0	0
RETICULOENDOTHELIAL HYPERPLASIA	1(0.1%)	0	0	0
THROMBOCYTHEMIA	3(0.4%)	0	0	0
WBC ABNORMAL	5(0.6%)	0	0	0
CARDIOVASCULAR SYSTEM				
ANY AE	23(3.0%)	0	14(3.1%)	14(2.7%)
VASODILATATION	4(0.5%)	0	6(1.3%)	6(1.2%)
HYPOTENSION	2(0.3%)	0	4(0.9%)	4(0.8%)
TACHYCARDIA	3(0.4%)	0	2(0.4%)	2(0.4%)
CARDIOMEGALY	0	0	1(0.2%)	1(0.2%)
HYPERTENSION	1(0.1%)	0	1(0.2%)	1(0.2%)
SUBDURAL HEMATOMA	0	0	1(0.2%)	1(0.2%)
CHEST PAIN	1(0.1%)	0	0	0
PALPITATION	2(0.3%)	0	0	0

(1) STUDIES INCLUDED: 98-0-050, FG-21-09, AND 98-0-047. STUDY 98-0-047 ONLY INCLUDES PATIENTS < 16 YEARS OLD WHO RECEIVED 1 MG/KG/DAY (BETWEEN .8 AND 1.2 MG/KG/DAY), AND >= 16 YEARS OLD WHO RECEIVED 50 MG/DAY DOSE OF FK463.
(2) WITHIN A BODY SYSTEM A PERSON MAY EXPERIENCE MORE THAN ONE ADVERSE EVENT.

Corresponds to Table for Item 18 in the applicant's submission dated January 10, 2005.
FK463 = micafungin

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TABLE 19 (continued)

INCIDENCE OF TREATMENT EMERGENT, RELATED ADVERSE EVENTS OF 50 MG FK463 AND FLUCONAZOLE
ALL TREATED PATIENTS (1)

BODY SYSTEM (2) COSTART TERM	FK463 (N=770)	FLUCONAZOLE 200 MG (N=60)	FLUCONAZOLE 400 MG (N=457)	FLUCONAZOLE TOTAL (N=517)
PHLEBITIS	6(0.8%)	0	0	0
SYNCOPE	1(0.1%)	0	0	0
THROMBOPHLEBITIS	2(0.3%)	0	0	0
VENTRICULAR TACHYCARDIA	1(0.1%)	0	0	0
SKIN AND APPENDAGES				
ANY AE	28(3.6%)	1(1.7%)	10(2.2%)	11(2.1%)
RASH	15(1.9%)	0	6(1.3%)	6(1.2%)
PRURITUS	6(0.8%)	0	3(0.7%)	3(0.6%)
DRY SKIN	0	0	1(0.2%)	1(0.2%)
SKIN DISORDER	2(0.3%)	0	1(0.2%)	1(0.2%)
SWEATING	2(0.3%)	0	1(0.2%)	1(0.2%)
URTICARIA	4(0.5%)	1(1.7%)	0	1(0.2%)
MACULOPAPULAR RASH	3(0.4%)	0	0	0
SKIN DISCOLORATION	1(0.1%)	0	0	0
INJECTION SITE REACTION				
ANY AE	7(0.9%)	10(16.7%)	0	10(1.9%)
INJECTION SITE INFLAMMATION	7(0.9%)	10(16.7%)	0	10(1.9%)
RESPIRATORY SYSTEM				
ANY AE	9(1.2%)	1(1.7%)	9(2.0%)	10(1.9%)
HICCUP	1(0.1%)	0	3(0.7%)	3(0.6%)
DYSPNEA	1(0.1%)	0	2(0.4%)	2(0.4%)
COUGH INCREASED	3(0.4%)	0	1(0.2%)	1(0.2%)
HYPERVENTILATION	0	1(1.7%)	0	1(0.2%)
LUNG DISORDER	0	0	1(0.2%)	1(0.2%)
PHARYNGITIS	3(0.4%)	0	1(0.2%)	1(0.2%)
RHINITIS	1(0.1%)	0	1(0.2%)	1(0.2%)
SINUSITIS	0	0	1(0.2%)	1(0.2%)
HYPOXIA	1(0.1%)	0	0	0
LUNG EDEMA	1(0.1%)	0	0	0
PNEUMONIA	1(0.1%)	0	0	0
SPECIAL SENSES				
ANY AE	4(0.5%)	0	2(0.4%)	2(0.4%)
EAR PAIN	0	0	1(0.2%)	1(0.2%)
TASTE PERVERSION	3(0.4%)	0	1(0.2%)	1(0.2%)
PHOTOPHOBIA	1(0.1%)	0	0	0
UROGENITAL SYSTEM				

(1) STUDIES INCLUDED: 98-0-058, FG-21-09, AND 98-0-047. STUDY 98-0-047 ONLY INCLUDES PATIENTS < 16 YEARS OLD WHO RECEIVED 1 MG/KG/DAY (BETWEEN .8 AND 1.2 MG/KG/DAY), AND >= 16 YEARS OLD WHO RECEIVED 50 MG/DAY DOSE OF FK463.
(2) WITHIN A BODY SYSTEM A PERSON MAY EXPERIENCE MORE THAN ONE ADVERSE EVENT.

Corresponds to Table for Item 18 in the applicant's submission dated January 10, 2005.
FK463 = micafungin

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TABLE 19 (continued)

INCIDENCE OF TREATMENT EMERGENT, RELATED ADVERSE EVENTS OF 50 MG FK463 AND FLUCONAZOLE
ALL TREATED PATIENTS (1)

BODY SYSTEM (2) COSTART TERM	FK463 (N=770)	FLUCONAZOLE 200 MG (N=60)	FLUCONAZOLE 400 MG (N=457)	FLUCONAZOLE TOTAL (N=517)
ANY AE	5(0.6%)	0	2(0.4%)	2(0.4%)
HEMATURIA	1(0.1%)	0	1(0.2%)	1(0.2%)
OLIGURIA	1(0.1%)	0	1(0.2%)	1(0.2%)
PENIS DISORDER	0	0	1(0.2%)	1(0.2%)
URINARY TRACT INFECTION	0	0	1(0.2%)	1(0.2%)
ACUTE KIDNEY FAILURE	2(0.3%)	0	0	0
URINARY RETENTION	1(0.1%)	0	0	0
MUSCULOSKELETAL SYSTEM				
ANY AE	6(0.8%)	0	1(0.2%)	1(0.2%)
BONE PAIN	0	0	1(0.2%)	1(0.2%)
ARTHRALGIA	3(0.4%)	0	0	0
MYALGIA	3(0.4%)	0	0	0
ENDOCRINE SYSTEM				
ANY AE	1(0.1%)	0	0	0
ADH INAPPROPRIATE	1(0.1%)	0	0	0

(1) STUDIES INCLUDED: 98-0-050, FG-21-09, AND 98-0-047. STUDY 98-0-047 ONLY INCLUDES PATIENTS < 16 YEARS OLD WHO RECEIVED 1 MG/KG/DAY (BETWEEN .8 AND 1.2 MG/KG/DAY), AND >= 16 YEARS OLD WHO RECEIVED 50 MG/DAY DOSE OF FK463.
(2) WITHIN A BODY SYSTEM A PERSON MAY EXPERIENCE MORE THAN ONE ADVERSE EVENT.

Corresponds to Table for Item 18 in the applicant's submission dated January 10, 2005.
FK463 = micafungin

7.1.7 Less Common Adverse Events

Hepatic, renal, hematologic and allergic-type adverse events were deemed to be of special interest for micafungin based upon what is know of this drug and other echinocandins.

7.1.7.6 Hepatic Adverse Events

An overall summary of hepatic adverse events, including hepatic laboratory abnormalities, for micafungin and fluconazole (400 mg) for patients enrolled in Studies 98-0-050 and 98-0-047 is shown in Table 20. Events are similar between micafungin and fluconazole in Study 98-0-050 and are generally lower than seen with micafungin in Study 98-0-047, which may have to do with the patient population studied.

TABLE 20

INCIDENCE OF HEPATIC TREATMENT EMERGENT ADVERSE EVENTS OF 50 MG FK463 AND FLUCONAZOLE, BY STUDY
ALL TREATED PATIENTS (1)

BODY SYSTEM (2) COSTART TERM	FK463 98-0-047 (N=281)	98-0-050 FK463 (N=425)	98-0-050 FLUCONAZOLE (N=457)
ALL SYSTEMS	53(100.0%)	129(100.0%)	150(100.0%)
METABOLIC AND NUTRITIONAL DISORDERS			
ANY AE	41(77.4%)	95(73.6%)	98(65.3%)
BILIRUBINEMIA	7(13.2%)	66(51.2%)	71(47.3%)
SGPT INCREASED	17(32.1%)	31(24.0%)	36(24.0%)
SGOT INCREASED	23(43.4%)	24(18.6%)	29(19.3%)
ALKALINE PHOSPHATASE INCREASED	19(35.8%)	11(8.5%)	15(10.0%)
GAMMA GLUTAMYL TRANSPEPTIDASE INCREASED	0	0	2(1.3%)
DIGESTIVE SYSTEM			
ANY AE	14(26.4%)	53(41.1%)	80(53.3%)
LIVER FUNCTION TESTS ABNORMAL	7(13.2%)	27(20.9%)	42(28.0%)
JAUNDICE	3(5.7%)	22(17.1%)	33(22.0%)
HEPATOMEGALY	2(3.8%)	7(5.4%)	8(5.3%)
HEPATIC FAILURE	0	0	2(1.3%)
HEPATOSPLENOMEGALY	2(3.8%)	0	2(1.3%)
CHOLESTATIC JAUNDICE	1(1.9%)	0	1(0.7%)
HEPATITIS, NONSPECIFIC	0	2(1.6%)	1(0.7%)
LIVER DAMAGE	1(1.9%)	0	1(0.7%)

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ON ORIGINAL

(1) STUDIES INCLUDED: 98-0-050 AND 98-0-047. STUDY 98-0-047 ONLY INCLUDES PATIENTS < 16 YEARS OLD WHO RECEIVED 1 MG/KG/DAY (BETWEEN .8 AND 1.2 MG/KG/DAY), AND >= 16 YEARS OLD WHO RECEIVED 50 MG/DAY DOSE OF FK463.
(2) WITHIN A BODY SYSTEM A PERSON MAY EXPERIENCE MORE THAN ONE ADVERSE EVENT.

Source: Table 3 for Item 1 in the applicant's submission of January 6, 2005
FK463=micafungin

Table 21 summarizes hepatic adverse events, by duration of therapy in Studies 98-0-050 and 98-0-047. Hyperbilirubinemia was seen more often in the patients who received more than 14 days of the drug. Hepatomegaly and non-specific hepatitis were also reported in patients who received more than 7 and 14 days, respectively, of micafungin but not with shorter durations of exposure.

TABLE 21

INCIDENCE OF HEPATIC TREATMENT EMERGENT ADVERSE EVENTS OF 50 MG FK463, BY TREATMENT DURATION
ALL TREATED PATIENTS (1)

BODY SYSTEM (2) COSTART TERM	--------DURATION (DAYS) OF 50MG FK463-------- 1-7 (N=141)	8-14 (N=153)	>14 (N=412)
ALL SYSTEMS	20(100.0%)	35(100.0%)	127(100.0%)
METABOLIC AND NUTRITIONAL DISORDERS			
ANY AE	11(55.0%)	28(80.0%)	97(76.4%)
BILIRUBINEMIA	4(20.0%)	8(22.9%)	61(48.0%)
SGPT INCREASED	3(15.0%)	11(31.4%)	34(26.8%)
SGOT INCREASED	4(20.0%)	13(37.1%)	30(23.6%)
ALKALINE PHOSPHATASE INCREASED	5(25.0%)	8(22.9%)	17(13.4%)
DIGESTIVE SYSTEM			
ANY AE	9(45.0%)	11(31.4%)	47(37.0%)
LIVER FUNCTION TESTS ABNORMAL	6(30.0%)	5(14.3%)	23(18.1%)
JAUNDICE	1(5.0%)	4(11.4%)	20(15.7%)
HEPATOMEGALY	0	2(5.7%)	7(5.5%)
HEPATITIS, NONSPECIFIC	0	0	2(1.6%)
HEPATOSPLENOMEGALY	0	1(2.9%)	1(0.8%)
CHOLESTATIC JAUNDICE	1(5.0%)	0	0
LIVER DAMAGE	1(5.0%)	0	0

APPEARS THIS WAY
ON ORIGINAL

(1) STUDIES INCLUDED: 98-0-050 AND 98-0-047. STUDY 98-0-047 ONLY INCLUDES PATIENTS < 16 YEARS OLD WHO RECEIVED 1 MG/KG/DAY (BETWEEN .8 AND 1.2 MG/KG/DAY), AND >= 16 YEARS OLD WHO RECEIVED 50 MG/DAY DOSE OF FK463.
(2) WITHIN A BODY SYSTEM A PERSON MAY EXPERIENCE MORE THAN ONE ADVERSE EVENT.

Source: Table 1 for Item 1 in the applicant's submission of January 6, 2005
FK463=micafungin

Clinical Reviewer's Comment: A complete review of the hepatic safety of micafungin as doses from 50 to 150 mg per day was reviewed by Dr. Mary Singer as part of the Medical Officer Review of NDA 21-754.

7.1.7.7 Renal

Study 98-0-050: Three renal adverse events occurred that were considered by the investigators to be related to micafungin. One micafungin patient discontinued study drug due to increased creatinine levels and the event was considered by the investigator to be possibly related to study drug.

Table 22 shows renal adverse events leading to discontinuation across all three studies compared to fluconazole.

Clinical Reviewer's Comment: Renal adverse event appear to occur similarly in micafungin treated patients and those treated with the 400 mg dose of fluconazole, which is the approved dose for prophylaxis.

TABLE 22

INCIDENCE OF TREATMENT EMERGENT RENAL TYPE ADVERSE EVENTS OF 50 MG FK463 AND FLUCONAZOLE
ALL TREATED PATIENTS (1)

BODY SYSTEM (2) COSTART TERM	FK463 (N=770)	FLUCONAZOLE 200 MG (N=60)	FLUCONAZOLE 400 MG (N=457)	FLUCONAZOLE TOTAL (N=517)
ALL SYSTEMS	82(10.6%)	0	78(17.1%)	78(15.1%)
METABOLIC AND NUTRITIONAL DISORDERS				
ANY AE	55(7.1%)	0	49(10.7%)	49(9.5%)
CREATININE INCREASED	41(5.3%)	0	35(7.7%)	35(6.8%)
BUN INCREASED	23(3.0%)	0	18(3.9%)	18(3.5%)
UROGENITAL SYSTEM				
ANY AE	31(4.0%)	0	34(7.4%)	34(6.6%)
KIDNEY FUNCTION ABNORMAL	10(1.3%)	0	19(4.2%)	19(3.7%)
KIDNEY FAILURE	13(1.7%)	0	13(2.8%)	13(2.5%)
ACUTE KIDNEY FAILURE	8(1.0%)	0	7(1.5%)	7(1.4%)

(1) STUDIES INCLUDED: 98-0-050, FG-21-09, AND 98-0-047. STUDY 98-0-047 ONLY INCLUDES PATIENTS < 16 YEARS OLD WHO RECEIVED 1 MG/KG/DAY AND >= 16 YEARS OLD WHO RECEIVED 50 MG/DAY DOSE OF FK463.
(2) WITHIN A BODY SYSTEM A PERSON MAY EXPERIENCE MORE THAN ONE ADVERSE EVENT.

Corresponds to Table R6 5 in the applicant's submission dated October 25, 2004.
FK463 = micafungin

7.1.7.8 Hematologic

Study 98-0-050: No comment was made by the applicant in their original study report on this subset of AEs.

Table 23 shows hematologic adverse events leading to discontinuation across all three studies compared to fluconazole.

Clinical Reviewer's Comment: Leukopenia and thrombocytopenia appear to occur less frequently in the micafungin treated patients than those treated with the 400 mg dose of fluconazole, which is the approved dose for prophylaxis. One micafungin patient experienced hemolysis, while no fluconazole treated patient experienced this adverse event.

TABLE 23

INCIDENCE OF TREATMENT EMERGENT HEMATOLOGIC ADVERSE EVENTS OF 50 MG FK463 AND FLUCONAZOLE
ALL TREATED PATIENTS (1)

BODY SYSTEM (2) COSTART TERM	FK463 (N=770)	FLUCONAZOLE 200 MG (N=60)	FLUCONAZOLE 400 MG (N=457)	FLUCONAZOLE TOTAL (N=517)
ALL SYSTEMS	433(56.2%)	10(16.7%)	405(88.6%)	415(80.3%)
HEMIC AND LYMPHATIC SYSTEM				
ANY AE	433(56.2%)	10(16.7%)	405(88.6%)	415(80.3%)
LEUKOPENIA	366(47.5%)	8(13.3%)	346(75.7%)	354(68.5%)
THROMBOCYTOPENIA	338(43.9%)	2(3.3%)	321(70.2%)	323(62.5%)
HEMOLYSIS	1(0.1%)	0	0	0

APPEARS THIS WAY
ON ORIGINAL

(1) STUDIES INCLUDED: 98-0-050, FG-21-09, AND 98-0-047. STUDY 98-0-047 ONLY INCLUDES PATIENTS < 16 YEARS OLD WHO RECEIVED 1 MG/KG/DAY AND >= 16 YEARS OLD WHO RECEIVED 50 MG/DAY DOSE OF FK463.
(2) WITHIN A BODY SYSTEM A PERSON MAY EXPERIENCE MORE THAN ONE ADVERSE EVENT.

Corresponds to Table R6 6 in the applicant's submission dated October 25, 2004.
FK463 = micafungin

7.1.7.9 Allergic Reactions, Including Rash:

Study 98-0-050: Allergic-type or histamine-related events considered related to study drug were observed in 32 patients (micafungin 15/425, 3.5%; fluconazole 17/457, 3.7%). Three micafungin patients discontinued study drug due to development of a rash that was considered, by the investigator, to be possibly related to study drug and one micafungin patient discontinued due to urticaria that was considered, by the investigator, to be possibly related to study drug. The rash persisted in all of these patients after discontinuation of study drug. The patients were also receiving multiple other medications. None of the fluconazole patients discontinued due to an allergic-type or histamine-related event considered by the investigator to be related to study drug.

Table 24 shows allergic-type or histamine-related adverse events leading to discontinuation across all three studies compared to fluconazole.

Clinical Reviewer's Comment: The incidence of allergic-type or histamine-related adverse events leading to discontinuation appear to be similar in the micafungin treated patients compared to those treated with the 400 mg dose of fluconazole, which the approved dose for prophylaxis, with the exception of anaphylactoid reaction (2 micafungin patients and no fluconazole patients) and eosinophilia (4 micafungin patients, 2 fluconazole 200 mg patients, and no fluconazole 400 mg patients).

TABLE 24

INCIDENCE OF TREATMENT EMERGENT HISTAMINE RELEASE/ALLERGIC TYPE EVENTS OF 50 MG FK463 AND FLUCONAZOLE
ALL TREATED PATIENTS (1)

BODY SYSTEM (2) COSTART TERM	FK463 (N=770)	FLUCONAZOLE 200 MG (N=60)	FLUCONAZOLE 400 MG (N=457)	FLUCONAZOLE TOTAL (N=517)
ALL SYSTEMS	328(42.6%)	5(8.3%)	295(64.6%)	300(58.0%)
SKIN AND APPENDAGES				
ANY AE	270(35.1%)	3(5.0%)	245(53.6%)	248(48.0%)
RASH	209(27.1%)	0	187(40.9%)	187(36.2%)
PRURITUS	95(12.3%)	1(1.7%)	93(20.4%)	94(18.2%)
MACULOPAPULAR RASH	25(3.2%)	1(1.7%)	14(3.1%)	15(2.9%)
URTICARIA	23(3.0%)	1(1.7%)	12(2.6%)	13(2.5%)
VESICULOBULLOUS RASH	10(1.3%)	0	10(2.2%)	10(1.9%)
CARDIOVASCULAR SYSTEM				
ANY AE	67(8.7%)	0	73(16.0%)	73(14.1%)
VASODILATATION	67(8.7%)	0	73(16.0%)	73(14.1%)
BODY AS A WHOLE				
ANY AE	63(8.2%)	1(1.7%)	48(10.5%)	49(9.5%)
ALLERGIC REACTION	61(7.9%)	1(1.7%)	48(10.5%)	49(9.5%)
ANAPHYLACTOID REACTION	2(0.3%)	0	0	0
HEMIC AND LYMPHATIC SYSTEM				
ANY AE	4(0.5%)	2(3.3%)	0	2(0.4%)
EOSINOPHILIA	4(0.5%)	2(3.3%)	0	2(0.4%)

APPEARS THIS WAY
ON ORIGINAL

(1) STUDIES INCLUDED: 98-0-050, FG-21-09, AND 98-0-047. STUDY 98-0-047 ONLY INCLUDES PATIENTS < 16 YEARS OLD WHO RECEIVED 1 MG/KG/DAY AND >= 16 YEARS OLD WHO RECEIVED 50 MG/DAY DOSE OF FK463.
(2) WITHIN A BODY SYSTEM A PERSON MAY EXPERIENCE MORE THAN ONE ADVERSE EVENT.

Corresponds to Table R6 7 in the applicant's submission dated October 25, 2004.
FK463 = micafungin

7.1.8 Laboratory Findings

Study 98-0-047: A number of patients experienced changes in metabolic parameters during the study.

Study FG-463-21-09: Hepatic and renal adverse events are discussed in Section 7.1.6 (Less Common Adverse Events) of this review. No other notable changes in laboratory parameters were discussed in the applicant's study report.

Study 98-0-050: Patients were undergoing intensive chemotherapy and bone marrow transplantation, changes in hematology and serum chemistry levels occurred commonly. The more common changes in serum chemistry parameters reported as an adverse event included hypomagnesemia, hypokalemia, and hypocalcemia. There was a modest decrease in the mean levels of magnesium, potassium, and calcium from baseline to end of therapy in both groups. One micafungin patient experienced hemolysis and another patient experienced hemolytic anemia; neither event was considered by the investigator to be related to study drug.

7.1.9 Vital Signs

Study 98-0-047: No notable changes in vital signs were discussed in the applicant's study report.

Study FG-463-21-09: No notable overall changes in pulse, body temperature, and systolic or diastolic blood pressure over time were reported.

Study 98-0-050: No notable changes in vital signs were discussed in the applicant's study report.

7.1.10 Electrocardiograms (ECGs)

In pre-clinical testing micafungin did not show a signal to prolong the QT interval. In the 4, 13, and 39 week dog studies, ECGs were obtained and there was no increase in the QT interval. In vitro, there was a slight reduction in the action potential duration of the guinea pig papillary muscle (-9.5 msec versus -43 msec for the positive control) at $1x10^{-5}$ g/ml. In the HERG assay, there was no difference from control at the same level (2 to 20 times expected clinical levels).

Clinical Reviewer's Comment: For a complete discussion of the study results, see the Pharmacology/Toxicology Review by Owen McMaster, Ph.D. filed with NDA 21-754.

ECGs were obtained in the following healthy volunteer drug interaction studies with a 200 mg dose of micafungin: FG-463-21-04 (tacrolimus), FG-463-21-05 (cyclosporine), FG-463-21-06 (prednisolone), FG-463-21-15 (ritonavir), and FG 463-21-16 (rifampicin). Overall there is minimal evidence of prolongation of QT/QTc intervals following administration of micafungin, as shown in Table 25.

TABLE 25
Summary of Mean QT/QTc Intervals in Healthy Volunteer Studies

QT (ms)				
	Pre-dose	**2hr**	**Pre-dose[1]**	**24hr[1]**
Mean	400	406	389	396
SD	27.8	25.4	24.5	20.6
Median	398	405	388	397
Min	345	349	345	338
Max	491	481	447	443
N	96	96	48	48
QTc (ms) – Bazett's formula				
	Pre-dose	**2hr**	**Pre-dose[1]**	**24hr[1]**
Mean	394	392	392	383
SD	17.4	19.8	17.1	19.8
Median	396	395	393	384
Min	345	342	345	341
Max	430	433	430	424
N	96	96	48	48

1: Studies FG-463-21-06 and FG-463-21-16 only

7.1.11 Immunogenicity

Not applicable. No data on immunogenicity was included in the current NDA submission.

7.1.12 Human Carcinogenicity

Not applicable. No data regarding human carcinogenicity was included in the current NDA submission.

7.1.13 Special Safety Studies

Not applicable. No special safety studies were included in the current NDA submission.

7.1.14 Withdrawal Phenomena and/or Abuse Potential

Not applicable. This product does not have potential for dependence or abuse.

7.1.15 Human Reproduction and Pregnancy Data

Micafungin has not been adequately studied in pregnant human subjects. There is no information in this submission on use of micafungin in pregnant women. Animal studies show that labeled micafungin and/or its metabolites are excreted into the breast milk. The

Pharmacology/Toxicology Reviewer has designated micafungin to be Pregnancy Category C, not [redacted] as requested by the applicant (see Section 3.2: "*Animal Pharmacology/Toxicology*").

7.1.16 Assessment of Effect on Growth

Not applicable. This product does not have potential for growth suppression.

7.1.17 Overdose Experience

Not applicable. No information on the safety of supratherapeutic doses was included in the current NDA submission.

7.1.18 Postmarketing Experience

Micafungin has been marketed in Japan since December 2002. The Division consulted the Office of Drug Safety, Division of Drug Risk Evaluation (DDRE) asking for a review of Japanese postmarketing experience for serious hepatic, renal, hematologic, hypersensitivity and cardiac events.

DDRE concluded the Japanese postmarketing safety data does provide some evidence that micafungin is associated with an increased risk for potentially clinically significant hepatic, renal, hematologic, hypersensitivity and cardiac events. However, the case numbers are limited, except for hepatic events, and almost all the cases are confounded by concomitant drugs and disease conditions which could themselves cause these events of concern.

DDRE made the following recommendations for the micafungin label:

- Consider adding a **PRECAUTION** for hepatic events and to continually assess the risk/benefit of micafungin therapy in patients who develop worsening hepatic function.
- Consider listing renal impairment as a **PRECAUTION**, with a recommendation to continually assess the risk/benefit of micafungin therapy in patients who develop renal dysfunction.
- Consider a **WARNING** [redacted] for anaphylactoid reactions during micafungin infusions with recommendations to discontinue micafungin and administer appropriate treatments.

Clinical Reviewer's Comment: For additional information see the complete consult conducted by DDRE for NDA 21-754.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

The primary clinical data sources used to evaluate the safety of a 50 mg dose of micafungin are discussed in Section 7.1 "*Methods and Findings*".

The duration of exposure to micafungin is listed by study and overall in Table 26.

TABLE 26

DURATION OF EXPOSURE TO 50 MG FK463
ALL TREATED PATIENTS (1)

		PROTOCOL			
TREATMENT DURATION	CLASS	98-0-047 (N=281)	98-0-050 (N=425)	FG-21-09 (N=64)	TOTAL (N=770)
OVERALL	N	281	425	64	770
	MEAN	12.0	19.2	16.3	16.3
	STD	10.49	6.88	4.21	8.90
	MIN	1.0	1.0	3.0	1.0
	MEDIAN	9.0	18.0	14.0	16.0
	MAX	98.0	51.0	22.0	98.0
AGE < 6 YEARS	N	27	14	0	41
	MEAN	12.6	28.2	.	18.0
	STD	9.66	8.23	.	11.78
	MIN	1.0	18.0	.	1.0
	MEDIAN	9.0	28.0	.	17.0
	MAX	42.0	51.0	.	51.0
AGE 6-12 YEARS	N	12	19	0	31
	MEAN	20.2	21.3	.	20.9
	STD	26.28	10.51	.	17.89
	MIN	1.0	5.0	.	1.0
	MEDIAN	10.0	21.0	.	18.0
	MAX	98.0	50.0	.	98.0
AGE 13-17 YEARS	N	4	12	0	16
	MEAN	8.8	18.8	.	16.3
	STD	2.59	6.13	.	7.11
	MIN	6.0	4.0	.	4.0
	MEDIAN	7.5	19.5	.	18.5
	MAX	14.0	28.0	.	28.0
AGE >=18 YEARS	N	238	380	64	682
	MEAN	11.5	18.8	16.3	16.0
	STD	9.16	6.40	4.21	8.06
	MIN	1.0	1.0	3.0	1.0
	MEDIAN	9.0	18.0	14.0	16.0
	MAX	65.0	46.0	22.0	65.0

[1] STUDIES INCLUDED: 98-0-050, FG-21-09, AND 98-0-047. STUDY 98-0-047 ONLY INCLUDES PATIENTS < 16 YEARS OLD WHO RECEIVED 1 MG/KG/DAY (BETWEEN .8 AND 1.2 MG/KG/DAY), AND >= 16 YEARS OLD WHO RECEIVED 50 MG/DAY DOSE OF FK463.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

No additional secondary clinical data sources were used to evaluate safety other than those described in Section 7.1.

7.2.3 Adequacy of Overall Clinical Experience

The current submission (amendment to NDA 21-506), including Studies 98-0-050, 98-0-47, and FG-463-21-09, in conjunction with the approval of NDA 21-574 (micafungin for the treatment of esophageal candidiasis), is considered adequate clinical safety data to support a 50 mg dose for the prophylaxis of *Candida* infections in adult patients undergoing hematopoietic stem cell transplantation.

However, the clinical experience with micafungin is not adequate enough to establish safety and effectiveness in pediatric patients.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

No data on special animal and/or in vitro testing were included in the current NDA submission.

7.2.5 Adequacy of Routine Clinical Testing

Clinical testing (laboratory parameters, vitals signs, etc), was considered adequate in the clinical trials conducted by the applicant.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

The pharmacokinetics, including metabolism and drug-drug interactions were determined previously for micafungin. No new information was submitted with the current NDA.

Clinical Reviewer's Comment: See Clinical Pharmacology/Biopharmaceutics review for the original NDA 21-506 and for NDA 21-754 (esophageal candidiasis).

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

During the review of this submission, the Division consulted John Senior, M.D., Associate Director for Science in the Office of Pharmacoepidemiology and Statistical Science (OPSS) to review all deaths due to hepatic failure and serious events of hepatic failure in the micafungin safety database. Dr. Senior reviewed 21 cases of "liver damage" and "hepatic failure" to assess the relationship between the adverse event and micafungin. A summary of his conclusions follows:

1. Possible causation of liver injury following use of micafungin cannot be entirely dismissed in the cases reviewed.

2. Systemic fungal diseases usually occur in otherwise very sick patients who are on other therapies and have underlying problems, which may make them more vulnerable to or

less able to recover from additional liver injury that may be caused by agents such as micafungin.

3. Micafungin labeling should indicate that some cases have been observed, that in the opinion of expert and well known specialists on hepatology may possibly be caused or worsened by micafungin. Caution should be exercised in its use, and the possibility that some patients may show liver injury should be borne in mind by clinicians prescribing echinocandin treatment of systemic or internal fungal infections in immunocompromised patients.

4. It may be shown that more patients are saved by micafungin treatment of their fungal infections than are injured, and the echinocandins may be safer than the previously available agents, but they should not be considered totally safe. Physicians should weigh carefully the relative benefits and risks of them, in managing these extremely serious and complex diseases.

The above recommendations were taken under advisement by the Division and the **PRECAUTIONS** label was modified to address these comments and to provide information to the prescriber consistent with the wording in the label for caspofungin, the only other approved echinocandin (see Section 9.4: *"Labeling Review"*)

Clinical Reviewer's Comment: For additional information, see the complete consult conducted by Dr. Senior for NDAs 21-506/21-754.

7.2.8 Assessment of Quality and Completeness of Data

The data on a daily dose of 50 mg of micafungin (1 mg/kg in patients ≤ 40 kg) is considered to be of acceptable quality and completeness.

7.2.9 Additional Submissions, Including Safety Update

A 120 safety update was submitted for NDA 21-754 (esophageal candidiasis) and was incorporated into the safety review for this submission.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

A summary of common adverse events (≥ 1% in either group) that were considered by the investigator to be related to study drug in Study 98-0-050 is presented in Table 27. The incidence of particular adverse events is similar between the micafungin and fluconazole groups.

TABLE 27
Common (≥ 1%) Drug-Related Adverse Events in Study 98-0-050

Body System COSTART Term	FK463 (n=425)		Fluconazole (n=457)	
Any Adverse Event	64	(15.1%)	77	(16.8%)
Body as a Whole				
Abdominal Pain	6	(1.4%)	7	(1.5%)
Chills	1	(0.2%)	6	(1.3%)
Asthenia	0	(0.0%)	5	(1.1%)
Cardiovascular System				
Vasodilatation	2	(0.5%)	6	(1.3%)
Digestive System				
Diarrhea	9	(2.1%)	15	(3.3%)
Nausea	10	(2.4%)	12	(2.6%)
LFTs Abnormal	4	(0.9%)	10	(2.2%)
Vomiting	7	(1.6%)	5	(1.1%)
Hemic and Lymphatic System				
Leukopenia	5	(1.2%)	4	(0.9%)
Thrombocytopenia	4	(0.9%)	5	(1.1%)
Metabolic and Nutritional Disorders				
Bilirubinemia	14	(3.3%)	14	(3.1%)
Hypokalemia	8	(1.9%)	8	(1.8%)
SGPT Increased	4	(0.9%)	9	(2.0%)
SGOT Increased	3	(0.7%)	9	(2.0%)
Hypomagnesemia	5	(1.2%)	6	(1.3%)
Hypophosphatemia	7	(1.6%)	4	(0.9%)
Nervous System				
Dizziness	0	(0.0%)	5	(1.1%)
Skin and Appendages				
Rash	8	(1.9%)	6	(1.3%)

Patient base: all randomized patients who received at least 1 dose of study drug.
Within a body system patients may experience more than 1 adverse event.
Common: ≥1% in either group
Related: considered by the investigator to have a possible, probable or definite relationship to study drug.
LFTs Abnormal: Increased liver function tests; increased transaminase levels, hepatic insufficiency, or sludge in liver.
Source: Table 21 in the applicant's original report of Study 98-0-050

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

Adverse event data was pooled by the applicant, as requested, across Studies FG-463-21-09, 98-0-047, and 98-0-050 for the 50 mg oral micafungin dose and 1 mg/kg dose IV dose for patients ≤ 40 kg (pediatrics). In study FG-463-21-09 a dose of 200 mg per day of fluconazole was used and in Study 98-0-050 a dose of 400 mg per day of fluconazole was used as the comparator. The applicant provided adverse event data for micafungin and fluconazole comparator as described in Section 7.1: "*Methods and Findings*".

7.4.2 Explorations for Predictive Factors

Additional explorations for predictive factors were not performed.

7.4.3 Causality Determination

Additional assessments of causality were not performed.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

FDA Comment (from the May 23, 2003 Letter):
"While, in principle, results from Study FG-463-21-09 of esophageal candidiasis could support the prophylaxis indication, the Agency is unable to ascertain at this time whether this is the case. The information you have so far provided to us appears to demonstrate a significantly poorer activity of the 50 mg intravenously once daily (IV QD) dose in the treatment of esophageal candidiasis compared to the150 mg IV QD dose. Please keep in mind that you would need to provide justification that the efficacy of the proposed dose for the treatment of esophageal candidiasis(150 mg IV QD) is relevant to the dose proposed for prophylaxis (50 mg IV QD) when the doses for the two indications are different. Any such justification would need to provide clear evidence of how the 150 mg IV QD dose for treatment of EC bears relevance to the 50 mg IV QD dose for prophylaxis against Candida infections in patients undergoing hematopoietic stem cell transplant.....The results of your Study 97-7-003suggest that the 50 mg IV QD dose may have activity against esophageal candidiasis; however, the activity appears significantly inferior to the 150 mg IV QD dose and is inconsistent with the observations in FG-463-21-0.

The applicant has submitted the following data to demonstrate that the 50 mg dose is appropriate for use in prophylaxis and why higher doses (100 mg to 150 mg) are required for esophageal candidiasis:

- Plasma concentrations of micafungin in adult BMT patients administered at 50 mg dose of micafungin are above the minimum effective concentration (MEC) based upon murine models of pulmonary aspergillosis and disseminated candidiasis over a 24-hour period.

- Endoscopic cure of esophageal candidiasis shows a clear dose-response. Although the cure rates with micafungin at 50 mg were lower than the higher doses, about 60% of patients were cured, which is higher than the placebo-response rate.
- In a single, non-comparative trial of candidemia, a 50 mg dose was shown to have an overall success rate of 74% (ITT) and 86% (PP).
- *Candidemia* and disseminated candidiasis can be prevented with lower doses of micafungin because micafungin is readily available in blood or interstitial fluid of the target organ (supported by PK and murine studies). In esophageal candidiasis (EC), which is a mucosal disease, it is more difficult of micafungin to penetrate the keratinized mucosal layer and it is not excreted well into saliva (supported by a rabbit model with anidulafungin; extrapolated to micafungin based on the similarity in molecular size of the two compounds). Therefore, higher doses of micafungin may be required to achieve a clinical cure in EC.

Clinical Reviewer's Comment: For more details of the supportive data submitted by the applicant see Section 14.2: "Recommended Dose of Micafungin for Prophylaxis."

The Reviewer agrees with the appropriateness of a 50 mg dose of micafungin for prophylaxis of Candida infections and accepts the rationale provided by the applicant as to why higher doses of micafungin are necessary to treat esophageal candidiasis, which relates to the pharmacokinetic characteristics of the echinocandin class of antifungals (poor penetration into mucosal tissue). In addition to the prophylaxis study (98-0-50), supportive data are available which demonstrates that the 50 mg dose is also effective for treatment of documented fungal infections: esophageal candidiasis (Study FG-463-21-09) and candidemia (Study 98-0-047).

It should also be noted that the efficacy of micafungin against infections caused by fungi other than Candida has not been established.

8.2 Drug-Drug Interactions

A total of 11 clinical drug-drug interaction studies in healthy volunteers were conducted to evaluate the potential for interaction between micafungin and drugs commonly used in patients at risk for mucosal or invasive candidiasis, including CYP3A substrates, inhibitors and inducers. Mycophenolate mofetil, cyclosporine, tacrolimus, prednisolone, sirolimus, nifedipine, fluconazole, ritonavir, and rifampin were evaluated. In these studies, no interaction that altered the pharmacokinetics of micafungin was observed.

There was no effect of single dose or multiple doses of micafungin on mycophenolate mofetil, cyclosporine, tacrolimus, prednisolone, and fluconazole pharmacokinetics. The effect of micafungin on the pharmacokinetics of ritonavir and rifampin was not evaluated.

Sirolimus AUC was increased by 21% with no effect on C_{max} in the presence of steady-state micafungin compared with sirolimus alone. Nifedipine AUC and C_{max} were increased by 18%

and 42%, respectively, in the presence of steady-state micafungin compared with nifedipine alone.

Clinical Reviewer's Comment: Patients with graft versus host disease comprise a significant population at risk for fungal infections. Caspofungin, another echinocandin, is labeled with a Warning against the concomitant use of cyclosporine, which is commonly used to treat graft versus host disease. The combination of caspofungin and cyclosporine has been shown to result in a 35% higher AUC for caspofungin and transient elevations in AST and ALT. Micafungin was not shown to have a pharmacokinetic interaction with cyclosporine, or several other medications used to treat graft versus host disease (including tacrolimus and prednisolone) and may provide an alternative prophylactic drug to caspofungin for this population of patients.

8.3 Special Populations

Clinical Reviewer's Comment: See the Medical Officer Review of the original NDA 21-506 for a complete discussion of the efficacy of micafungin as prophylaxis of Candida infections in patients undergoing hematopoietic stem cell transplant. In summary, no major differences were found to require micafungin dose adjustments for reasons of efficacy based upon in age, gender, or race. See also Section 6.1.4 of this review for a summary of the efficacy results for Study 98-0-050 by age and gender.

The safety of a 50 mg per day dose (or 1 mg/kg per day in patients ≤ 40 kg) of micafungin in patients less than 18 years of age was compared to patients 18 years of age and older; and in males compared to females in Section 7.1.4 of this review. In summary, no major differences were found to require micafungin dose adjustments for reasons of safety based upon age or gender.

Clinical Reviewer's Comment: See Medical Officer Review of the original NDA 21-506 for a complete discussion of the safety of micafungin in different racial groups. In summary, no major differences were found to require micafungin dose adjustments for reasons of safety based upon in race.

Micafungin has not been adequately studied in pregnant human subjects. There is no information in this submission on use of micafungin in pregnant women. Animal studies show that labeled micafungin and/or its metabolites are excreted into the breast milk. The Pharmacology/Toxicology Reviewer has designated micafungin to be Pregnancy Category C, not as requested by the applicant (see Section 3.2: "*Animal Pharmacology/Toxicology*").

8.4 Pediatrics

8.4.1 Pharmacokinetics

The pharmacokinetic data submitted by the applicant as part of the original NDA 21-506 (Study 98-0-043 conducted in 72 pediatric patients with febrile neutropenia) are not considered adequate to characterize exposure of the drug in patients between 2 and 17 years due to errors in blood sampling (contamination by residual micafungin in the catheter port). No new pharmacokinetic information on this patient population was included in the current submission.

Clinical Reviewer's Comment: See Clinical Pharmacology/Biopharmaceutics Review filed with the original NDA 21-506 and the current submission.

8.4.2 Pediatric Efficacy

Of the three clinical studies evaluating the 50 mg dose micafungin (1 mg/kg in patients ≤ 40 kg), only two included pediatric patients: Study 98-0-050 for the prophylaxis of fungal infections and Study 98-0-047 for the treatment of candidemia, disseminated or hepatosplenic candidiasis, or esophageal candidiasis.

In Study 98-0-50 there were 39 patients less than 16 years old (age range 6 months to 17 years; mean age 7 years) and success rates were lower in these patients (27/ 39 [69.2%]) than in adults (313/386 [81.1%]). The applicant attributes the lower success rates in pediatric patients in both groups to the high proportion of allogeneic transplant recipients, which are known to do worse than those receiving autologous transplants.

In Study 98-0-047 there were 30 patients less than 16 years old who were treated with micafungin (7 were between 0 and 1 year, 17 were between 2 and 11 years, and 6 were between 12 and 15 years of age). *Note, some of these patients received doses greater than 1 mg/kg (maximum daily dose of 1.1 mg/kg for de novo patients, 1.3 for micafungin plus other antifungals, and 2.9 mg/kg for those who failed other antifungals).*

As shown in Table 28, treatment success rates were lower in both groups that received micafungin alone (the de novo and antifungal failure groups) for the younger patients compared to adults.

Clinical Reviewer's Comment: Table 28 was excerpted from a larger table prepared by the applicant.

TABLE 28
Summary of Treatment Success by Subgroup

		Previous Efficacy Failures		
Age Group	Micafungin de novo	Micafungin plus other antifungal	Micafungin alone	Total
< 16 years	9/13 (69.2%)	10/13 (76.9%)	2/4 (50%)	21/30 (70%)
≥ 16 years	132/152 (86.8%)	18/35 (51.4%)	23/33 (69.7%)	173/220 (78.6%)

De novo: patients must have had less than 48 hours of systemic antifungal therapy.
Efficacy failure: patients must have had documented clinical and microbiological evidence of continuing disease despite >5 days of therapy with systemic antifungal agents prior to study entry; patients received either a regimen of micafungin alone or micafungin was added to their prior systemic antifungal regimen.
Source: Excerpted from Table 13.3.3.1 in the applicant's original submission of NDA 21-506

8.4.3 Pediatric Safety

Difference, if any, seen in adverse event rates between pediatric patients and adults are not considered clinically meaningful. For adverse events summarized by age, see Section 7.1.4: *"Other Search Strategies."*

8.4.4 Pediatric Summary

Pharmacokinetic data submitted by the applicant are not considered adequate to characterize exposure of the drug in patients between 2 and 17 years. The number of pediatric patients exposed to a 50 mg dose of micafungin is relatively small and fungal efficacy rates for prophylaxis or treatment success are lower in pediatric patients than in adults. Differences, if any, seen in adverse event rates between pediatric patients and adults are not considered clinically meaningful.

the **PRECAUTIONS**, Pediatric Use section of the label will reflect the fact that safety and efficacy have not been established in this population. (see Section 9.4: *"Labeling Review"*)

8.5 Advisory Committee Meeting

No Advisory Committee Meeting was held to discuss this submission.

8.6 Literature Review

See Section 11: *"Appendix I: Review of Antifungal Prophylaxis in Clinical Trials"* for a comprehensive discussion of the meta-analysis, review articles, and individual trials of antifungal prophylaxis to reduce the incidence of invasive yeast infections in cancer patients with neutropenia.

8.7 Postmarketing Risk Management Plan

The postmarketing risk management plan was discussed with representatives from the Office of Drug Safety at the Pre-Approval Safety Meeting on February 4, 2005. The following is a summary of the safety issues identified by the Division and the proposed plan for managing each issue. The recommendations outlined in this list was agreed to by ODS.

Safety Issues	Risk Management Plan
Anaphylaxis/anaphylactoid reactions	Warning in label Postmarketing surveillance
Hypersensitivity: -Rash, erythema multiforme, TEN	Adverse events section in label Postmarketing surveillance (serious rash, EM, and TEN)
Hepatic safety: - hepatic laboratory abnormalities - hepatic failure or dysfunction	Precaution in label Postmarketing surveillance (serious hepatic failure or impairment, liver damage)
Drug interactions: - increased ALT in mycophenolate-micafungin interaction study	Precaution in label Postmarketing commitment to evaluate mycophenolate-micafungin hepatic safety
Renal safety: - renal failure, renal impairment, - renal laboratory abnormalities -hemolytic uremic syndrome	Precaution in label Postmarketing surveillance (serious renal failure, hemolytic uremic syndrome)
Hematologic safety: - hemolysis, hemolytic anemia - leukopenia, anemia, thrombocytopenia, pancytopenia, thrombotic thrombocytopenic purpura	Precaution in label (hemolysis) Adverse events section in label Postmarketing surveillance (serious hemolysis, hemolytic anemia, thrombocytopenic purpura, pancytopenia)

Vascular Reactions: -phlebitis, thrombophebitis	Adverse Events section in label Postmarketing surveillance (serious deep venous thrombosis, arterial thrombosis, pulmonary embolism, mycocardial infarct or ischemia, stroke)
Cardiovascular Safety: Shock, cardiac arrest, arrhythmia, (QT prolongation)	Adverse Events section in label Postmarketing surveillance (serious events of shock, cardiac arrest, arrhythmia, and QT prolongation)
Infusion-related Reactions: Hypertension, hypotension, vasodilatation, tachycardia, dyspnea cyanosis, chills/rigors	Adverse Events section in label Postmarketing surveillance (serious events of hypertension, hypotension, cyanosis)

8.8 Other Relevant Materials

Other relevant reviews on file regarding micafungin safety and efficacy pertinent to NDA 21-506 include:

- Medical Officer's Review of the original NDA 21-506
- Medical Officer's Review of NDA 21-754 (esophageal candidiasis)
- ODS consult regarding hepatic safety of micafungin in Japanese post-marketing reports
- Consult from Dr. John Senior, OPSS, regarding hepatic safety of micafungin cases resulting in death or serious events of hepatic failure in the micafungin safety database.

9 OVERALL ASSESSMENT

9.1 Conclusions

The applicant received on Approvable Letter from the FDA on January 29, 2003 for NDA 21-506. The letter stated that Study 98-0-050, the one study submitted in support of prophylaxis of [redacted] in patients undergoing hematopoietic stem cell transplantation (HSCT), by itself, did not provide sufficiently robust statistical evidence of superiority of micafungin over fluconazole, a comparator not approved for this indication. Prior to approval of micafungin for prophylaxis, the letter continued, the Agency expects demonstration of the activity of micafungin in the treatment of documented invasive fungal infections.

Fluconazole is approved for a narrower indication "to decrease the incidence of candidiasis in patients undergoing bone marrow transplantation who receive cytotoxic chemotherapy and/or radiation therapy." In addition to demonstration of a mortality benefit in the bone marrow transplant population, fluconazole was also approved based on efficacy in the treatment of systemic fungal infections.

The current submission (amendment to NDA 21-506), contains a proposed a re-analysis conducted by the applicant of the incidence of proven *Candida* infection in Study 98-0-050 relying on incidence rates of proven breakthrough infections with *Candida* in previously conducted trials in the literature, mainly the Goodman, et al. study [1992] and the Slavin, et al. study [1995].

The applicant has submitted a new NDA (21-754) for the treatment of esophageal candidiasis concurrently with the amendment to NDA 21-506, to fulfill the requirement for demonstration of micafungin efficacy in a treatment indication. Unlike the azole class of antifungals (including fluconazole) the echinocandins (including micafungin) have limited penetration into mucosal tissues. Therefore, demonstration of the efficacy of an echinocandin in esophageal candidiasis is felt by the Agency to be a robust test of efficacy. Upon review of NDA 21-754, the Agency believes that the efficacy of micafungin at a dose of 150 mg, which is three times the prophylaxis dose, has established the efficacy of micafungin for the treatment of esophageal candidiasis.

Other supportive evidence demonstrating the efficacy of micafungin in the treatment of *Candida* infections was included by the applicant in this amendment, including an open-label study of micafungin for the treatment of candidemia (Study 98-0-047, submitted to the original NDA 21-506). In this study, the dose of micafungin was initiated at 75 mg, which is higher than the prophylaxis dose and one-half the dose for esophageal candidiasis.

The applicant's re-analysis of in Study 98-0-050, contained in this amendment to NDA 21-506, changed the emphasis of the primary endpoint from the absence of a fungal infection of any kind, to the incidence of proven *Candida* infections and a new treatment difference was established. Proven *Candida* infections were considered treatment failures while probable/suspected infections and deaths during the study were considered treatment successes. The Clinical and Statistical Reviewers concluded from their review that this approach is statistically inappropriate as a method to determine non-inferiority of micafungin to fluconazole. Additionally, re-defining the primary endpoint from absence of fungal infections during study to incidence of *Candida* infections was also considered by the Reviewers to be statistically invalid.

The Clinical and Statistical Reviewers re-reviewed the data in the original report for Study 98-0-050 used to generate the primary endpoint, as defined in the protocol. The Reviewers concluded that the applicant defined suspected infections as those who received empirical antifungal therapy rather than adhering to the protocol-defined criteria. A suspected systemic fungal infection defined as patients with neutropenia (ANC <500 cells/mm^3); persistent or recurrent fever (while ANC <500 cells/mm^3) of no known etiology; and failure to respond to at least 96 hours of broad spectrum antibacterial therapy. A persistent fever was defined as four consecutive days of fever greater than 38°C. A recurrent fever was defined as having at least one

day with temperatures ≥ 38.5 °C after having at least one prior temperature > 38 °C; or having two days of temperatures > 38 °C after having at least one prior temperature > 38°C. In addition, transplant recipients who died or were lost to follow-up during the study were considered failures of prophylactic therapy.

To accurately account for all treatment failures in Study 98-0-050, especially cases of suspected fungal infection, the Division requested from the applicant a detailed breakdown of all patients who died, were lost to follow-up, developed proven/probable/suspected infections (as defined by the protocol), and those who did not meet the criteria for a suspected fungal infection but did receive empirical antifungal therapy.

As a result of the re-evaluation of failures (deaths, patients lost to follow-up, and proven/probable infections through the end of study and suspected infections through the end of treatment), success was correctly defined as 80.7% in micafungin patients and 73.7% in fluconazole patients (95% CI = 1.5%, 12.5%). The number of proven and probable fungal infections did not change as a result of the re-evalution. The number of proven *Candida* infections was 4 in the micafungin group and 2 in the fluconazole group.

Although not part of the primary endpoint, use of systemic antifungal therapy post-therapy evaluated by the Reviewers, since it also provides a perspective on the efficacy of prophylaxic therapy. The use of systemic antifungals following prophylactic therapy was 42% in both groups.

At the time the Approvable letter for NDA 21-506 was written, the Agency did not feel that the results of Study 98-0-050 were robust enough to warrant and indication for prophylaxis of —— —— in HSCT patients, especially since the applicant did not have any data demonstrating efficacy for a treatment indication. However, with the approval of NDA 21-754, the Agency has concluded that micafungin has demonstrated efficacy for the treatment of esophageal candidiasis. Given the non-inferiority of micafungin compared to fluconazole for the primary end point in Study 98-0-050 and supported by efficacy of micafungin in the treatment of *Candida* infections, the Clinical Reviewer believes the applicant has demonstrated non-inferiority of micafungin to fluconazole for the narrower indication of prophylaxis of *Candida* infections in patients undergoing HSCT.

The incidence of drug-related adverse events was similar between micafungin and fluconazole treated patients in Study 98-0-050, including serious events and those resulting in study drug discontinuation.

The number of pediatric patients exposed to a 1 mg/kg mg dose of micafungin in Study 98-0-050 was relatively small (N=39) and fungal efficacy rates for prophylaxis or treatment success were lower in pediatric patients than in adults, as shown in Studies 98-0-050 and 98-0-047. Safety data on 244 pediatric patients enrolled across all micafungin clinical trials showed a higher incidence of adverse events in major organ systems compared to fluconazole. Finally, the pharmacokinetics in pediatric patients aged 2 to 17 years has not been adequately characterized.

9.2 Recommendation on Regulatory Action

Micafungin sodium (Mycamine®) for injection, at a dose of 50 mg intravenously once daily, should be approved for prophylaxis of *Candida* infections in adult patients undergoing hematopoietic stem cell transplantation.

Insufficient data are contained within this submission to provide evidence of the safety and efficacy of micafungin sodium (Mycamine®) for injection for the prophylaxis of *Candida* infections in pediatric patients undergoing hematopoietic stem cell transplantation and therefore, it should not be approved — . in pediatrics.

9.3 Recommendation on Postmarketing Actions

There are no recommendations for risk management activity or required Phase 4 studies at this time.

9.3.1 Risk Management Activity

None.

9.3.2 Required Phase 4 Commitments

None.

9.3.3 Other Phase 4 Requests

None.

9.4 Labeling Review

The following summarizes the major changes/additions to each section of the label as proposed by the FDA to the applicant:

DESCRIPTION
An alternative chemical formula replaced the formula proposed by the applicant.

CLINICAL PHARMACOKINETICS

— , was removed from this section. —

MICROBIOLOGY

Information on the —
has been removed, as both indications being granted (esophageal candidiasis and prophylaxis) are specific to *Candida* species. In addition, —
— was not deemed acceptable by the Microbiology Reviewer and replaced with "The potential for development of drug resistance is not known."

INDICATIONS AND USAGE

Wording has been added which states that "The efficacy of MYCAMINE against infections caused by fungi other than *Candida* has not been established." Both indications being granted (esophageal candidiasis and prophylaxis) are specific to *Candida* species.

CONTRAINDICATIONS

No changes.

WARNINGS

A warning that alerts the prescriber to the possible development of serious anaphylactic and anaphylactoid reactions to micafungin has been added.

PRECAUTIONS

Wording has been added which encompasses hepatic, renal, hematologic, and other events of concern.

Hepatic Effects

It is noted in this section that liver function abnormalities have been seen in healthy volunteers. Also, patients have experienced hepatic abnormalities, some of whom were taking multiple concomitant medications or had serious underlying conditions. Patients who develop abnormal liver function tests during therapy with micafungin should be monitored for worsening hepatic function and evaluated for the risk/benefit of continuing drug therapy.

Carcinogenesis, Mutagenesis and Impairment of Fertility

Information relating mg/kg doses in animals to the equivalent clinical dose has been added, as well as a more detailed description of the results of the male fertility studies in rats and dogs.

Pregnancy Category

The Pregnancy Category has been designated as "C" —, as requested by the applicant based upon the Pharmacology/Toxicology Review and additional description of the abnormalities seen in pregnant rabbits has been added.

Pediatric Use

Information proposed by the applicant has been removed from this section and the following wording inserted "The safety and efficacy of MYCAMINE in pediatric patients has not been established in clinical studies." There were no pediatric patients less than 16

years old enrolled in the esophageal candidiasis trials and only 39 patients less than 16 in the prophylaxis study (Study 98-0-050). Fungal efficacy rates for prophylaxis or treatment success were lower in pediatric patients than in adults, as shown in Studies 98-0-050 and 98-0-047. Safety data on 244 pediatric patients enrolled across all micafungin clinical trials showed a higher incidence of adverse events in major organ systems compared to fluconazole. Finally, the pharmacokinetics in pediatric patients aged 2 to 17 years has not been adequately characterized.

Geriatric Use
Information on the number of patients 75 years of age and older was added, as well as a general statement that "other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out," as per the CFR.

ADVERSE REACTIONS
Additional information regarding phlebitis and histamine-mediated reactions was added.

A general statement cautioning the reader that adverse reaction rates observed in clinical trials cannot be directly compared to the rates in clinical trials of another drug and may not reflect the rates observed in clinical practice.

Rates of common micafungin-related adverse events using MedDRA were reported for those occurring in at least 0.5% in either group for the tables reporting events for the esophageal candidiasis studies and the prophylaxis study. The table containing overall adverse events were also modified to include micafungin drug-related adverse events occurring in at least 0.5% of patients.

In the subsection describing the overall safety experience, the information was limited to the number of patients treated for esophageal and/or oropharyngeal candidiasis, those who were prophylaxed for a hematopoietic stem cell transplant and volunteers in the Phase I studies who received single or multiple doses of micafungin. Information on the number of patients who received 150 mg/day of micafungin for a minimum of 10 days was included, as it is relevant to the esophageal candidiasis indication.

Other clinically significant serious adverse events which occurred in less than 0.5% of patients in the overall safety database were also included as a list.

A summary of postmarketing events from Japan, including hepatic, renal, hematologic, and vascular was added.

OVERDOSAGE
Information relating mg/kg overdoses in animals to the equivalent clinical dose has been added

DOSAGE AND ADMINISTRATION

[redacted] has been removed. A footnote to the dosing table has been added which indicates the mean treatment duration in patients with esophageal candidiasis treated in clinical studies and the mean duration of prophylaxis in patients who were considered successes.

Reconstitution

A precautionary statement has been added alerting the reader to visually inspect the reconstituted product for particular matter and/or discoloration and to not use the product if either is in evidence. Neither the micafungin powder nor the diluent contains preservatives or bacteriostatic agents.

Infusion Volume and Duration

Information on [redacted] has been removed, as [redacted] may result in more frequent histamine-mediated reactions.

ANIMAL TOXICOLOGY

This entire section has been added to detail the damage to the liver seen in rat and dog studies using high doses micafungin (5-times the clinical exposure and higher).

CLINICAL STUDIES

The Clinical Studies section was moved from [redacted] to the last section of the label, as per the CRF. This section has been extensively revised to adequately characterize the efficacy of micafungin for the treatment of esophageal candidiasis and as *Candida* prophylaxis in HSCT recipients. This section also points out the lack of corroborating evidence for efficacy of micafungin in non-*Candida* fungal infections. Relapse rates in patients with esophageal candidiasis and oropharyngeal candidiasis have been added in the subsection on esophageal candidiasis. The subsection regarding the prophylaxis study focuses on the primary endpoint (absence of a proven, probable, or suspected systemic fungal infection through the end of therapy and the absence of a proven or probable systemic fungal infection through the end of the 4-week post-therapy period) and includes deaths/lost-to-follow-up as failures of therapy, as per the Clinical and Statistical Reviewers' analysis. The applicant's re-analysis based upon proven *Candida* infections has not been included, although the number of infections (4 in the micafungin group and 2 in the fluconazole group) are mentioned in the text.

9.5 Comments to Applicant

During the review, the Clinical Reviewer sent multiple requests to the applicant asking for additional data analyses. The applicant's responses to these requests can be found at:

- \\Cdsesub1\n21506\N_000\2004-10-25\041025 (Attachment 6 - summary adverse event tables for micafungin 50 mg)
- \\Cdsesub1\n21506\N_000\2004-10-29\041029 (Clinical narratives for patients with proven and probable fungal infections in Study 98-0-050)

- \\Cdsesub1\n21506\N_000\2005-01-10A (Attachments 15 through 18 – revised adverse event tables for micafungin 50 mg)
- \\Cdsesub1\n21506\N_000\2005-02-04\FEB3RESP (Clarification of the primary endpoint used in Study 98-0-050)
- \\Cdsesub1\n21506\N_000\2005-02-09\N21506 (Listing of the individual components of the primary endpoint used in Study 98-0-050)
- \\Cdsesub1\n21506\N_000\2005-02-15\N21506 (Re-analysis of primary endpoint in Study 98-0-050 using protocol-specified criteria of suspected fungal infection)

During labeling negotiations, the applicant was informed [redacted] This decision was based upon the fact that (1) there were no pediatric patients less than 16 years old enrolled in the esophageal candidiasis trials and only 39 patients less than 16 in the prophylaxis study (Study 98-0-050); (2) safety data on 244 pediatric patients enrolled across all micafungin clinical trials showed a higher incidence of adverse events in major organ systems compared to fluconazole; and (3) the pharmacokinetics in pediatric patients aged 2 to 17 years have not been adequately characterized.

APPEARS THIS WAY
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10 APPENDIX I: REVIEW OF ANTIFUNGAL PROPHYLAXIS IN CLINICAL TRIALS

10.1 Background

At a Meeting between the applicant and the Division on March 8, 2004, the applicant provided an analysis of the incidence of proven *Candida* infection in Study 98-0-050. They relied on incidence rates of proven breakthrough infections with *Candida* in previously conducted trials in the literature, mainly the Goodman, et al. study [1992] and the Slavin, et al. study [1995]. The Division requested offer more insight into the changes in risk-over-time for invasive fungal infections in a neutropenic patient population. The applicant agreed to look further into the literature for this additional insight and in their submission have included a literature review of studies using antifungal prophylaxis over the past 20 years. These studies are divided into meta-analyses, key review articles, and randomized placebo- or comparator-controlled studies, with special focus on those studies evaluating the use of fluconazole.

Clinical Reviewer's Comment: Literature review articles were compiled and summarized by the applicant. The Reviewer abstracted the applicant's summaries for clarity and brevity.

10.2 Meta-Analyses of Antifungal Prophylaxis

10.2.1 Tabular Summary

Six recent meta-analyses have been published that assess the effect of antifungal prophylaxis in neutropenic cancer patients, including recipients of bone marrow or hematopoietic stem cell transplants (BMT/HSCT). A tabular summary (Table 1) and synopses of these analyses are provided below. These meta-analyses show that antifungal prophylaxis with fluconazole, itraconazole or amphotericin B reduces the incidence of systemic fungal infections in neutropenic cancer patients. The effect is most pronounced in patients undergoing bone marrow transplant (BMT) or hematopoietic stem cell transplant (HSCT).

Clinical Reviewer's Comment: Table 1 was created by the Reviewer.

TABLE 1
Summary of Meta-Analyses Conducted on Antifungal Prophylaxis Studies in Neutropenic Cancer Patients

Author	Number of Studies and Patient Population	Treatment	Results	Comments
Gøtzsche PC and Johansen HK [1997]*	24 total; 21 prophylaxis, 3 empiric; randomized, controlled trials (placebo or no-treatment)	Amphotericin B, fluconazole, miconazole, ketoconazole, and agents overall	Overall no significant effect on mortality, but significantly decreased invasive fungal infection and colonization	Fluconazole by itself did not decrease significantly decrease mortality, but did decrease fungal invasive fungal infections (OR 0.34; 95% CI [0.22, 0.52])
Kanda et al. [2000]	16 prophylaxis; randomized, controlled trials (placebo, no-treatment, or polyene-controlled); 8 BMT and non-BMT patients, 6 non-BMT, and 2 BMT only (Goodman 1992 and Slavin 1995)	Fluconazole (Oral)	Overall (BMT plus non-BMT) a significant reduction in fungal-related deaths with fluconazole compared to controls (OR 0.45; 95% CI [0.29, 0.72]); also significant reduction in systemic fungal infections (OR 0.42; 95% CI [0.31, 0.57])	Subgroup analyses of non-BMT only showed a significant reduction in invasive fungal infections in non-BMT patients ONLY when incidence in control group was > 15%
Bow et al. [2002]	38 prophylaxis; randomized, controlled trials (placebo, no-treatment, or polyene-controlled)	Fluconazole, itraconazole, ketoconazole, miconazole, and amphotericin B (IV)	Overall no significant effect on mortality , but there was a significant effect on fungal-related mortality (OR 0.58; 95% CI [0.41, 0.82])	Also, overall a significant reduction in invasive fungal infection (OR 0.44; 95% CI [0.35, 0.55])

Author	Number of Studies and Patient Population	Treatment	Results	Comments
Glasmacher A, et al. [2003]	13 prophylaxis; all placebo-controlled	Itraconazole	Itraconazole significantly decreased mortality (2.2%) compared to control (3.3%) (OR 0.65; 95% CI [0.43, 0.98])	Also significantly decreased invasive yeast infections (1.1%) compared to control (2.4%) (OR 0.47, 95% CI [0.38, 0.79]),
Gøtzsche PC and Johansen HK [2004]	30 total; 27 prophylaxis, 3 empiric; randomized, controlled trials (placebo or no-treatment)	Amphotericin B, fluconazole, miconazole, ketoconazole, itraconazole, and agents overall	Overall no significant effect on mortality; amphotericin B by itself had smallest RR of 0.73 [94% CI 0.52, 1.03]	Fluconazole significantly decreased invasive fungal infection (4.4%) compared to control (11.1%) (RR 0.39; 95%CI [0.27, 0.57])
Johansen HK and Gøtzsche PC [2004]	16 total; 9 prophylaxis, 6 empiric	Fluconazole (IV, oral) vs. Amphotericin B (IV)	No significant difference in mortality or invasive fungal infection between Flu and Ampho B	Analysis may have biased against Ampho B

* NOTE: This meta-analysis was updated with studies published or presented through November 2001 (see Gøtzsche PC and Johansen HK 2004).

10.2.2 Synopses of Articles

Gøtzsche PC and Johansen HK [1997]: The authors reviewed 24 randomized trials published or presented through February 1996 to evaluate whether antifungal agents (amphotericin B, lipid soluble formulations of amphotericin B, fluconazole, ketoconazole, miconazole, or itraconazole) administered as prophylaxis or empiric therapy decreased mortality, invasive fungal infections and colonization in patients with cancer complicated by neutropenia, as compared to placebo or no treatment.

Results: There was no effect on overall mortality by prophylactic therapy for antifungals as a group. There was a significant decrease (odds ratio: 0.58; 95% CI: 0.37, 0.93) in mortality with amphotericin B, although the studies were small and the numerical difference in the number of deaths was also small. Overall, antifungal agents significantly decreased the incidence of invasive fungal infection (odds ratio 0.47; 95% CI: 0.35, 0.64) and fungal colonization (odds

ratio 0.45; 95% CI: 0.30, 0.69). Both fluconazole and amphotericin B significantly decreased the incidence of invasive fungal infections. The overall odds ratios and 95% CI for each study drug compared to control are provided in Table 2.

Clinical Reviewer's Comment: Table 2 was created by the applicant.

TABLE 2
Treatment Effect for Invasive Fungal Infections by Study Drug and Overall

Treatment	Odds Ratio	95% CI
Amphotericin	0.38	0.19, 0.76
Fluconazole	0.34	0.22, 0.52
Ketoconazole	1.36	0.67, 2.78
Miconazole	0.51	0.20, 1.30
Overall	0.47	0.35, 0.64

Source: Table 3 in Appendix I of applicant's submission

There was no apparent survival benefit from antifungal agents administered for prophylaxis or empiric therapy in neutropenic cancer patients and that the use of antifungal agents should be restricted to patients with proven infections.

NOTE: This meta-analysis was updated with studies published or presented through November 2001 (see Gøtzsche PC and Johansen HK 2004).

Kanda et al. [2000]: The efficacy of oral fluconazole as compared with placebo, no treatment, or oral polyenes as prophylaxis for fungal infections during chemotherapy induced neutropenia was evaluated in 16 prospective, randomized studies of neutropenic patients. Of the 16 studies reviewed, 8 studies included both bone marrow transplantation (BMT) and non-BMT patients, 6 studies had only non-BMT patients, and 2 studies [Goodman et al, 1992; and Slavin et al, 1995] included only BMT patients.
Results: Oral fluconazole showed a significant effect compared to placebo, no treatment or oral polyenes in reducing fungal-related deaths (odds ratio 0.45; 95% CI: 0.29, 0.72) and the incidence of proven systemic fungal infections (odds ratio 0.42; 95% CI: 0.31, 0.57). When the analysis was restricted to non-BMT studies, there was no significant difference between fluconazole and control in the incidence of fungal-related deaths and systemic fungal infections. However, fluconazole was effective in reducing the incidence of systemic fungal infections in non-BMT studies when the incidence of invasive fungal infections was >15% in the control (untreated) group. The incidence of systemic fungal infections in the control patients were in the range of 15.8% to 17.6% in the BMT studies and 0 to 7.6% in the non-BMT studies.

Bow et al. [2002]: A meta-analysis was conducted to evaluate azoles (fluconazole, itraconazole, ketoconazole, and miconazole) or intravenous amphotericin B formulations compared with placebo/no treatment or polyene-based controls in severely neutropenic chemotherapy recipients.
Results: Antifungal prophylaxis significantly reduced the use of parenteral antifungal therapy (odds ratio 0.57; 95% CI: 0.48, 0.68), and the incidence of invasive fungal infections (odds ratio

0.44; 95% CI: 0.35, 0.55) and fungal infection-related mortality (odds ratio 0.58; 95% CI: 0.41, 0.82). Overall mortality was not significantly reduced. Proven invasive infections were reduced with use of all agents except miconazole. Ranges for incidence of proven invasive fungal infections are presented by drug in Table 3.

Clinical Reviewer's Comment: Table 3 was created by the applicant.

TABLE 3
Incidence Rates for Proven Invasive Fungal Infections by Study Drug

Study Drug, Control (No. Trials)	Study Drug	Control
Fluconazole, Placebo (8)	2.8% - 9.8%	6.3% - 31.0%
Fluconazole, Polyenes (9)	0.8% - 4.9%	0 – 20.8%
Itraconazole, Placebo (3)	2.5% - 10.9%	4.4% - 19.6%
Itraconazole, Polyenes (2)	2.8% - 4.9%	4.7% - 5.3%
Ketoconazole, Placebo/No Treatment (5)	0 – 14.0%	0 – 10.5%
Ketoconazole, Polyenes (5)	0 – 21.6%	0 – 71.4%
Miconazole, Placebo (2)	1.0% - 6.7%	7.2% - 13.3%
Low-Dose IV Amphotericin B, Placebo (4)	0 – 11.8%	2.3% - 27.8%

Source: Table 2 in Appendix I of applicant's submission

Multivariate meta-regression analyses suggested that treatment effects were more likely to be observed in trials in which the rate of proven invasive fungal infection among control patients was high and in which the majority of patients were undergoing hematopoietic stem cell transplant (HSCT), particularly allogeneic HSCT. These authors conclude that their results support the current CDC/IDSA/ASBMT guidelines for prophylaxis in HSCT recipients.

Glasmacher A, et al. [2003]: This meta-analysis was conducted to evaluate new evidence of efficacy of antifungal prophylaxis in randomized, controlled trials of itraconazole in neutropenic patients with hematologic malignancies. This analysis of 13 trials included 3,597 patients with invasive fungal infections that were treated with itraconazole versus control. In the control group, one trial compared itraconazole capsules to placebo only, one trial to no control treatment, five trials compared itraconazole to oral polyenes, and six trials use fluconazole for comparison. Results: Antifungal prophylaxis with itraconazole significantly reduces invasive fungal infections (3.3% with itraconazole versus 5.3% of control; odds ratio: 0.60; 95% CI [0.43 to 0.83]), invasive yeast infections (1.1% versus 2.4%; odds ratio 0.74; 95% CI [0.38 to 0.79]), and death (2.2% versus 3.3%; odds ratio 0.65; 95% CI [0.43 to 0.98]) from these infections in neutropenic patients with hematologic malignancies and myelosuppressive chemotherapy. The authors conclude that, in view of these data, patients with acute leukemia who receive myelosuppressive cytotoxic chemotherapy and patients who have undergone allogeneic stem cell transplantation should receive antifungal prophylaxis with itraconazole.

Gøtzsche PC and Johansen HK [2004]: The primary aim of this review was to evaluate whether antifungal agents (amphotericin B, fluconazole, ketoconazole, itraconazole, and

miconazole) decrease mortality as compared to placebo or no treatment when given prophylactically (N=27 trials) or to patients with persistent fever (N=3 empiric therapy trials). The effect on mortality was reviewed in a total of 30 randomized trials involving 4094 cancer patients with neutropenia. Patients were included who had invasive fungal infections, defined as positive blood culture, esophageal candidiasis, lung infection or microscopically confirmed deep tissue infection.

Results: There was considerable heterogeneity with no clear differences between drugs. Prophylactic or empirical treatment with antifungals as a group had no statistically significant effect on mortality. As individual agents, the incidence of invasive fungal infection was significantly decreased with intravenous amphotericin B, fluconazole and itraconazole, but not with miconazole and ketoconazole, as shown in Table 4.

Clinical Reviewer's Comment: Table 4 was created by the applicant.

TABLE 4
Overall Incidence of Invasive Fungal Infections and Relative Risk by Treatment

Study Drug	Treatment n/n %	Control n/n %	Relative Risk (fixed) [95% CI]
Amphotericin B	11/361 3.0%	27/362 7.4%	0.39 [0.20 to 0.76]
Fluconazole	35/785 4.4%	84/754 11.1%	0.39 [0.27 to 0.57]
Ketoconazole	18/281 6.4%	13/281 4.6%	1.32 [0.68 to 2.54]
Miconazole	6/112 5.4%	13/126 10.3%	0.52 [0.20 to 1.31]
Itraconazole	13/354 3.7%	26/359 7.2%	0.51 [0.27 to 0.96]
Combination†	0/30	0/10	Not estimable

† Itraconazole + Ketoconazole + Amphotericin B
Source: Table 1 in Appendix I of applicant's submission

Johansen HK and Gøtzsche PC [2004]: The review compared the effect of fluconazole and amphotericin B on mortality, invasive fungal infections, colonization, use of rescue antifungal therapy and adverse effects leading to discontinuation of therapy in patients with cancer complicated by neutropenia. This meta-analysis reviewed 16 studies that enrolled a total of 3760 patients; 9 were studies of prophylaxis treatment and 6 were studies of empiric treatment.

Results: No statistically significant differences were found between fluconazole (IV, oral) and amphotericin B (IV) in mortality or incidence of invasive fungal infections. Although no difference was detected between fluconazole and amphotericin B, but several of the trials were designed or analyzed such that the authors concluded that amphotericin B was disadvantaged (i.e., given less frequently in recent years because of the availability of less toxic alternatives) in their analysis.

10.3 Key Review Articles on Antifungal Prophylaxis

The following studies show that antifungal prophylaxis is associated with a reduced incidence of invasive fungal infections.

Gubbins PO et al. [1998]: The authors conducted a literature search of data published within 5 years to identify the risk factors, epidemiology, and chemoprophylaxis of invasive mycosis in BMT recipients. The effect of systemic, intranasal, and lipid formulations of amphotericin B, fluconazole, and itraconazole were evaluated for effect on the development of fungal colonization, frequency of superficial and invasive mycosis, and overall mortality, and that due to invasive mycoses in BMT recipients.
Results: Without prophylaxis, infections due to *Candida* were found to occur in approximately 11% of all transplant recipients and, depending on the underlying malignancy, approximately 5% to 13% of BMT recipients were shown to develop invasive *Aspergillus* infections. The authors noted that the literature indicated that fluconazole prophylaxis in neutropenic patients and BMT recipients reduces colonization with and the number of infections due to *Candida albicans* as well as that data from a multicenter, randomized, prospective, double-blind, placebo-controlled trial clearly showed that prophylactic fluconazole reduces the frequency of superficial fungal infections.

Tollemar J [1999]: This author reviews the rationale for antifungal prophylaxis in transplant recipients.
Results: The incidence of invasive fungal infections in allogeneic BMT recipients was found to range up to 30% with *Candida* and *Aspergillus* species being the most common pathogens. The incidence of verified invasive fungal infections was considered to have decreased over the prior 5- to 7-year periods based on two studies at the Huddinge Hospital, Department of Transplantation Surgery, in Sweden and was reported to be 16.5% among BMT recipients. Fluconazole 400 mg/kg per day is recommended until the end of the neutropenic period to reduce fungal infections in BMT recipients.

Marr KA and Bowden RA [1999]: The authors review several studies and publications regarding epidemiology of fungal infections, especially candidiasis and invasive aspergillosis, and treatment and prevention strategies in patients undergoing blood and marrow transplantation.
Results: The period of greatest risk for acute candidiasis is the pre-engraftment period, corresponding with the time period of greatest neutropenia for BMT patients. Prophylaxis with azoles was considered by these authors to be related to a decreased number of infections caused by *Candida albicans* and *Candida tropicalis* and the emergence of azole-resistant species such as *Candida glabrata* and *Candida krusei*. Overall, the incidence of candidiasis has decreased from 11.9% to 4.6% after adoption of fluconazole prophylaxis at their institution with a consequent decrease in fungal-related mortality.

Maertens JA and Boogaerts MA [1999]: This article summarized a review of experience with triazoles and systemic and aerosolized amphotericin B for antifungal prophylaxis of *Candida* and *Aspergillus* infections in neutropenic patients.
Results: No prophylactic modality other than fluconazole in BMT patients and the use of HEPA-filters against airborne fungal spores has unequivocally proven to be efficacious in the prevention of systemic fungal infections in neutropenic patients. Important factors that may affect current treatment strategies include the advent of improved noninvasive diagnostic methods, the availability of new antifungal drugs or formulations, and new treatments aimed at

reducing the duration of neutropenia. Early empirical or pre-emptive treatment strategies that target a subset of a high-risk population were considered to potentially reduce toxicity, as well as the development of drug resistance, and the costs of therapy.

Böhme A et al.; [1999]: This is a critical review and discussion of the results of multiple studies investigating prophylactic modalities including 15 studies of fluconazole and itraconazole and 8 studies of intravenous and aerosolized amphotericin B in neutropenic patients with hematologic malignancy. Only preventive measures for *Candida* and *Aspergillus* infections were reviewed.
Results: A prophylactic effect on systemic *Candida* infections was demonstrated with fluconazole (400 mg/day) in bone marrow transplant (BMT) patients. Several studies suggested efficacy at lower doses of fluconazole. No benefits were clearly demonstrated for neutropenic nontransplant leukemia patients with either triazoles or amphotericin B. No proven, successful prevention was demonstrated for patients with *Aspergillus* infections.

Prentice HG et al. [2000]: This review discusses prevention, diagnosis and treatment of fungal infections, as well as the current fungal pathogens of concern, patient populations at risk, and various treatment strategies. The results of several trials and meta-analyses were also reviewed.
Results: The risk of invasive fungal infections ranges from 2% to 40% based on studies of patients with neutropenia resulting from chemotherapy or BMT. This risk increases with the length of neutropenia, with neutropenia of less than 7 days duration carrying the least risk. The risk is dependent on the underlying disease, the type of treatments given (steroid use, indwelling catheters, graft-versus-host-disease, total body irradiation, colonization, bacteremia, use of broad-spectrum antibiotics, cytomegalovirus, type of chemotherapy) and the prophylaxis used. The authors concluded that evidence of the benefit of prophylaxis is proven in high-risk groups and appropriate for use in intermediate-risk groups, but not to be used in low-risk patients. New and promising antifungals as well as augmentation of the host response and prophylactic granulocyte infusion using granulocyte-macrophage colony-stimulating factor (GM-CSF)-mobilized donor cells may soon provide alternative approaches.

Mahfouz T and Anaissie E. [2003]: This article proposes a risk-adjusted approach to the management of fungal infections in the immunocompromised host to balance the toxicity, high cost, and potential emergence of resistance that can be associated with antifungal prophylaxis and the high morbidity and mortality of invasive antifungal infections.
Results: A strategy is presented for a risk-adjusted approach based on the determination of risk categories from the risk factors involved; i.e., fungal exposure, net state of immunosuppression, and organ dysfunction. Antifungal strategies such as determining clinical and laboratory procedures for evaluation of the fungal infection and use of antifungal treatment are to be made according to risk category (high, moderate and low). The authors conclude that the recommended risk-adjusted strategy provides a balance between the problems associated with antifungal prophylaxis and the high morbidity and mortality of invasive fungal infections in the immunocompromised host. The authors also estimate the incidence of invasive fungal infections in cancer patients before and after introduction of the triazoles. The incidence of invasive *Candida* infections before prophylactic use of the triazoles ranged from 10% in acute lymphocytic leukemia and autologous BMT patients to 15-20% in acute myeloid leukemia and

allogeneic BMT patients; the incidence after introduction of triazoles has fallen to less than 5% across all patient populations.

Cornely OA et al. [Blood 2003]: The goal of this review was to aid the reader in making evidence-based decisions for antifungal prophylaxis of cancer patients. The authors conducted an evidence-based review of major studies on antifungal prophylaxis published in the previous 15 years using the Infectious Disease Society of America (IDSA) guidelines for evidence-based criteria. Issues discussed in the review article include the question of clinical need for prophylaxis and evaluation of antifungal agents for prophylaxis. Of the 16 randomized, controlled, blinded studies, 8 studies included some BMT patients.
Results: Prophylaxis support was found for fluconazole (400 mg), which showed significant benefit (Level A1 evidence) in allogeneic hematopoietic stem cell transplantation (HSCT) recipients. The authors agree with the current Center for Disease Control (CDC), IDSA, and the American Society of Blood and Marrow Transplantation (ASBMT) treatment recommendations. No clear evidence-based contraindication was found for the use of antifungal prophylaxis.

Cornely OA et al. [Ann Hematol 2003]: The objective of this review article was to accumulate data on approximately 10,000 patients to assess evidence-based criteria regarding the efficacy of antifungal prophylaxis in neutropenic cancer patients. A guideline was prepared by a panel of experts in the field of infectious diseases in the immunosuppressed host and a peer review was conducted by leading experts in infectious diseases in hematology and oncology. The recommendations are based on scientific publications and information published at conferences by the Infectious Diseases Working Party of the German Society for Hematology and Oncology with application of the IDSA criteria.
Results: Risk factors were identified as neutropenia >10 days, allogeneic and autologous BMT/HSCT, prolonged corticosteroid therapy, other sustained immunosuppression, graft-versus-host disease, and concomitant viral infections. The authors cited the two most relevant trials were Goodman et al [1992] and Slavin et al [1995], because they were placebo-controlled, double-blinded, and involved mainly allogeneic transplant recipients. Other trials were regarded as having examined a "mixed bag" of different underlying conditions and risk groups causing them to fail to demonstrate an advantage over the comparator drug. They conclude there is good evidence (Level AI) that primary prophylaxis with fluconazole 400 mg per day reduces the incidence of invasive fungal infections and the mortality rate in allogeneic BMT or HSCT recipients.

Castagnola E et al. [2004]: This article reviews the most important clinical trials conducted in the use of antifungal prophylaxis in patients at risk for fungal infections, excluding patients infected with human immunodeficiency virus, and attempts to put the results in perspective compared to other studies that showed or suggested the possibility that prophylaxis might carry some undesirable effect (e.g., induction of resistance). Issues of interest include the role of fungal infections as a cause of morbidity and mortality in hospitalized patients, causative organisms, at risk population, advantages and disadvantages related to the use of antifungal prophylaxis, and current antifungal armamentarium.
Results: The authors agree with available evidence suggesting that prophylaxis decreases fungus-related mortality, although with little effect on overall mortality, and considers this to probably

be due to the severe underlying diseases of this population. Review of studies showed a well-documented increase in fungal infections in cancer patients, especially leukemia patients and those undergoing BMT or HSCT. There are indications that the pattern of infecting fungal organisms may be changing with molds increasing more than yeasts. The authors state that both itraconazole and fluconazole have shown activity, but have concern over the toxicity profile of itraconazole and the risk of drug interactions. They also considered the positive effects of fluconazole prophylaxis to be less impressive in patients with acute leukemia. The authors' opinion was that there is clear evidence that prophylaxis of infectious complications in immunocompromised patients should be tailored to the individual patient's risk, to local epidemiological factors and to the results of clinical trials. Triazole antifungal prophylaxis for prevention of *Candida* infections may be recommended in allogeneic BMT patients (especially those undergoing transplantation from unrelated donors and mismatch transplants).

10.4 Placebo-Controlled Trials of Antifungal Prophylaxis

Eighteen randomized, blinded, placebo-controlled antifungal prophylaxis trials have been conducted and published from 1983 to the present. Table 5 summarizes the results of these studies.

Clinical Reviewer's Comment: Table 5 was created by the applicant.

The following 6 trials included only BMT patients:

- Amphotericin - Riley et al [1994], Tollemar et al [1993a,b], and Perfect et al [1992]
- Fluconazole - Slavin et al [1995] and Goodman et al [1992]
- Ketoconazole - Benhamou et al [1991]

The fluconazole treatment effect (placebo minus fluconazole) for reducing the overall incidence of systemic fungal infections in BMT patients (Slavin and Goodman trials) ranged from 11% to 13%.

The large range in the incidence of invasive fungal infections and in overall mortality may be due to the heterogeneous patient populations treated with respect to underlying disease, level of immunosuppression, and antifungal prophylaxis used; risk factors determined by meta-analyses and anti-fungal review articles discussed in Sections 11.1 and 11.2 of this review.

The Goodman trial was a multi-center, randomized, placebo-controlled trial in BMT patients. The Slavin trial, conducted at a single-center, is also randomized, placebo-controlled trial performed in BMT patients, smaller than the Goodman trial, in a primarily allogeneic transplant population. The applicant believes these two studies represent the best estimates to date of the effect of fluconazole prophylaxis in patients undergoing BMT/HSCT.

TABLE 5
Randomized, Blinded, Placebo-Controlled Antifungal Prophylaxis Trials

Study Treatment Groups	No. Patients	No. Centers/ Location	% Allo/ % Auto/ % Non- HSCT	Incidence Proven Invasive Infection†	Overall Mortality
Fluconazole					
Rotstein et al [1999], Laverdière et al [2000]		14 Canada	0/44/56		
Flu 400 mg	141			3%	11%
Placebo	133			17%	11%
Slavin et al [1995], Marr et al [2000]		1 US	88/12/0		
Flu 400 mg	152			7%	20%
Placebo	148			18%	35%
Schaffner & Schaffner [1995]		1; Switzerland	0/10/90		
Flu 400 mg	75			11%	5%
Placebo	76			11%	7%
Chandrasekar et al [1994a, 1994b]		1; US	41/7/52		
Flu 400 mg	23			9%	17%
Placebo	23			4%	13%
Winston et al [1993]		18; US	NR		
Flu 400 mg	123			4%	21%
Placebo	132			8%	18%
Goodman et al [1992]		17; US	48/52/0		
Flu 400 mg	179			3%	31%
Placebo	177			16%	26%
Amphotericin B					
Kelsey et al [1999]		5; EU	53/31/16		
L-Amph 2 mg/kg (3 X week)	74			0	15%
Placebo	87			2%	14%
Riley et al [1994]		1; US	69/31/0		
Amph 0.1 mg/kg	17			0	0
Placebo	18			28%	22%
Tollemar et al [1993a, 1993b]		1; Sweden	83/17/0		
L-Amph 1 mg/kg	36			3%	44%
Placebo	40			8%	33%
Perfect et al [1992]		1; US	0/100/0		
Amph 0.1 mg/kg	91			1%	3%
Placebo	91			10%	12%
Itraconazole					
Nucci et al [2000]		2; Brazil	0/15/85		
Itra 200 mg	104			5%	8%
Placebo	106			8%	7%
Menichetti et al [1999]		39; Italy	0/18/82		
Itra 5 mg/kg	201			3%	7%

Study Treatment Groups	No. Patients	No. Centers/ Location	% Allo/ % Auto/ % Non-HSCT	Incidence Proven Invasive Infection†	Overall Mortality
Placebo	204			4%	9%
Vreugdenhil et al [1993]		1; Netherlands	NR		
Itra 400 mg	46			11%	22%
Placebo	46			20%	30%
		Ketoconazole			
Palmblad et al [1992]		5; Sweden	NR		
Keto 200 mg	50			6%	16%‡
Placebo	57			0	16%‡
Benhamou et al [1991]		1; France	8/92/0		NR
Keto 200 mg capsules¶	63			5%	
Placebo	62			9%	
Estey et al [1984]		1	NR		
Keto 400 mg	32	US		3%	22%‡
Placebo	38			18%	16%‡
Brincker [1983]		1	NR		
Keto 400 mg	19	Denmark		11%	NR
Placebo	19			11%	NR
Miconazole					
Wingard et al [1987]		1; US	33/7/60		
Miconazole 5 mg/kg	97			1%	4%
Placebo	111			7%	3%

Allo: allogeneic; Auto: autologous; NR: not reported; Flu: fluconazole; Amph: amphotericin B; L-Amph: lipid amphotericin B; Itra: itraconazole; Keto: ketoconazole.
† Based on the definition of proven invasive infection used in each respective study.
‡ Infection-related mortality.
¶ 200 mg capsules were administered according to patient's weight: 0.5 capsule for 10-22 kg, 1 capsule for 22-32 kg, 1.5 capsules for 32-50 kg, 2 capsules for >50 kg (in the first 34 patients); and, after plasma levels of ketoconazole were found to be very low, the dose was adjusted by weight to the following: 1 capsule for 10-22 kg, 1.5 capsules for 22-32 kg, 2 capsules for 32-40 kg, 2.5 capsules for 40-45 kg, and 3 capsules for >45 kg.
Source: Applicant's Table 1 in Section 2.3 of their submission

10.5 Comparative-Controlled Trials of Antifungal Prophylaxis

Seven randomized, comparative studies of antifungal prophylaxis in neutropenic cancer patients have been published and the findings are summarized in Table 6. In these studies IV or oral fluconazole was compared with either oral or IV itraconazole or IV amphotericin B.

Clinical Reviewer's Comment: Table 6 was created by the applicant.

One trial studied only BMT patients:
Oral fluconazole versus oral itraconazole – Annaloro et al. [1995]

Two trials studied only allogeneic hematopoietic stem cell transplant (HSCT) patients:
IV /oral fluconazole versus IV/oral itraconazole – Winston et al [2003] and Marr et al. [2004]

One trial studied both BMT and HSCT patients:
IV/oral fluconazole versus IV amphotericin B – Wolff et al [2000]

Annaloro et al. reported an incidence of proven invasive fungal infections for fluconazole of 4% while patients were neutropenic.

The incidence of proven invasive fungal infections for fluconazole in the Winston trial was relatively high at 25% during the pre-engraftment period though 180 days post-transplant. The authors state that the high incidence of invasive infections was due to approximately 85% of patients in both groups receiving systemic corticosteroids for the prevention of graft-versus-host disease.

Marr et al. report an incidence of 9% invasive fungal infections for fluconazole, which was also determined though 180 days post-transplant or until 4 weeks after discontinuation of graft-versus host disease.

In contrast to the Winston and Marr trials, Study 98-0-050 (micafungin versus fluconazole) assessed the incidence of breakthrough fungal infections through the pre-engraftment period until 5 days following neutrophil recovery or primary graft failure (up to 42 days following transplant), which is the period of highest risk.

The trial by Wolff et al [2000] studied related allogeneic BMT, unrelated allogeneic BMT, as well as autologous BMT/HSCT patients until resolution of neutropenia. The incidence of invasive fungal infections was 4% for related allogeneic BMT patients, 1% unrelated allogeneic BMT, and 3% for the autologous BMT/HSCTP patients.

TABLE 6
Randomized, Comparative Studies of Antifungal Prophylaxis in Neutropenic Cancer Patients

Study Treatment Groups	No. Patients	No. Centers/ Location	% Allo/ % Auto/ % Non-HSCT	Incidence Proven Invasive Infection	Overall Mortality
Fluconazole versus Itraconazole					
Marr et al [2004]		1; US	100/0/0		
Flu 400 mg	148			9%	31%
Itra 200 mg IV†	151			10%	39%
Winston [2003]		5; US	100/0/0		
Flu 400 mg	67			25%	42%
Itra 400 mg‡	71			9%	45%
Morgenstern [1999]		17; UK	11/40/49		
Flu 100 mg	227			3%	NR
Itra oral sol'n 5 mg/kg	218			0.5%	NR
Huijgens [1999]		1; Netherlands	0/57/43		
Flu 100 mg	101			4%	7%
Itra capsules 200 mg§	101			4%	11%
Annaloro [1995]		1; Italy	39/61/0		
Flu 300 mg	28			4%	7%
Itra capsules 400 mg¶	31			13%	6%
Fluconazole versus IV Amphotericin B					
Wolff [2000]		7; US	29/71/0		
Amph 0.2 mg/kg	159			8%	12%
Flu 400 mg	196			4%	12%
Bodey [1994]		1; US	NR		
Amph 0.5 mg/kg 3 X week	36			8%	11%
Flu 400 mg	41			5%	15%

Flu: fluconazole; Itra: Itraconazole; Amph: amphotericin; sol'n: solution; IV: intravenous; NR: not reported
† Itraconazole administered as 200 mg IV or 7.5 mg/kg oral solution
‡ Itraconazole administered as IV 400 mg on days 1-2, and 200 mg on days 3-14, and as oral solution 400 mg on days 15-100.
§ Itraconazole administered with amphotericin 6 mg intranasal
¶ Itraconazole administered with nystatin 4.5 million units
Source: Applicant's Table 2 in Section 2.4 of their submission

10.6 Reviewer's Conclusions

Meta-analyses of antifungal prophylaxis studies, which include BMT/HSCT patients, do not consistently show a significant reduction in mortality, although most do show a significant reduction in the number of invasive fungal infections. The effect was most pronounced in patients at high risk for prolonged neutropenia (allogeneic HSCT) and where the incidence of systemic infections in control patients was high (> 15%).

Review articles of antifungal prophylaxis also routinely noted that fluconazole had a significant effect in reducing systemic *Candida* infections. The effect is primarily seen in patients undergoing allogeneic BMT/HSCT. The period of greatest risk for infection due to *Candida* is the neutropenic, pre-engraftment phase in BMT recipients and the longer the duration of neutropenia (> 7 days), the higher the risk of infection. The incidence of invasive fungal infections appears to have decreased over time and has definitely decreased with the institution of routine triazole prophylaxis. Prevention of infection has become the most important parameter impacting overall outcome.

There was a wide range in the incidence of invasive fungal infections in the placebo-controlled studies, which may reflect the heterogeneous patient populations and treatment modalities. As a result of the increased use of colony stimulating factors (i.e., GCSF) and the introduction of nonmyeloablative transplant conditioning regimens, episodes of neutropenia in HSCT appear to be shorter now than in the past. On the other hand, other factors, such as graft versus host disease, appear to have emerged as "new" risk factors of greater significance in BMT/HSCT patients and have made it difficult to reliably estimate the true incidence of invasive fungal infection.

In the Goodman and Slavin trials, two large placebo-controlled trials in BMT/HSCT patients, the fluconazole treatment effect (placebo minus fluconazole) for reducing the overall incidence of systemic fungal infections ranged from 11% to 13%.

11 APPENDIX II: COMPARISON OF STUDY 98-0-050; GOODMAN ET AL. AND SLAVIN ET AL. TRIALS

11.1 Background

At a March 8, 2004 meeting between the applicant and the Agency, in anticipation of the current submission, the Agency requested information from the applicant regarding the "rationale for comparability of the Goodman *et al.* and Slavin *et al.* trials to Study 98-0-050 in terms of patient population, study endpoints, and study designs."

The studies performed by Goodman et al [1992] and Slavin et al [1995] are the two largest randomized, placebo-controlled trials performed to evaluate the effect of fluconazole prophylaxis in BMT recipients. The applicant believes these two studies provide a robust estimate of the effect of fluconazole prophylaxis in this high risk patient population. As noted by the applicant:

Study 98-0-050 is the largest randomized, blinded, comparative antifungal prophylaxis trial conducted in HSCT recipients. The study was designed in collaboration with BAMSG (Bacteriology and Mycology Study Group), part of the National Institute of Allergy and Infectious Disease (NIAID). The applicant believes the design is consistent with Centers for Disease Control (CDC), Infectious Disease Society of America (IDSA) and American Society of Blood and Marrow Transplantation (ASBMT) guidelines for antifungal prophylaxis in HSCT patients [CDC MMWR 2000] and reflects current practices in transplantation methodology and supportive care.

11.2 Study Comparison

The Goodman study included 17 centers in the U.S. and Study 98-0-050 included 70 centers in the U.S. and Canada. While the Slavin study was a single-center trial conducted at the Fred Hutchinson Cancer Center in Seattle, Washington; it is the largest randomized trial to enroll primarily allogeneic recipients. The Goodman study and Study 98-0-050 are similar with regard to the proportion of patients undergoing an allogeneic transplant, duration of study drug therapy, and time to neutrophil recovery. The dose of fluconazole in all three trials was 400 mg (once daily).

Clinical Reviewer's Comment: When fluconazole was being developed in the late 1980s and the Goodman and Slavin trials were being designed, a 400 mg per day dose was selected in the hope that higher plasma concentrations may overcome Aspergillus resistance to fluconazole. However, it has subsequently been shown that Aspergillus is intrinsically resistant to fluconazole and that regardless of the drug concentrations achieved, fluconazole will not treat infections due to the organism. [Prentice and Donnelly 2001]. In 2002 [MacMillan et al. 2002] studied 200 mg compared to 400 mg of fluconazole prospectively in a randomized trial and showed that 200

mg is also an effective dose for prevention of infections due to Candida. Study 98-0-050 was designed prior to 2002 and used the FDA-approved prophylaxis dose of 400 mg of fluconazole.

The following tables provide direct comparison of study design features between Goodman et al. [1992], Slavin et al. [1995], and Study 98-0-050. Comparisons of study design features [Table 1], key entry criteria [Table 2], endpoints [Table 3], patient characteristics [Table 4], results [Table 5] and incidence of proven and probable fungal infections [Table 6] are summarized.

Clinical Reviewer's Comment: Tables 6-11were created by the applicant.

TABLE 1
Study Design Comparison

Design Features	Goodman	Slavin	Study 98-0-050
Prospective, randomized, double-blind			
Randomization	1:1	1:1	1:1
Stratification	Transplant type	Transplant type, HLA match, type of isolation room	Age, transplant type, risk of transplant related mortality
Primary Analysis Population Set	All enrolled patients	Received transplant And ≥ 1 dose	Received ≥ 1 dose†
Initiation of Study Drug	At initiation of conditioning regimen	Within 24 hours of initiation of preparative regimen	Within 48 hours of initiation of preparative regimen
Duration of Study Drug Therapy	7 days after neutrophil recovery (ANC >1000 cells/mcL) or development of suspected or proven fungal infection (10 weeks maximum)	Until Day 75 after transplantation or development of a proven systemic fungal infection	Up to 5 days after neutrophil recovery (ANC ≥ 500 cells/mm^3) or development of a proven, probable or suspected systemic fungal infection (up to maximum 42 days after transplant)
Last Follow-up Visit	14 days after last dose	10-14 days after last dose	4 weeks after last dose

NR: not reported; HLA: human leukocyte antigen; ANC: absolute neutrophil count; mcL: microliter
† Two micafungin patients did not receive transplant but did receive at least one dose of study drug and are included in the full analysis set.
Source: Applicant's Table 6 in Appendix III of their submission

TABLE 2
Key Entry Criteria Comparison

Entry Criteria	Goodman	Slavin	Study 98-0-050
Age	13 years	>12 years	6 months†
Transplant Type	Allogeneic or autologous bone marrow transplant†	Allogeneic or autologous marrow transplant for hematologic malignancy	Allogeneic HSCT or autologous HSCT for hematologic malignancy
Antifungal therapy	No systemic antifungal therapy within 2 weeks prior	No systemic antifungal therapy within 72 hours prior	No systemic antifungal therapy within 72 hours prior
Fungal Infection	No preexisting systemic fungal infection	No documented systemic fungal infection	No evidence of an active deep or disseminated fungal infection
Liver function	AST, ALT or alk phos ≤ 5 X ULN or total bilirubin ≤ 2.5 mg/dL	AST, ALT or alk phos ≤ 3 X ULN or total bilirubin ≤ 3.0 mg/dL	AST, ALT or alk phos ≤ 5 X ULN or total bilirubin ≤ 2.5 X ULN

HSCT: hematopoietic stem cell transplant; AST: aspartate aminotransferase; ALT: alanine aminotransferase; ULN: upper limit of normal
† autologous transplant recipients were not restricted to only those with hematologic malignancy (i.e., leukemia or lymphoma) as the other two studies did
Source: Applicant's Table 7 in Appendix III of their submission

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TABLE 3
Endpoint Comparison

Endpoint	Goodman	Slavin	Study 98-0-050
Proven Fungal Infection	(Definite Fungal Infection) Clinical evidence of blood or tissue infection and a culture or biopsy specimen from involved site demonstrating pathogenic organism	(Systemic Fungal Infection) Positive culture or hyphal elements on biopsy from a normally sterile site. Also included urinary tract infection, defined as clean-catch specimen yielding $\geq 10^4$ CFU of yeast/mL	Biopsy proven (with or without culture), invasive (sinus, lungs, liver, brain, etc.), or disseminated infection (positive culture)
Probable Fungal Infection	NA	NA	Probable Pulmonary Aspergillosis: clinical evidence of pneumonia plus characteristic findings on chest X-ray or imaging plus BAL culture or histology showing fungal elements. Probable Chronic Disseminated Candidiasis: persistent or intermittent fever for ≥ 2 weeks despite treatment with broad-spectrum antibiotics, with fever persisting after neutrophil recovery plus characteristic abnormal findings on abdominal imaging
Suspected Fungal Infection	Any episode, such as persistent fever despite treatment with broad-spectrum antibacterial agents, for which physician felt compelled to treat empirically with amphotericin B but for which a fungal infection could not be established	Fever of unknown origin unresponsive to broad-spectrum antibiotics after 3-5 days. Empirical therapy with amphotericin B was initiated and study drug was continued during empirical therapy	Neutropenic (ANC <500 cells/mm3), persistent or recurrent fever of ≥ 100.4°F (≥ 38°C) for which there is no known etiology and patient failed to respond to at least 96 hours of broad-spectrum antibacterial therapy

NA: not applicable; ANC: absolute neutrophil count; CFU: colony forming units
Sponsor's Table 8 in Appendix III of their submission

TABLE 4
Patient Characteristics Comparison

Characteristic	Goodman		Slavin		Study 98-0-050	
	Fluconazole (n=179)	Placebo (n=177)	Fluconazole (n=152)	Placebo (n=148)	FK463 (n=425)	Fluconazole (n=457)
% Male	59%	44%	57%	60%	60%	60%
Mean age - years (range)	NR	NR	36.5 (13-60)	36.2 (13-65)	43.2 (0.6-73)	41.9 (0.6-71)
Transplant type: Allogeneic Autologous	52% 48%	44% 56%	88% 12%	89% 11%	52% 48%	56% 44%
Fungal colonization at baseline†	44%	39%	40%	48%	27%	30%
Duration of study drug - mean days (range)	23	20	NR§	NR§	19 (1-51)	19 (1-51)
Time to neutrophil recovery - median days (range) ‡	16	13	20 (mean time to engraftment)	20 (mean time to engraftment)	13 (3-54) [ANC ≥ 500 cells/mm^3]	13 (7-44) [ANC ≥ 500 cells/mm^3]

NR: not reported; ANC: absolute neutrophil count
† Fungal colonization at baseline only collected from oropharynx for Study 98-0-050.
‡ Time to neutrophil recovery imputed for Goodman study (duration of study drug minus 7 days) since study drug was continued for 7 days after neutrophil recovery.
§ Overall mean duration of study drug administration was 64 days for fluconazole and 55 days for placebo.
Source: Applicant's Table 9 in Appendix III of their submission

The patient population enrolled in Study 98-0-050 is similar to the Goodman study, both enrolled approximately 50% of patients having an allogeneic transplant (which is associated with a longer duration of neutropenia than an autologous transplant), although the Goodman study did not restrict the autologous transplant recipients to only those with leukemia or lymphoma. In contract, the Slavin trial enrolled primarily allogeneic transplant recipients (almost 90%).

The rate of fungal colonization at baseline was lower in Study 98-0-050 (about 30%) compared to both the Goodman and Slavin studies (above 40%).

The median time to neutrophil recovery in Study 98-0-050 was similar to the Goodman study (both about 13-16 days), whereas in the Slavin study it was longer (mean time to engraftment of 20 days).

TABLE 5
Results Comparison

Endpoint	Goodman		Slavin		Study 98-0-050	
	FLU (n=179)	Placebo (n=177)	FLU (n=152)	Placebo (n=148)	FK463 (n=425)	FLU (n=457)
Proven and Probable fungal infection	2.8%	15.8%	6.6%	17.6%	1.6%	2.4%
Suspected fungal infection	56%	66%	38%	55%	15%	21%
Time to failure median (days) †	21	17	21	18	17	17

FLU: Fluconazole
† Time to failure was calculated as:
- Goodman: median time to initiation of empirical therapy;
- Slavin: median time to initiation of empirical therapy;
- Study 98-0-050: median time to failure (proven, probable or suspected infection).

Source: Applicant's Table 10 in Appendix III of their submission

Clinical Reviewer's Comment: The applicant defined suspected infections in Study 98-0-050 as those patients who received empirical antifungal therapy rather than adhering to the protocol-defined criteria. The Clinical and Statistical Reviewers asked the applicant to re-evaluate those patients who met the protocol definition of suspected fungal infections, regardless of whether or not the patient received empirical therapy. A suspected systemic fungal infection defined as patients with neutropenia (ANC <500 cells/mm^3); persistent or recurrent fever (while ANC <500 cells/mm^3) of no known etiology; and failure to respond to at least 96 hours of broad spectrum antibacterial therapy. A persistent fever was defined as four consecutive days of fever greater than 38°C. A recurrent fever was defined as having at least one day with temperatures ≥ 38.5 °C after having at least one prior temperature > 38 °C; or having two days of temperatures > 38 °C after having at least one prior temperature > 38°C.

The resulting numbers of patients with a suspected fungal infection, through the end of therapy, was 12.5% (53/425) in the micafungin group and 83/457 in the fluconazole group.

TABLE 6
Comparison of Incidence of Proven and Probable Systemic Fungal Infections by Organism

Organism	Goodman		Slavin		Study 98-0-050	
	Fluconazole (n=179)	Placebo† (n=177)	Fluconazole (n=152)	Placebo‡ (n=148)	FK463 (n=425)	Fluconazole (n=457)
Candida	1.7%	13.6%	1.3%	12.2%	0.9%	0.4%
Aspergillus	0.6%	1.1%	2.0%	1.4%	0.2%	1.5%
Fusarium	0	0	0.7%	0.7%	0.2%	0.4%
Zygomyces	0	0	0	0	0.2%	0
Mucor	0.6%	0.6%	0	0	0	0
Unknown	0	0	1.3%	0	0	0

† Calculated from Tables 1 & 2 of Goodman manuscript.
‡ Calculated from Table 2 of Slavin manuscript.
Source: Applicant's Table 11 in Appendix III of their submission

Study 98-0-050 had a relatively lower rate of empirical therapy use (lower incidence of suspected fungal infection), as shown in Table 5, than either the Goodman or Slavin studies. There are several possible explanations, as put forth by the applicant, for this low use of empirical therapy:

- Improvements in transplant technique
- Mindset differences between physicians today compared to 10 years ago. In the Goodman and Slavin studies, the clinician was cognizant that approximately one-half of his/her patients were receiving placebo, so the tendency to switch patients to an active alternative, even if it was the nephrotoxic agent amphotericin, was stronger than in the current study where all patients were receiving active yeast prophylaxis, with yeast infections being the more common type of fungal infection during neutropenia.
- Advances in the understanding of the epidemiology of fungal infections in transplant patients. Clinicians have become more comfortable with managing neutropenic patients with fever and were less likely to remove them from prophylactic therapy to initiate a potentially more toxic empirical regimen.

The criteria for initiating empirical antifungal therapy in Study 98-0-050 were based on pre-defined criteria. According to the protocol, empirical therapy for a suspected systemic fungal infection could be initiated if all of the following criteria were met for at least 96 hours: neutropenia (ANC < 500 cells/mm^3); persistent or recurrent fever ($\geq$ 100.4°F, $\geq$ 38.0°C) for which there was no known etiology; and failure to respond to at least 96 hours of broad spectrum antibacterial therapy. The Slavin study had similar criteria (failure of broad-spectrum antibiotics for 3 to 5 days). However, in contrast, in the Goodman study initiation of empirical therapy for a suspected infection was less rigorously defined and often relied on the investigator's clinical judgment, which led to widespread use of amphotericin B.

In addition to a pre-defined definition for empirical therapy, the definitions of proven and probable infections in Study 98-0-050 were also designed prospectively and consistent with current guidelines.[8] In addition, after locking the database, all infections judged by local investigators to be proven or probable were reviewed separately in a blinded manner.[9]

11.3 Reviewer's Conclusions

The Goodman and Slavin trials, two large placebo-controlled trials of fluconazole in BMT/HSCT patients, were compared in terms of study design, key entry criteria, endpoints,

8 Ascioglu S, Rex JH, de Pauw B, et al. Defining opportunistic invasive fungal infections in immunocompromised patients with cancer and hematopoietic stem cell transplants: an international consensus. Clin Infect Dis 2002; 34:7-14

9 Consultant: Thomas J. Walsh, M.D., National Institute of Health, Bethesda, Maryland

12 APPENDIX III: REANALYSIS OF STUDY 98-0-050

12.1 Background

At a March 8, 2004 meeting between the applicant and the Agency, in anticipation of the current submission, the applicant proposed a re-analysis of the incidence of proven *Candida* infection in Study 98-0-050 which relied on incidence rates of proven breakthrough infections with *Candida* in previously conducted trials in the literature, mainly the Goodman, et al. study [1992] and the Slavin, et al. study [1995]. Details of the applicant's submitted re-analysis are summarized in below. The reviewer has included a detailed summary of individual patients who developed a proven or probable fungal infection during the study using, in part, clinical narratives of these patients supplied by the applicant.

12.2 Incidence of Proven *Candida* Infections in the Goodman and Slavin Trials

The incidence of proven systemic *Candida* infections in the Goodman and Slavin trials reported in respective publications were recalculated after exclusion of urinary tract infections. The incidence of systemic fungal infections for patients in the fluconazole and placebo groups is provided in Table 1.

Clinical Reviewer's Comment: Tables 1-5 and 7 were created by the applicant.

TABLE 1
Incidence of Proven Systemic *Candida* Infections from Historical Controls

Publication Incidence	Fluconazole	Placebo
Goodman et al, 1992		
Incidence of Systemic Fungal Infections	5/179 (2.8%)	28/177 (15.8%)
Incidence of Systemic *Candida* Infections†	**3/179 (1.7%)**	**24/177 (13.6%)**
Slavin et al, 1995		
Incidence of Systemic Fungal Infections	10/152 (6.6%)	26/148 (17.6%)
Incidence of *Candida* or Yeast Infections††	4/152 (2.6%)	29/148 (19.6%) §
Incidence of Systemic *Candida* Infections††	**2/152 (1.3%)**	**18/148 (12.2%)**
Incidence of Nonsystemic *Candida* Infections	2/152 (1.3%)	11/148 (7.4%) §§

† Calculated from Table 2 of published manuscript; fluconazole: 3 blood infections; placebo: 12 blood, 10 tissue, 2 esophagus (excluded 1 urinary tract infection)
†† Calculated from Table 2 of published manuscript
§ 32 infections in 26 patients; the published manuscript did not describe the patients with multiple infections; therefore, Table 2 was used to determine rates of *Candida* or yeast infections
§§ Per text on page 1547 of published manuscript; 2 fluconazole and 11 placebo patients with urinary infections; assumed these were due to *Candida* or yeast and excluded (FLU: 4 infections - 2 UTI = 2 systemic *Candida* infections; Placebo: 29 infections - 11 UTI = 18 systemic *Candida* infections).
Source: Applicant's Table 1 in Appendix III

12.2.1 Derivation by the Applicant of Incidence of Systemic *Candida* Infections from Slavin Trial

The incidence of proven systemic infections taken from Table 3 of the Slavin publication is presented in Table 2 and the sites of infection are shown in Table 3. In the placebo group there were 32 infections (Table 3) in 26 patients (Table 2). Three infections in the placebo group were noted as occurring at multiple sites.

TABLE 2
Proven Systemic Infections – Slavin Trial

	Fluconazole (n=152)	Placebo (n=148)
Number of patients with proven systemic infection	10	26
Incidence rate	7%	18%

Source: Applicant's Table 2 in Appendix III

TABLE 3
Sites of Proven Systemic Infections – Slavin Trial

Site	Fluconazole	Placebo
Blood	3	11
Lung	3	2
Brain	1	1
Multiple	1	3
Gastrointestinal	0	3
Sinus	0	1
Urinary tract infection	2	11
Total	**10**	**32**

Source: Applicant's Table 3 in Appendix III

The causative fungal organisms of proven systemic infections in the Slavin publication are presented Table 4.

TABLE 4
Causative Fungal Organisms of Proven Systemic Infections – Slavin Trial

Organism	Fluconazole	Placebo
Candida		
albicans	0	18
glabrata	3	6
tropicalis	0	2
guilliermondii	1	0
parapsilosis	0	1
pseudotropicalis	0	1
Yeast (unspecified)	0	1
Total *Candida*	**4**	**29**
Other Organisms		
Aspergillus fumigatus	3	2
Fusarium species	1	1
Unknown	2	0
Overall Total	**10**	**32**

Source: Applicant's Table 4 in Appendix III

The applicant calculated the incidence rate of fungal infections for the Slavin trial in two different ways, as shown in Table 5. The first method is based upon the number of *Candida* infections and the second method assumes that the maximum number of infections cannot exceed the number of patients with an infection. The incidence of infection in the fluconazole group is the same by both methods. However, in the placebo group by Method 1 the total number of infections due to *Candida* is 29 (out of 32 total infections) and the number of *Candida* systemic infections is 18 (subtracting out the UTI infections). Using Method 2 the maximum number of *Candida* infections is 26 (equaling the number of patients with an infection) and the number of *Candida* systemic infections is 15 (subtracting out the UTI infections). The overall incidence rate is 12.2% (18/148) in the placebo group by Method 1 and 10.1% (15/148) by Method 2. Method 2 gives the most conservative estimate of the placebo rate in the Slavin trial.

TABLE 5
Calculation of Incidence Rates – Slavin Trial

	Fluconazole	Placebo
Method 1		
# infections / # patients	10/10	32/26
# *Candida* infections	4	29
# non-systemic/UTI infections	2	11
# systemic (non-UTI) infections	2	18
Incidence of systemic *Candida* infections	2/152 1.3%	18/148 12.2%
Method 2†		
# infections / # patients	10/10	32/26
# *Candida* infections	4	26
# non-systemic/UTI infections	2	11
# systemic (non-UTI) infections	2	15
Incidence of systemic *Candida* infections	2/152 1.3%	15/148 10.1%

† Assumes that the maximum number of *Candida* infections cannot exceed the number of patients; therefore, it is assumed that 26 patients had at least one of 29 *Candida* infections. There was no difference between Method 1 and 2 for fluconazole.
Source: Applicant's Table 5 in Appendix III

12.2.2 Estimate of Non-Inferiority Margin Using Goodman and Slavin Trials

The incidence of proven invasive *Candida* infection with fluconazole and placebo in the Goodman and Slavin trials, is shown in Table 6; along with the difference, calculated by the applicant, for fluconazole minus placebo and the corresponding 95% confidence intervals. The difference both Method 1 and Method 2 for the placebo group in the Slavin study is also shown.

Clinical Reviewer's Comment: Table 6 was created by the reviewer using data from Section 2.2 of Appendix III (Re-analysis of Study 98-0-050) in the Applicant's study report.

TABLE 6
Treatment Difference by Trial

		Fluconazole	Placebo	Treatment difference (fluconazole minus placebo)	95 % Confidence Interval
Goodman Trial		3/179 (1.7%, 0.017)	24/177 (13.6%, 0.136)	0.119	0.065, 0.173
Slavin Trial	Method 1	2/152 (1.3%, 0.013)	18/148 (12.2%, 0.122)	0.108	0.053, 0.164
	Method 2	2/152 (1.3%, 0.013)	15/148 (10.1%, 0.101)	0.088	0.036, 0.140

The rates from the two studies were combined by the applicant using a meta-type analysis. A fixed effects model was used with drug therapy as a factor. The inverse of standard error of observed mean was used as weight given to each study. Using this approach the difference and 95% confidence interval was calculated for each method. The applicant proposes that an acceptable, conservative non-inferiority margin is one-half the lower bound of the confidence interval. [Snapinn, 2000]. The non-inferiority margin for the overall combined data (Goodman and Slavin) using placebo rate in Slavin trial based on Method 1 and Method 2, respectively is shown below:

- For the overall combined data (Goodman and Slavin) using placebo rate in Slavin trial based on Method 1 = **0.04**

The difference and 95% confidence interval was 0.114 (0.079, 0.149). Taking one-half this lower bound, 0.04 is the margin.

- For the overall combined data (Goodman and Slavin) using placebo rate in Slavin trial based on Method 2 = **0.035**

The difference and 95% confidence interval was 0.105 (0.070, 0.139). Taking one-half this lower bound, 0.035 is the margin.

12.3 Incidence of Proven *Candida* Infections in Study 98-0-050

The applicant's definitions of proven and probable infections, as defined in the protocol for Study 98-0-050, are shown below.

Criteria for Proven Infection:

a. Patients with biopsy-proven (with or without culture) invasive (sinus, lung, liver, brain, etc.) or disseminated infection (positive culture). Proven pulmonary fungal infection as defined below.

b. Immunocompromised patients with sinusitis or a pulmonary infiltrate and an acceptable positive culture for *Aspergillus* or *Fusarium* or the agents of mucor (zygomycosis) from the upper respiratory tract.

Criteria for Probable Infection:
Immunocompromised patients (neutropenia, chronic steroid therapy, etc.) with the characteristic clinical or radiological (chest X-ray, CT scan, other) picture of pulmonary aspergillosis or chronic disseminated candidiasis (see examples below).

Site Specific Diagnostic Criteria

1. **Diagnosis of Invasive Pulmonary Disease**

   Proven Pulmonary Fungal Infection:

   - **Chest radiograph(s) with acute infiltrate, clinically compatible with fungal pneumonia, PLUS**

- Acceptable lower respiratory tract culture/histology which identifies *Aspergillus*, *Fusarium* or *Mucor* species, (NOTE: Acceptable lower respiratory culture/histology includes: transthoracic needle aspiration OR transtracheal aspiration OR sheathed bronchoscopic brushings or biopsy), OR
- Hyphae noted by gram or another appropriate stain, or biopsy demonstrating characteristic invasive fungal elements.

Probable Pulmonary Fungal Infection:

- Clinical evidence of pneumonia (cough, dyspnea, pleuritic pain, rales, rhonchi or pleural rub); **PLUS**
- Characteristic findings on chest x-ray or imaging. Examples are:
  - pulmonary infiltrates on chest x-ray suggestive of aspergillosis - nodules, wedge-shaped or cavitating lesions,
  - "halo sign" on CT scan,
  - progression of lesions from infiltrates to cavitary or crescent lesions; **PLUS**
- Bronchoalveolar lavage reveals (culture or histology) fungal elements and is negative for other agents known to cause the observed pneumonic process such as CMV.

2. **Diagnosis of Sinusitis**
   Symptomatic and radiographic evidence suggesting acute sinusitis, PLUS a sinus needle aspiration or biopsy culture positive or histologically positive for fungus.

3. **Fungemia**
   One blood culture is positive AND the clinical picture supports the pathogenicity of the fungus.

4. **Abscess (Including CNS)**
   Radiographic, nuclear medicine or nuclear magnetic resonance evidence of an inflammatory focus, **PLUS** biopsy or aspiration culture positive or histologically positive for fungus.

5. **Invasive Skin/Subcutaneous Fungal Infection**
   Diagnosis will require biopsy ± culture documentation.

6. **Esophagitis, Tracheitis or Bronchitis**
   Endoscopically visualized plaques clinically suggestive of fungal infection **PLUS** hyphae or pseudohyphae noted by gram or other appropriate stain or biopsy demonstrating invasive fungal elements.

7. **Funguria**
   Clean catch or catheterized urine sediment containing ≥ 10^3 cfu/mL of fungi.

8. **Chronic Disseminated Candidiasis (Hepatosplenic Candidiasis)**[9]

   a. Proven Chronic Candidiasis

   - *Persistent or intermittent fever for* ≥ 2 weeks despite treatment with broad-spectrum antibiotics, with fever persisting after recovery from neutropenia, **PLUS**
   - Any abdominal signs and symptoms (such as upper abdominal pain or tenderness, jaundice, hepatomegaly, and/or splenomegaly), **PLUS**
   - Elevated liver function tests, especially serum alkaline phosphatase, **PLUS**
   - Abnormal findings on abdominal imaging (ultrasound, computed tomography, or magnetic resonance imaging) consistent with the radiologic picture of chronic disseminated candidiasis, **PLUS**
   - Recovery of *Candida* species from blood culture or culture or histologic confirmation from biopsy of an involved organ.

   b. Probable Chronic Disseminated Candidiasis

   - Persistent or intermittent fever for ≥ 2 weeks despite treatment with broad-spectrum antibiotics, with fever persisting after recovery from neutropenia, **PLUS**
   - Abnormal findings on abdominal imaging (ultrasound, computed tomography, or magnetic resonance imaging) consistent with the radiologic picture of chronic disseminated candidiasis.

9. **Other Focus**

The Investigator should specify site in detail, and the diagnosis should be supported by biopsy showing invasive fungal elements or positive culture from a normally sterile site.

Based on the original protocol-specified diagnostic criteria for breakthrough invasive fungal infection, there were seven breakthrough infections in the micafungin group (6 proven, 1 probable) as compared with 11 breakthrough infections in the fluconazole group (8 proven, 3 probable), as defined by the independent investigator, and shown in Table 7. Thus, the overall incidence of breakthrough invasive fungal infections was 1.6% (7/425) for the micafungin patients and 2.4% (11/457) for the fluconazole patients.

Clinical Reviewer's Comment: The case report forms for all patients with an investigator-reported proven or probable breakthrough invasive fungal infection were reviewed in a blinded manner using the protocol-specified diagnostic criteria. This review confirmed all investigator-reported proven invasive fungal infections. However, 12/16 patients with reported probable invasive fungal infections did not meet protocol-specified diagnostic criteria. The 12 patients originally classified as investigator-reported probable infections (i.e., failures) were reclassified by the applicant, upon request by the Division, as shown below. Nine of the 12 patients were retained as failures. The 3 patients who received systemic antifungal therapy were re-classified from failures in the original analysis to successes. However, this reassignment does not change the overall outcome and conclusions from the study.

The 12 patients originally classified as investigator-reported probable infections, were reclassified as:

Deaths:
1253104 (fluconazole), 4181001 (fluconazole)

Proven Infection (based upon applicant's independent reviewer):
0323003 (micafungin)

Suspected Infection (using strict protocol criteria):
0082502, 0203505, 0321009, 0352504, 0523101, 1252103 (all micafungin patients)

Received systemic antifungal therapy:
0311006 (micafungin), 0892001 (fluconazole), 1233502 (micafungin)

Removing the probable infections, leaves 6 proven infections in the micafungin group and 8 infections in the fluconazole group. All patients had received an allogeneic transplant. Of the 6 proven infections in the micafungin group, 4 occurred during prophylactic therapy and 2 occurred during the 4 week post-therapy period. Of the 8 proven infections in the fluconazole group, 5 occurred during prophylactic therapy and 3 occurred during the 4 week post-therapy period.

TABLE 7
Proven or Probable Fungal Infections by Organism

Organism	Micafungin (n=425)		Fluconazole (n=457)	
Proven	6	(1.4%)	8	(1.8%)
Aspergillus species	0	(0.0%)	4	(0.9%)
Candida species	4	(0.9%)	2	(0.4%)
Fusarium species	1	(0.2%)	2	(0.4%)
Zygomyces species	1	(0.2%)	0	(0.0%)
Probable	1	(0.2%)	3	(0.7%)
Aspergillus species	1	(0.2%)	3	(0.7%)

Patient base: all randomized patients who received at least 1 dose of study drug (full analysis set).
Proven: includes biopsy-proven (with or without culture) invasive or disseminated fungal infection
Probable: includes patients with the characteristic clinical or radiological (chest x-ray, CT scan, other) picture of pulmonary aspergillosis plus a positive BAL specimen.
Source: Applicant's Table 18 in NDA 21-506, submission dated 4/29/02

Clinical Reviewer's Comment: Of the proven infections in the micafungin group, all Candida infections were isolated from blood cultures, but there were micafungin susceptibility test results for only two Candida species (see Table 8A). According to the Microbiology Review for the original NDA 21-506 submission, both of these organisms, C. lusitaniae (MIC = 0.125 μg/mL) and C. glabrata (≤ 0.063 μg/mL) were susceptible to micafungin. Two of the other proven infections in the micafungin group were due to Fusarium species and Zygomycetes, which are organisms resistant to micafungin.

Fluconazole is known to have no significant antifungal activity against Aspergillus species, Fusarium species, and Zygomyces. One of the two proven Candida bloodstream infections was due to C. krusei, which is also resistant to fluconazole. The other infection was due to C. parapsilosis, which is not usually resistant to fluconazole. No MIC information is available from the patient who developed a C. parapsilosis infection.

Detailed patient information on the proven infections is shown in Tables 7A and 7B for micafungin and fluconazole, respectively. There were 4 infections due to *Candida* spp. in the micafungin group and 2 in the fluconazole group. Detailed clinical narratives for patients who died due to fungal infection, those surviving with proven infection in the micafungin group, and those surviving with proven infection in the fluconazole group, respectively, are provided following the tables. A description of probable infections follows in Tables 8A and 8B for micafungin and fluconazole, respectively.

Clinical Reviewer's Comment: Tables 8A, 8B, 9A, and 9B were created by the reviewer from data in NDA 21-506, submission dated 4/29/02. Clinical narratives on surviving patients with proven and probable fungal infections were requested by the Reviewer and were submitted by the applicant on October 29, 2004.

Clinical Reviewer's Comment: According to the protocol, in addition to proven and probable infections, the applicant defined a category of "suspected" fungal infection consisting of three components:

- *Patients with neutropenia (ANC < 500/mm^3) AND*
- *Persistent fever of ≥ 100.4 °F (≥ 38 °C) for which there is no known etiology OR a recurrent fever of > 100.4 °F (> 38 °C) on two measurements of temperature at least 3 hours apart or a single measurement of ≥ 101.3 °F (≥ 38.5 °C) AND*
- *Failed to respond to 96 hours of adequate broad spectrum antibacterial therapy.*

In the applicant's original study report, patients who received empirical antifungal therapy were considered to have met the criteria of suspected fungal infection. However, it was noted that some patients who received empirical therapy did not meet the protocol defined definition of suspected fungal infection prior to the initiation of empirical therapy.

Therefore, at a teleconference on February 14, 2005, the Reviewer requested the applicant re-analyze the patient population and identify patients who met the protocol-defined criteria for a suspected fungal infection, regardless of whether or not they received empirical therapy. In a submission dated February 15, 2005, the applicant identified 53 (12.5%) patients in the micafungin group and 83 patients (18.2%) in the fluconazole group who met the criteria, after removing patients who died or developed proven/probable infections. Of the remaining patients (excluding those who died or who developed a proven/probable/suspected infection), 42% in each group received empirical antifungal therapy. The criteria used by the applicant for defining a suspected fungal infection in the re-analysis are included below:

A suspected systemic fungal infection was diagnosed in patients with neutropenia (ANC <500 cells/mm^3); persistent or recurrent fever (while ANC <500 cells/mm^3) of no known etiology; and failure to respond to at least 96 hours of broad spectrum antibacterial therapy. A persistent fever was defined as four consecutive days of fever greater than 38°C. A recurrent fever was defined as either having at least one day with temperatures ≥ 38.5 °C after having at least one prior temperature > 38 °C; or having two days of temperatures > 38 °C after having at least one prior temperature > 38°C.

TABLE 8A
Micafungin Group - Description of Proven Fungal Infections due to *Candida*
(Proven Fungal Infections due to Non-*Candida* Species Also Listed)

Patient Number/ Sex/Age (yrs)	Organism/Site	Source of Diagnostic information/*In Vitro* Susceptibility	Transplant Features* Transplant type/ Donor type/ Cell type/ Risk group	Time of Diagnosis in Relation to Study Drug
013-3501/F/47	*C. lusitanae*/ blood	Positive blood culture on Day 16; Micafungin: MIC, MEC and MFC = 0.125 µg/mL; Fluconazole: MIC and MEC ≤ 0.5, MFC > 64 µg/mL	Al, O, B, H	**During Treatment** (micafungin discontinued on Day 16 for lack of efficacy)
020-3520/M/38	*C. albicans*/ blood	Positive blood cultures on Days 19, 21, and 22; Micafungin: MIC and MEC ≤ 0.063, MFC = 0.25 µg/mL Fluconazole: MIC and MEC ≤ 0.5 and MFC > 64 µg/mL	Al, O, C, H	**During Treatment** (micafungin discontinued on Day 20 due to lack of efficacy)
032-3003/M/34	*C. glabrata*/ lung	CT of lung showed infiltrates and consolidation on Day 17; Positive BAL fluid on Day 18; chest X-ray on Day 21 showed increasing opacitifcation; repeat CT of lung on Day 30 showed ground glass opacities and bilateral pleural effusions; Positive repeat BAL on Day 31; Positive blood culture on Day 32; Positive catheter tip on Day 34; No MIC data available (*Note: candidemia, not pneumonia, met criteria for proven infection*)	Al, O, B, L	**Post-Treatment** (Patient received 16 days of micafungin and was discontinued for probable *Candida glabrata* in the lung; blood culture and catheter tip were not positive, yielding a proven infection, until Day 45)

TABLE 8A (continued)
Micafungin Group - Description of Proven Fungal Infections due to *Candida*
(Proven Fungal Infections due to Non-*Candida* Species Also Listed)

Patient Number/ Sex/Age (yrs)	Organism/Site	Source of Diagnostic information/*In Vitro* Susceptibility	Transplant Features* Transplant type/ Donor type/ Cell type/ Risk group	Time of Diagnosis in Relation to Study Drug
042-2003/F/53	*C. parapsilosis*/ blood	Positive blood culture on Day 35; No MIC data available	Al, M, P, L	**During Treatment** (micafungin discontinued on Day 34 due to lack of efficacy)
057-2528/F/33	*Fusarium* spp./ Skin and bone	MRI showed bone involvement of right great toe on Day 13; Positive skin biopsy on Day 15; Micafungin: MIC and MFC > 16, MEC = 1.0 µg/mL Fluconazole: MIC, MEC, and MFC > 100 µg/mL	Al, M, P, H	**Post-Treatment** (micafungin discontinued on Day 9 due to lack of efficacy – febrile and neutropenic)
405-3601/M/7	*Zygomyces* spp./ disseminated	Autopsy (Primary cause of death: multifocal fungal emboli with acute infarct of right middle cerebral artery and left thalamus); No MIC data available	Al, O, C, H	**During Treatment** (patient received 9 days of micafungin, discontinued due to lack of efficacy, and died on Day 12)

* Transplant features:
transplant type, Allogeneic (Al), autologous (Au);
donor type, matched sibling (M), other (O);
cell type, bone marrow (B), cord blood (C), peripheral blood cells (P);
risk group, low (L), high (H); N.A., not applicable/did not meet protocol-specified criteria
MIC = minimum inhibitory concentration
MEC = minimum effective concentration
MFC = minimum fungicidal concentration

TABLE 8B (continued)
Fluconazole Group - Description of Proven Fungal Infections due to *Candida*
(Proven Fungal Infections due to Non-*Candida* Species Also Listed)

Patient Number/ Sex/Age (yrs)	Organism/Site	Source of Diagnostic information/*In Vitro* Susceptibility	Transplant Features* Transplant type/ Donor type/ Cell type/ Risk group	Time of Diagnosis in Relation to Study Drug
037-3501/M/27	*Fusarium* species/ toe	Positive culture of pus from toe on Day 48; gallium scans showed osteomyelitis of toe on Days 49 and 54; Fluconazole MIC, MEC, and MFC > 100 µg/mL Micafungin MIC, MEC, and MFC > 16 µg/mL Itraconazole MIC, MEC, and MFC > 12.5 µg/mL Amphotericin B: MIC, MEC, and MFC = 2 µg/mL	Al, O, B, H	**Post-Therapy** (fluconazole was completed on Day 26)
057-2513/M/67	*Fusarium solani*/ Skin and lung	Positive histology and culture of skin biopsy on Day 9; tracheal tissue showed branching hyphae; Fluconazole: MIC, MEC, and MFC > 100 µg/mL, Micafungin: MIC and MFC, > 16, MEC = 16 µg/mL	Al, M, P, H	**During Therapy** (fluconazole was discontinued on Day 11 due to lack of efficacy)
059-3601/F/11	*Aspergillosis* non-speciated/ Lung	Chest X-ray on Day 17 was consistent with fungal ball in lung; CT scans on Days 21 and 24 also suggestive; BAL fluid on Day 30 showed hyphal fragments; CT scan showed lesions in lung on Day 36; Positive histology from lung biopsy on Day 38; No MIC data available	Al, O, B, H	**During Treatment** (fluconazole discontinued on Day 16 due to lack of efficacy)

TABLE 8B (continued)
Fluconazole Group - Description of Description of Proven Fungal Infections due to *Candida*
(Proven Fungal Infections due to Non-*Candida* Species Also Listed)

Patient Number/ Sex/Age (yrs)	Organism/Site	Source of Diagnostic information/*In Vitro* Susceptibility	Transplant Features* Transplant type/ Donor type/ Cell type/ Risk group	Time of Diagnosis in Relation to Study Drug
125-3105/F/9	*C. parapsilosis*/ blood	Positive blood cultures on Days 15, 16 and 18; No MIC data available	Al, O, B, L	**During Treatment** (fluconazole discontinued on Day 20 due to lack of efficacy)
262-3601/M/10	*A. fumigatus*/ lung	CT showed lung mass on Day 21; positive histology from lung biopsy on Day 21; Positive culture from lung aspirate on Day 21; Fluconazole: MIC, MEC, and MFC > 100 µg/mL Micafungin: MIC and MFC > 16, MEC ≤ 0.063 µg/mL Amphotericin B: MIC, MEC, MFC = 0.5 µg/mL	Al, O, B, H	**During Treatment** (fluconazole discontinued on Day 18 due to lack of efficacy – febrile and neutropenic)

* Transplant features:
transplant type, Allogeneic (Al), autologous (Au);
donor type, matched sibling (M), other (O);
cell type, bone marrow (B), cord blood (C), peripheral blood cells (P);
risk group, low (L), high (H); N.A., not applicable/did not meet protocol-specified criteria
MIC = minimum inhibitory concentration
MEC = minimum effective concentration
MFC = minimum fungicidal concentration

TABLE 9A
Micafungin Group - Description of Probable Fungal Infections

Patient Number/ Sex/Age (yrs)	Probable Organism/Site	Source of Diagnostic information/*In Vitro* Susceptibility	Transplant Features* Transplant type/ Donor type/ Cell type/ Risk group	Time of Diagnosis in Relation to Study Drug
005-2505/F/42	*Aspergillus* spp./*Candida albicans*	Chest CT on Day 1 showed density on consolidation; BAL fluid on Day 3 showed septate hyphae; Chest X-ray on Day 8 showed consolidation (probable pulmonary aspergillosis and *Candida albicans*);	Al, M, P, H	**During Therapy** (micafungin was discontinued on Day 3 due to lack of efficacy)

* Transplant features:
transplant type, Allogeneic (Al), autologous (Au);
donor type, matched sibling (M), other (O);
cell type, bone marrow (B), cord blood (C), peripheral blood cells (P);
risk group, low (L), high (H)

TABLE 9B
Fluconazole Group - Description of Probable Fungal Infections

Patient Number/ Sex/Age (yrs)	**Probable Organism/Site**	**Source of Diagnostic information/*In Vitro* Susceptibility**	**Transplant Features* Transplant type/ Donor type/ Cell type/ Risk group**	**Time of Diagnosis in Relation to Study Drug**
020-2503/M/60	*Aspergillus* spp.	CT of chest showed nodules on Day 13; histology of BAL fluid on Day 13 showed branching septate hypae consistent with *Aspergillus* spp.	Al, M, P, H	**During Therapy** (fluconazole was discontinued on Day 12 due to lack of efficacy; patient died on Day 21; Investigator's opinion was death due to fungal infection, but unrelated to study drug)
042-2503/M/51	*Aspergillus* spp.	Chest X-ray on Day 20 showed bibasilar atelectasis with possible pneumonia or small pleural effusion with increased vascular prominence consistent with a fungal infection; Chest CT scan on Day 21 showed pleural fluid collection; Chest X-ray on Day 22 showed increased bilateral opacities with a somewhat nodular appearance; Positive BAL fluid on Day 23 for fungal organisms compatible with *Aspergillus* spp.; Chest CT scan on Day 31 showed progression in size and number of nodules consistent with probable pulmonary aspergillosis	Al, M, P, H	**During Therapy** (fluconazole was discontinued on Day 21 due to lack of efficacy – febrile and neutropenic)

TABLE 9B (continued)
Fluconazole Group - Description of Probable Fungal Infections

Patient Number/ Sex/Age (yrs)	Probable Organism/Site	Source of Diagnostic information/*In Vitro* Susceptibility	Transplant Features* Transplant type/ Donor type/ Cell type/ Risk group	Time of Diagnosis in Relation to Study Drug
042-3004/F/40	*Aspergillus* spp.	Day 9 developed severe chest pain, Day 10 developed pulmonary edema; Day 17 developed multi-organ failure also a CT scan showed multifocal areas of lung consolidation with small nodules with a bronchiolar distribution suggested of an airway spread of an infectious process with multifocal pneumonia; Day 21 sputum culture was positive for *Aspergillus* spp.	Al, B, L	**During Therapy** (fluconazole was discontinued on Day 17 due to lack of efficacy)

* Transplant features:
transplant type, Allogeneic (Al), autologous (Au);
donor type, matched sibling (M), other (O);
cell type, bone marrow (B), cord blood (C), peripheral blood cells (P);
risk group, low (L), high (H)

TABLE 8B
Fluconazole Group - Description of Proven Fungal Infections due to *Candida*
(Proven Fungal Infections due to Non-*Candida* Species Also Listed)

Patient Number/ Sex/Age (yrs)	Organism/Site	Source of Diagnostic information/*In Vitro* Susceptibility	Transplant Features* Transplant type/ Donor type/ Cell type/ Risk group	Time of Diagnosis in Relation to Study Drug
013-3502/F/50	*Aspergillosis* spp./invasive/ disseminated in lungs	Autopsy – histology; No MIC data available	Al, O, B, H	**Post-Treatment** (patient received one dose of fluconazole and then was removed from the study and enrolled into a treatment protocol for [redacted]
020-3509/F/53	*A. fumigatus*/ lung	Positive lung biopsy on Day 54; Positive culture of lung mass aspirate on Day 59; Positive histology of pleural fluid on Day 60 No MIC data available	Al, O, C, H	**Post-Therapy** (fluconazole was completed on Day 35)
020-3510/M/26	*C. krusei*/ blood	Positive blood culture on Day 22; Fluconazole: MIC and MEC = 32, MFC > 64 µg/mL Micafungin: MIC, MEC, and MFC = 0.5 µg/mL	Al, O, B, H	**During Therapy** (fluconazole was discontinued on Day 23)

12.3.1 Narratives of Deaths in Patients with Proven Infections

Patient #: 133502
This 50-year-old Caucasian female was diagnosed in — with acute myelogenous leukemia in relapse at the time of randomization. The patient was admitted to the hospital on — initially for the diagnosis of fevers. The patient subsequently underwent an allogeneic bone marrow cell transplant with an associated high risk of transplant related mortality.

The patient's conditioning regimen included cytarabine and pentostatin. The Patient was treated with cefepime, vancomycin, metronidazole, ciprofloxacin, fluconazole, acyclovir, clotrimazole troche, nystatin, and famciclovir prior to initiation of study drug. Significant baseline clinical conditions included neutropenic fever, left pleural effusion, neutropenia, hypotension, anemia, asthma, thrombocytopenia, renal insufficiency, hypocalcemia, hematuria, vancomycin-resistant *Enterococcus* spp. (VRE) bacteremia, hypomagnesemia, mucositis, fluid overload, mitral valve prolapse, sinusitis, and elevate liver function test levels. On —, the patient had no evidence of a fungal infection.

Clinical Course:

The patient was randomized to receive fluconazole. Study drug therapy was initiated on — (Day 1) at a dose of 200 mg due to a creatinine clearance of 34 mL/min.

Discontinuation:
The patient was discontinued from study drug on Day 1 due to removal from study for enrollment into a different protocol for —

Outcome:
Fluconazole therapy was administered on Day 2 and from Day 6 to Day 12 for antifungal prophylaxis. The patient underwent an allogeneic bone marrow transplant on Day 5. On Day 12 the patient developed multi-organ system failure. The patient expired on Day 14 due to multi-organ system failure with the contributing condition of gram-positive (VRE) thrombus, subclavian vein that in the Investigator's opinion was not related to study drug or a fungal infection. Upon autopsy, the patient was found to have a proven invasive/disseminated fungal infection of the lungs due to *Aspergillus* spp. The patient did not achieve neutrophil recovery during the study.

Patient #: 405-3601
This 7-year-old Caucasian male was diagnosed in — with acute lymphocytic leukemia (ALL) in relapse at the time of randomization. The patient was admitted to the hospital on — for an allogeneic cord blood transplant with an associated high risk of transplant related mortality. The patient's conditioning regimen included idarubicin, vincristine, melphalan, antithymocyte globulin and total body irradiation with cyclosporine, methotrexate and methylprednisolone therapy for graft-versus-host disease (GVHD) prophylaxis. The patient was also treated with filgrastim to promote marrow production

The patient was treated with fluconazole, sulfamexazole-trimethoprim, ceftazidime and vancomycin prior to initiation of study drug. Significant baseline clinical conditions included leukopenia, thrombocytopenia, anemia, neutropenia and fever. Or — the patient had no evidence of a fungal infection.

Clinical Course:
The Patient was randomized to receive micafungin. Study drug therapy was initiated on —
(Day 1) at a dose of 22.3 mg. The patient underwent an allogeneic cord blood transplant on Day 8. On Day 9 the Patient experienced a right middle cerebral artery stroke that in the Investigator's opinion was unlikely related to study drug.

Discontinuation:
The Patient was discontinued from study drug on Day 9 due to lack of efficacy. (Upon autopsy, the patient was found to have a disseminated fungal infection due to *Zygomyces* spp.)

Outcome:
Despite treatment, the patient's neurological status deteriorated. The patient expired on Day 12 due to multi-focal fungal emboli with acute infarct of right middle cerebral artery territory and left thalmus with the contributory conditions of an allogeneic stem cell transplant and refractory ALL. The patient's death, in the Investigator's opinion, was unlikely related to study drug yet related to a fungal infection. The patient did not achieve neutrophil recovery during the study.

12.3.2 Narratives of Surviving Patients with Proven Infections – Micafungin Group

Clinical Reviewer's Comment: The following narratives were requested from the applicant by the Reviewer and were submitted on October 29, 2004.

Patient #013-13501

This 47-year-old Caucasian female was diagnosed with myelodysplasia RAEB on [redacted] which was active at the time of randomization. The patient was admitted to the hospital on [redacted] for an unrelated allogeneic bone marrow transplant. The risk of transplant related mortality for this patient was considered high. The conditioning regimen included cytarabine, idarubicin, and total body irradiation. Other medications administered during the 14 days prior to randomization included fluconazole (day -15 to day -5), ciprofloxacin, vancomycin, cefepime, nystatin, methylprednisolone, hydrocortisone, and acyclovir. The following conditions were present at baseline: anemia, lower extremity pruritic erythematosis rash, hypoalbuminemia, headache, constipation, anxiety, thrombocytopenia, elevated lactic dehydrogenase (LDH), dysuria, pheresis catheter site inflammation, insomnia, anorexia, chronic fatigue syndrome, neutropenia (baseline ANC value of 0 cells/mm^3), and esophagitis. An assessment on Day -1 indicated there were no signs of fungal infection prior to study enrollment.

Clinical Course:

The patient was randomized to micafungin and received the first dose of micafungin 50 mg on [redacted] (Day 1). The patient underwent an allogeneic bone marrow transplant on Day 6. Study drug was held on the day of the transplant as per the local site transplant protocol. Cyclosporine was started on Day 5 to prevent graft versus host disease (GVHD). However, Grade II GVHD developed on Day 8 for which methylprednisolone and prednisolone were added. The patient also received methrotrexate from Day 7 to Day 9 for myelodysplasia RAEB. On Day 8, the patient developed a neutropenic fever with temperature spikes ranging from 38.6°C to 40.1°C. On Day 16, a blood culture was drawn which revealed *Candida lusitanae*. Significant conditions that developed during the study drug treatment included mucositis, hypertension, nausea, vomiting, abdominal pain, and chest pain. None of the events were serious in nature.

Discontinuation:

The patient was discontinued from study drug on Day 16 due to lack of efficacy. The patient was still neutropenic (ANC <100 cells/mm^3) at the time of study drug discontinuation.

Outcome:

The patient received conventional amphotericin B from Day 17 to Day 18 and was switched to AmBisome from Day 19 through Day 31 for treatment of the candidemia. Blood cultures drawn on Days 17 and 18 were negative. The patient engrafted on Day 19 with an ANC of 506 cells/mm^3. A serious adverse event of severe hyperbilirubinemia was reported on Day 19 that continued beyond the post-therapy period. Prophylactic fluconazole was started on Day 42. No new fungal infections developed during the post-therapy period as indicated at the post-therapy visit on Day 45. The patient was alive at the last study visit.

Patient #020-3520

This 38-year-old Caucasian male was diagnosed with acute lymphocytic leukemia on [redacted], which was active at the time of randomization. The patient was admitted to the hospital on [redacted] for an unrelated allogeneic cord blood transplant. The risk of transplant related mortality for this patient was considered high. The conditioning regimen included total body irradiation and cyclophosphamide. Significant conditions present at baseline included anxiety, nausea, and Hickman catheter discomfort. An assessment on Day -1 indicated there were no signs of fungal infection prior to study enrollment.

Clinical Course: The patient was randomized to micafungin and received the first dose of 50 mg on [redacted] (Day 1). The patient underwent an allogeneic bone marrow transplant on Day 8. Study drug was not given on Day 11. Cyclosporine, methylprednisolone, and antithymocyte immunoglobulin were given to prevent graft versus host disease post-transplant. Neutropenia developed on Day 8 with an ANC of less than 500 cells/mm^3 and continued through-out the period of prophylaxis despite treatment with granulocyte colony stimulating factor (GCSF). On Days 19, 21, and 22, blood cultures were drawn which revealed *Candida albicans*. Significant conditions that developed during therapy included mucositis, thrombocytopenia, bleeding from the Hickman site, and hypokalemia. None of the events were serious in nature. No adverse events were considered related to study drug.

Discontinuation

The patient was discontinued from study drug on Day 20 due to lack of efficacy. The patient was still neutropenic (ANC <500 cells/mm^3) at the time of study drug discontinuation.

Outcome:

The patient received conventional amphotericin B from Day 21 to Day 22 and was switched to Abelcet® from Day 23 through Day 44 for treatment of the candidemia. No follow-up blood cultures were reported, however, a stop date of the fungal infection was reported as Day 23. The patient did not engraft during the study. No serious adverse events were reported and the patient was alive at the last study visit. Prophylactic fluconazole was started on Day 45. No new fungal infections developed during the post-therapy period as indicated at the post-therapy visit on Day 48.

Patient #032-3003

This 34-year-old Caucasian male was diagnosed with chronic myelogenous leukemia (CML) on [redacted] which was in remission at the time of randomization. The patient was admitted to the hospital on Day -3 for an unrelated allogeneic bone marrow transplant, with an associated low risk of transplant related mortality. The patient's conditioning regimen included cyclophosphamide, hydroxycarbamide and total body irradiation. Significant baseline clinical conditions included anemia, hematuria, heart disease and Herpes Simplex I and II. Fungal infection was absent at the time of enrollment.

Clinical Course:

The patient was randomized to receive micafungin and received the first dose of 50 mg on — (Day 1). The patient's graft-versus-host-disease (GVHD) prophylaxis included cyclosporine on Day 3. The patient underwent an allogeneic bone marrow transplant on Day 4. The patient was initiated on methotrexate on Day 6. The patient became neutropenic on Day 7, with an ANC of 497 cells/mm^3. The patient experienced a serious adverse event of hypotension on Day 12, which the Investigator considered unlikely related to study drug. The patient experienced GVHD on Day 15. The patient received methylprednisolone to treat GVHD. Surveillance cultures of the oropharynx taken on Day 5 and Day 11 revealed yeast, non-speciated. A CT scan of the chest taken on Day 17 revealed diffuse bilateral opacities in the air space.

Discontinuation:
The patient discontinued study drug therapy on Day 16 due to lack of efficacy and probable *Candida glabrata* infection in the lung based on the CT scan obtained on Day 17 of the chest and cultures from the BAL revealing *Candida glabrata.*

Outcome:
Amphotericin B therapy was administered from Day 17 to Day 19, and Abelcet® was initiated on Day 20. A BAL culture taken on Day 18 revealed *Candida glabrata.* An x-ray of the chest taken on Day 21 revealed persistent infiltrates, increasing opacification and suprapneumonia. CT scan of chest taken on Day 30 revealed patchy ground glass opacities in the upper and lower left lobes and bilateral pleural effusions. The patient experienced a serious adverse event of dyspnea on Day 31 and a BAL culture taken on Day 31 revealed *Candida glabrata.* On Day 32 the patient developed a proven *Candida glabrata* infection in the blood, based upon a blood culture taken on Day 32 and a catheter tip culture taken on Day 34. Multiple chest x-rays taken from Day 34 through Day 47, as well as continuing dyspnea were evidence of continuing fungal disease. Hypotension continued throughout the post-therapy period. The patient's GVHD continued throughout the post-therapy period, with a maximum Grade of II. The patient did not achieve neutrophil recovery throughout the post-therapy period. The patient was alive at the time of the last study visit.

Clinical Reviewer's Comment: The Candida glabrata candidemia met the protocol specified criteria for a proven Candida infection; however, the Candida glabrata pneumonia was considered "probable" and did not meet the criteria for a proven infection. This assessment was made by Dr. Thomas Walsh from the National Institutes of Health, who performed a blinded review of all the cases of proven and probable breakthrough fungal infections which occurred during the study.

Patient #042-2003
This 53-year-old Caucasian female was diagnosed with Non-Hodgkin's Lymphoma on — which was in remission at the time of randomization. The patient was admitted to the hospital on Day -1 for a matched allogeneic peripheral stem cell transplant with an associated low risk of transplant related mortality. Significant baseline conditions included hypomagnesemia, neuropathy, creatinine clearance decreased, abnormal kidney function,

increased serum creatinine, and hypertension. Absolute neutrophil count (ANC) on Day -1 was 2700 cells/mm^3.

Clinical Course:
The patient was randomized to receive micafungin and received her first dose on — (Day 1). The patient had no evidence of fungal infection at time of enrollment. On Days 1 to 4 the patient received total body irradiation as a pre-conditioning regimen. On Days 5 and 6 the patient received cyclophosphamide as part of the pre-conditioning regimen. Ciprofloxacin was administered on Days 1 through 10. On Day 6 the patient received cyclosporine for GVHD prophylaxis and on Day 9 was started on methotrexate. The patient received a matched sibling peripheral stem cell transplant on Day 8. On Day 8 the patient's ANC was 970 cells/mm^3 and on Day 10 the ANC had dropped to less than 200 cells/mm^3. On Day 11 the patient experienced grade IV mucositis which continued past the post-therapy visit. The patient experienced sepsis from Day 10 to 12 for which the patient received vancomycin and imipenem. On Day 33 the patient achieved neutrophil recovery with an ANC of 584 cells/mm^3. A blood culture taken on Day 35 was positive for *Candida parapsilosis* infection. The patient was diagnosed with a proven *Candida parapsilosis* candidemia. None of the adverse events during prophylaxis were serious in nature or related to study drug.

Discontinuation:
The patient was discontinued from study drug therapy on Day 34 due to lack of efficacy.

Outcome:
The patient started on fluconazole 200 mg on Day 35 for prophylaxis. On Day 37 the patient's fluconazole dose was increased to 400 mg for treatment. The patient was then switched to Abelcet® 400 mg on Day 40. A culture of a catheter tip was positive for *Candida parapsilosis* on Day 37 and a blood culture on Day 40 was positive for *Candida parapsilosis*. Blood cultures on Days 42, 44, and 49 showed no growth. On Day 50 the patient was switched to fluconazole 400 mg for prophylaxis and continued until Day 61. The patient was hospitalized on Day 60. The patient was alive at the last study visit.

12.3.3 Narratives of Surviving Patients with Proven Infections – Fluconazole Group

Patient #020-3510
This 26-year-old Caucasian male was diagnosed with chronic myelogenous leukemia on — which was active at the time of randomization. The patient was admitted to the hospital on Day -1 for an allogeneic bone marrow transplant with an associated high risk of transplant related mortality. The patient's conditioning regimen included cyclophosphamide and total body irradiation. Significant baseline conditions included vomiting, nausea and bradycardia. Day -1 chest x-ray revealed reduced lung volume. Absolute neutrophil count (ANC) on Day -1 was 51600 cells/mm^3.

Clinical Course:
The patient was randomized to receive fluconazole and received his first dose on — (Day 1). The patient had no evidence of fungal infection at time of enrollment. On Days 4 through 7

the patient underwent total body irradiation as part of the pre-conditioning regimen. On Day 5 the patient was started on cyclosporine for graft versus host disease (GVHD). On Day 6 the patient started on antithymocyte immunoglobulin and methylprednisolone for GVHD prophylaxis. On Day 9 the patient received an allogeneic bone marrow transplant. On Day 9 the patient developed neutropenia with an ANC less than 500 cells/mm^3. On Day 22 the patient had a blood culture which was positive for *Candida krusei*. Based on the blood culture a diagnosis of proven *Candida krusei* candidemia was made. The patient experienced no serious adverse events or adverse events that were considered related to study drug.

Discontinuation:
The patient was discontinued from study drug therapy on Day 23 due to lack of efficacy. On Day 23 the ANC was less than 500 cell/mm^3.

Outcome:
The patient started on amphotericin B at a dose of 70 mg on Day 24. On Day 26 the patient switched to Abelcet® 330 mg. On Day 28 the dose of Abelcet was raised to 470 mg. On Day 28 the blood culture was negative. Blood culture on Day 29 showed *Candida krusei* and blood culture on Day 30 was negative. On Day 38 the patient achieved neutrophil recovery. On Day 45 the Abelcet was stopped and on Day 53 the patient was restarted on itraconazole 400 mg for prophylaxis. The patient was alive at the last study visit.

Patient #125-3105
Patient Narratives
This 9-year-old Caucasian female was diagnosed with aplastic anemia on ___ which was active at the time of randomization. The patient was admitted to the hospital for an unrelated allogeneic bone marrow transplant. The risk of transplant related mortality for this patient was considered low. The conditioning regimen consisted of dexamethasone and thiotepa. Other medications administered during the 14 days prior to randomization included filgrastim, and acyclovir. The following conditions were present at baseline: neck pain associated with central line placement, thrombocytopenia, neutropenia, intracranial hypertension, hypokalemia, hypoplastic left lung, anemia, and cardiovascular disorder. An assessment on Day -1 indicated an absence of fungal infection; however, cultures collected from the oropharynx showed colonization with *Candida albicans*. A CT scan of the patient's chest confirmed the patient's hypoplastic left lung. At the time of enrollment the patient was receiving ondansetron.

Clinical Course:
The pediatric patient received the first dose of fluconazole 8mg/kg (229 mg) on ___ (Day 1). Day 7 urine cultures indicated no growth. On Day 1 the patient was administered acyclovir, trimethoprim/sulfamethoxazole, amoxicillin, gentamicin, acetaminophen, phytonadione, and chlorhexidine oral rinse. On Day 2 the patient began furosemide, cyclophosphamide, human blood platelets and mesna. The patient underwent an allogeneic bone marrow transplant on Day 7. On Day 5 the patient experienced an event of fever, a reaction attributed to antilymphocyte globulin. The event resolved the same day and the investigator felt that the event was not related to the study drug. On Day 10 the patient began cyclosporine for prophylaxis of graft versus host disease. Blood cultures collected on Days 15, 16 and 18 were

positive for *Candida parapsilosis*. On Day 12 a *Staphlycoccus epidermis* sepsis was identified. The patient's baseline neutropenia continued based on Day 15 with ANC values of < 100 cells/mm^3. The sepsis resolved on Day 18 and the investigator felt that this event was not related to the study drug. During the prophylaxis period the patient developed vomiting, nausea, hematuria, mucositis, bradycardia, and headaches which the investigator felt were unlikely related to the study drug. Events of anorexia, hypertension, alopecia, diarrhea, Broviac site irritation, and epistaxis were also noted, which the investigator felt were not related to the study drug.

Discontinuation:
The patient was discontinued from study drug on Day 20 due to lack of efficacy. The patient's ANC was >100 cells/mm^3 at the time of study drug discontinuation. Significant conditions that developed during the prophylaxis period and continued at the end of therapy included hypertension, thrombocytopenia, and anorexia.

Outcome:
On Day 21 amphotericin was administered to the patient. On Days 22 and 23 blood cultures collected reported no fungal growth. On Day 23 a coagulase-negative *Staphlycoccus* sepsis was noted. The sepsis resolved on Day 26 and the investigator felt that this event was not related to the study drug. A CT scan performed on Days 32 of the chest reported no evidence of fungus, however, in the left lung there was a small pulmonary hypoplasia. On Day 36 and MRI of the chest noted right basal ganglia enhancing lesion with significant surrounding edema. The MRI report indicated that the lesion most likely represents an infectious process given the history of bone marrow transplant. Administration of liposomal amphotericin was continued intermittently from Day 21. The patient was alive at the last study visit.

12.3.4 Efficacy of Micafungin in Study 98-0-050 for Preventing Proven *Candida* Infections Using the Non-Inferiority Margin Estimated From the Goodman and Slavin Trials

As shown in Table 10, the difference between micafungin and fluconazole is 0.005 (or 0.5%). The upper bound of the 95% CI (0.016) is less than the 0.04 margin. The upper bound of the 99% CI (0.019) is also less than the margin. Therefore, micafungin is shown to be non-inferior to fluconazole using the 4% estimate of non-inferiority. The applicant further reduced the margin by half (0.02) to be more conservative. The resulting upper limit of both the 95% and 99% CIs are still less than the 2% margin.

Using the margin of 0.035 based on the combined data (Goodman and Slavin) using the placebo rate in Slavin trial from Method 2, the upper bound of the 95% CI (0.016) and the upper limit of the 99% CI (0.019) are both less than 0.035. Therefore, micafungin is shown to be non-inferior to fluconazole using the 3.5% estimate of non-inferiority. The applicant further reduced the margin by half and the upper limit of 95% CI (0.016) is still less than 0.018 (1.8%). The upper limit of 99% CI (0.019) is just slightly greater than the 0.018 margin.

TABLE 10
Incidence of Proven *Candida* Infections in Study 98-0-050

Micafungin	Fluconazole	Difference Micafungin minus Fluconazole	95% Confidence Interval†	99 % Confidence Interval†
Overall				
4/425 0.0094 (0.94%)	2/457 0.0044 (0.44%)	0.0050 (0.5%)	-0.006, 0.016 (-0.6%, 1.6%)	-0.009, 0.019 (-0.9%, 1.9%)

†Difference = micafungin minus fluconazole (confidence interval calculated using normal approximation)
Source: Table 1 in Appendix III, Section 2.3 of the applicant's submission

12.4 Reviewer's Conclusions

In changing emphasis from the absence of either a yeast or mold infection, as in the original NDA, to the incidence of breakthrough proven *Candida* infections, a new efficacy difference was established by the applicant in the current submission. In choosing an acceptable margin, the applicant relied on the Goodman and Slavin trials as a clinically relevant historical control.

The analysis considered breakthrough *Candida* infections as failures while all other breakthrough infections and deaths during the study were considered successes. The Clinical and Statistical Reviewers consider this approach statistically inappropriate as a method to determine non-inferiority of micafungin to fluconazole. Additionally, the applicant's re-defining of the primary endpoint from absence of fungal infections during study to incidence of *Candida* infections is also statistically invalid.

The Clinical and Statistical Reviewers re-reviewed the data in the original report for Study 98-0-050 used to generate the primary endpoint, as defined in the protocol. As a result of the re-evaluation of failures (deaths, patients lost to follow-up, and proven/probable infections through the end of study and suspected infections through the end of treatment), success was correctly defined as 80.7% in micafungin patients and 73.7% in fluconazole patients (95% CI = 1.5%, 12.5%). The number of proven and probable fungal infections did not change as a result of the re-evalution. The number of proven *Candida* infections was 4 in the micafungin group and 2 in the fluconazole group.

At the time the Approvable letter for NDA 21-506 was written, the Agency did not feel that the results of Study 98-0-050 were robust enough to warrant and indication for prophylaxis of —
— in HSCT patients, especially since the applicant did not have any data demonstrating efficacy for a treatment indication. However, with the approval of NDA 21-754, the Agency has concluded that micafungin has demonstrated efficacy for the treatment of esophageal candidiasis. Given the non-inferiority of micafungin compared to fluconazole for the primary end point in Study 98-0-050 and supported by efficacy of micafungin in the treatment of *Candida* infections, the Clinical Reviewer believes the applicant has demonstrated non-inferiority of micafungin to

fluconazole for the narrower indication of prophylaxis of *Candida* infections in patients undergoing HSCT.

13 APPENDIX IV: OTHER ISSUES

13.1 Background

In a letter dated May 23, 2003 from the Agency to the applicant, commenting on the indication for *Candida* prophylaxis and supportive data in patients with esophageal candidiasis (EC), the Agency commented that a 50 mg dose of micafungin appeared to be less effective than a higher (100 to 150 mg dose) for the treatment of esophageal candidiasis. The Agency requested justification to provide clear evidence of how the 150 mg IV QD dose for treatment of EC bears relevance to the 50 mg IV QD dose for prophylaxis against *Candida* infections in patients undergoing hematopoietic stem cell transplant.

Further discussion about the content and format of the proposed response to the Approvable letter occurred at a meeting between the Agency and the applicant on March 8, 2004. The applicant was asked to support the rationale for using the Goodman and Slavin trials to compare to Study 98-0-050 given the potential for "secular trends and differences in patient population."

In response to the above requests, the applicant has compiled literature to address the question: "*Has the risk of invasive fungal infections changed*?" In addition, they have provided pharmacokinetic (plasma concentrations) data, clinical efficacy data, as well as a rationale based on the pathophysiology of disease, as to why the 50 mg dose is appropriate for use in prophylaxis and why higher doses (100 to 150 mg) are required to treat esophageal candidiasis.

13.2 Risk of Invasive Fungal Infection

The Goodman and Slavin trials were conducted in the late 1980s and early 1990s, approximately 10 years prior to Study 98-0-050. They were both conducted around the same time, although the Slavin study manuscript was in preparation for a longer period of time and thus has a later publication date.

Clinical Reviewer's Comment: The applicant's discussion from Section 3.1.1.3 of their submission has been condensed here by the Reviewer for brevity and clarity.

The incidence of proven systemic *Candida* infections in Study 98-0-050 was 0.9% in the micafungin group and 0.4% in the fluconazole group. Incidence rates for proven invasive *Candida* infections (excluding urinary tract infections) were 1.7% for the Goodman study and 1.3% for the Slavin study for patients enrolled on the active drug (fluconazole). The slightly lower incidence of systemic *Candida* infections in Study 98-0-050 compared to the Goodman and Slavin studies is likely partially reflective of changes in transplant methodology as well as improvements in the supportive care management of BMT/HSCT complications. For example, the introduction of improved cell collection techniques has led to the utilization of peripheral stem cells and cord blood cells along with bone marrow cells compared to the prior use of only

bone marrow cells. Colony stimulating factors, such as G-CSF and GM-CSF, became commercially available in the early 1990's. As delineated in the 1996 American Society of Clinical Oncology guidelines [American Society of Clinical Oncology, 1996] (updated again in 2000), hematopoietic growth factors were widely used in Study 98-0-050 for mobilization of peripheral blood progenitor cells and to speed hematopoietic reconstitution following bone marrow or peripheral cell transplantation during the pre-engraftment period. With the use of colony stimulating factors and the changes that have evolved over 10 years in transplant technique, the overall median duration of neutropenia was 13 days in both prophylactic groups in Study 98-0-050.

Clinical Reviewer's Comment: Although patients in Study 98-0-050 were given hematopoietic growth factors, the median time to neutrophil recovery was similar to the Goodman trial (a median of 13 days in both groups of Study 98-0-050 compared to a mean 16 days for fluconazole and 13 days for placebo in the Goodman trial. The Slavin trial reported a slightly longer duration of 20 days as the mean time to engraftment.

The fact that antifungal prophylaxis could be of benefit to neutropenic patients where the neutropenia is of less than 14 days duration is further evidenced by the results of the empirical therapy trial comparing voriconazole with AmBisome [Walsh et al, 2002]. This study was conducted from 1998 to 1999 and is contemporary to Study 98-0-050. The median duration of neutropenia prior to randomization (meeting the criterion for empirical systemic antifungal therapy of Study 98-0-050) was 7.7 days in the voriconazole group and 7.6 days in the AmBisome group. The incidence of breakthrough invasive yeast and mold infections was 1.9% for voriconazole and 5.0% for AmBisome; the incidence of breakthrough *Candida* infections was 0.5% and 1.4%, respectively.

Clinical Reviewer's Comment: Voriconazole and AmBisome have activity against Aspergillus species and are indicated for the treatment of invasive aspergillosis (first line therapy and for refractory patients, respectively), unlike fluconazole, which is discussed below.

Fluconazole is not active against *Aspergillus* species; therefore, there should be a low but continued occurrence of invasive aspergillosis among fluconazole-treated patients, if neutropenic patients are still at a substantial risk of developing invasive fungal infection. In Study 98-0-050, HSCT recipients who received no prophylactic coverage for *Aspergillus* (i.e., fluconazole group), the incidence of proven or probable infections as defined by the European Organization for Research and Treatment of Cancer-Mycoses Study Group (EORTC-MSG) [Ascioglu et al 2002] was 1.5% during the pre-engraftment period. This rate compares favorably with the incidence of invasive aspergillosis in the fluconazole group in the Goodman study (0.6%) and in the Slavin study (2.0%).

Clinical Reviewer's Comment: Also of interest is the risk of invasive aspergillosis in the placebo groups of the Goodman and Slavin studies, which was 1.1% and 1.4%, respectively.

The incidence of *Candida* infections in the Goodman, and Slavin trials exceeded the incidence of *Aspergillus* infections among placebo-treated patients. The ratio of invasive *Candida* to *Aspergillus* infections in placebo-treated patients was 12.4 in the Goodman trial and 8.7 in the Slavin trial. Applying the above ratios to determine a placebo rate of yeast infections for Study 98-0-050, the incidence of invasive *Candida* infections in Study 98-0-050, where aspergillosis occurred at 1.53% (7/457), would be expected to be as high as 13% to 19% without fluconazole prophylaxis. This compares with the observed incidence in the placebo groups of the prior trials (13.6% Goodman and 12.2% Slavin).

The benefits of antifungal prophylaxis have been shown to persist following drug administration and neutrophil recovery. The disrupted mucosal barrier in patients following HSCT persists and breakthrough invasive infections can still occur following the period of neutropenia. Marr and colleagues [2000] evaluated effects of fluconazole prophylaxis up to 8 years later in BMT recipients by accessing the long-term follow-up database for patients who were enrolled in the Slavin study at the Fred Hutchinson Cancer Research Center. Fluconazole prophylaxis, administered for up to 75 days after transplant in this study with a mean duration of use of 64 days, was associated with reduced gut graft versus host disease (GVHD) and persistent protection against disseminated candidal infections and candidiasis-related death. The overall survival benefit in allogeneic BMT recipients compared to placebo-treated patients demonstrated at the day + 110 fixed time point evaluation of the Slavin study was confirmed by Marr's re-examination of follow-up 8 years later.

The effect of antifungal prophylaxis on survival was evaluated in a different approach by Van Burik et al [1998]. Patients who were assigned to receive fluconazole in the Slavin study were part of the cohort for the 1990-1994 autopsy study at the Fred Hutchinson Cancer Research Center published in 1998. *Candida* infections were less common in autopsied patients who received fluconazole prophylaxis (8%) compared to autopsied patients who received no prophylaxis (27%), while *Aspergillus* infections were more common in patients who received fluconazole prophylaxis compared to those who received no prophylaxis (29% versus 18%, respectively). The 62 patients who had *Candida* infections at autopsy died at a median of 26 days after their last bone marrow transplant. However, patients who did not receive fluconazole prophylaxis died a median of 25 days (range: 6-167 days), which was 13 days earlier than patients who received fluconazole prophylaxis (median: 38 days; range: 4 to 277 days). The 84 patients who had mold infections (i.e., *Aspergillus*, agents of zygomycosis) at autopsy died at a median of 62 days after their last BMT. These data demonstrate the relatively high incidence of *Candida* and *Aspergillus* infections among both neutropenic and non-neutropenic BMT recipients and the associated time-course for fatal events among those HSCT patients who receive antifungal prophylaxis therapy during neutropenia and slightly beyond compared with those who do not receive such prophylaxis.

Clinical Reviewer's Comment: In the Van Burik study, patients who received fluconazole prophylaxis had fewer Candida infections at autopsy and lived a median of 13 days longer than those who did not receive prophylaxis; however, it is not clear that there was actually a survival benefit for patients who received fluconazole. Aspergillus and mold infections were more common in patients who received fluconazole prophylaxis compared to those who received no prophylaxis (29% versus 18%, respectively) and the fluconazole prophylaxis patients with mold infections died at a median of 60 days after the last BMT, compared with 38 days in those who had Candida infections at autopsy. Van Burik et al. postulate that "the death of a patient with Aspergillus infection at day 62 after transplant could possibly be attributed in part to decreased mortality from Candida infections, which occurred at day 26." The longer length of survival may dispose toward acquisition of mold infections. The authors have not included information in the paper on the contribution of fungal infection to cause of death, since the cause may be multifactorial and open to interpretation.

A recent estimate of the current incidence of combined yeast and mold invasive fungal infections with fluconazole prophylaxis is approximately 4% at the time the white cell line engrafts [MacMillan et al, 2002], which is consistent with that reported in Study 98-0-050. The rate prior to tolerable systemic antifungal prophylaxis as noted in the meta-analysis by Bow et al [2002] was much higher, at ≥ 15%.

It is evident from published literature that the incidence of invasive fungal infections in more recent trials for myeloablative HSCT is similar to that observed in the Goodman and Slavin trials. Therefore, neutropenic patients continue to be at risk of invasive fungal infections. In addition, there is a substantial evidence to conclude that antifungal prophylaxis reduces morbidity and continues to improve patient survival in this at-risk patient population.

Clinical Reviewer's Comment: The applicant also notes that nonmyeloablative HSCT has become more common in recent years. The intensity of the nonmyeloablative preparative regimen is less than standard chemotherapy regimens for HSCT, but still accompanied by a period of neutropenia, which can last as long as 30 days. In Study 98-0-050 planned nonmyeloablative HCST was an exclusion criterion.

13.3 Recommended Dose of Micafungin for Prophylaxis

The applicant was asked by the FDA to "provide justification that the efficacy of the proposed dose for the treatment of esophageal candidiasis (150 mg IV once daily) is relevant to the dose proposed for prophylaxis [against *Candida* infections in patients undergoing hematopoietic stem cell transplant] (50 mg IV once daily)..."[10] Therefore the applicant compiled a response using pharmacokinetic and efficacy data to address why a 50 mg dose is appropriate for the prophylaxis indication and why a higher dose (150 mg) is required for esophageal candidiasis.

10 FDA Meeting Minutes, March 8, 2004

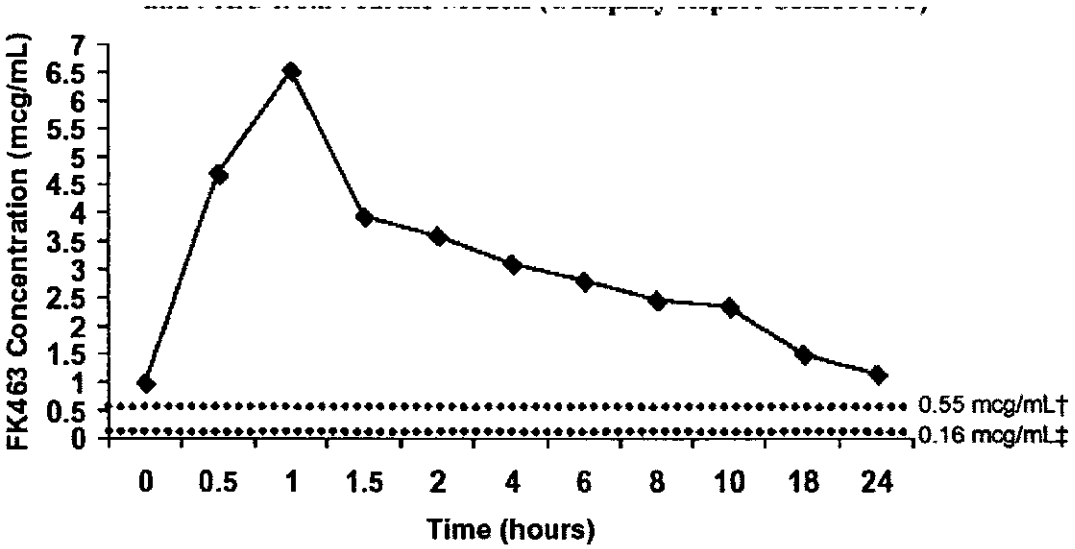
Clinical Reviewer's Comment: The applicant's discussion from Section 3.23 of their submission has been condensed here by the Reviewer for brevity and clarity.

13.3.1 Rationale Based on Pharmacokinetics

The dose used in Study 98-0-050 was selected based on the mean plasma concentrations from studies with micafungin in adult BMT recipients as well as the minimum effective concentration (MEC) demonstrated in murine models and preliminary treatment data in patients with invasive candidiasis. In-vivo studies of micafungin (0.25, 0.5, 1.0 mg/mL; implanted mini-osmotic pump) in murine models of disseminated disease were performed to determine the MEC. The MEC was determined from the minimum concentration of micafungin required to cause a significant reduction in viable fungal cells compared to that in the control group.

As shown in Figure 1, mean plasma micafungin concentrations in adult BMT patients administered a 50 mg dose of micafungin were above the MEC from murine models of pulmonary aspergillosis and disseminated candidiasis over a 24-hour period (Study 97-0-041 and Company Report CRE010073).

FIGURE 1
Mean Plasma Concentrations from Adult Bone Marrow Transplant Patients Given a 50 mg Dose of Micafungin (Study 97-0-041) in Relation to the Minimum Effective Concentration (MEC) Obtained in Murine Models of Infection (Fujisawa Report CRE010073)



†Murine pulmonary aspergillosis ‡Murine disseminated candidiasis

Source: Figure 2 from Section 3 of the applicant's submission

Clinical Reviewer's Comment: The microbiology reviewer for the original NDA 21-506 submission, states in their review:

"The Applicant did not provide any animal data on the use of micafungin prophylactically to prevent *Candida albicans* or *Aspergillus fumigatus* infections. They did provide information of the micafungin treatment of immunocompromised mice and rabbits infected with *C. albicans* and *A. fumigatus*. From the data provided it appeared that micafungin was successful in reducing the number of infecting organisms and prolonging the survival of the infected animals. However, it should be noted that these animals were infected with isolates of *C. albicans* and *A. fumigatus* that were susceptible to low concentrations of micafungin. It is difficult to extrapolate the results of animal experiments to human results and when the experiments are done with a limited number of organisms that are susceptible to low concentrations of a drug it is even more difficult. The value of the experimental animal data provided by the Applicant for predicting whether prophylactic administration of micafungin would be successful in preventing fungal infections in humans is of limited value."

The Clinical Pharmacology reviewer has stated that the pharmacokinetic information from BMT patients given a 50 mg dose of micafungin in Study 97-0-041 are not reliable because many of the blood samples were drawn from the drug infusion port of the catheter and not the collection port. Therefore, pharmacokinetic data from another population (patients with esophageal candidiasis in Study FG-463-21-09) are provided here for reference.

Pharmacokinetic parameter values (mean ± SD) for micafungin determined following the first and steady-state intravenous infusion of daily micafungin doses over an hour to HIV-positive patients with esophageal candidiasis (Study FG-463-21-09).

Time	*PK Parameter*	*50 mg/day (n = 20)*	*100 mg/day (n = 20)*	*150 mg/day (n = 14)*
After First Dose	*Cmax (μg/mL)*	*4.1 ± 1.4*	*8.0 ± 2.4*	*11.6 ± 3.1*
	AUCτ (μg-hr/mL)	*35.7 ± 8.9*	*74.5 ± 18.7*	*104.3 ± 26.3*
	AUC∞ (μg-hr/mL)	*53.4 ± 17.8*	*107.9 ± 30.7*	*150.6 ± 44.6*
	CL (mL/hr/kg)	*19.3 ± 5.9*	*19.8 ± 5.4*	*20.4 ± 5.5*
	Vz (mL/kg)	*401 ± 124*	*388 ± 114*	*407 ± 103*
	t½ (hr)	*14.9 ± 4.3*	*13.8 ± 3.0*	*14.1 ± 2.6*
*At Steady State**	*Cmax (μg/mL)*	*5.1 ± 1.1*	*10.1 ± 2.6*	*16.4 ± 6.5*
	AUCτ (μg-hr/mL)	*54.3 ± 13.1*	*115.3 ± 24.9*	*166.5 ± 40.4*
	CL (mL/hr/kg)	*18.1 ± 4.2*	*18.1 ± 4.3*	*17.5 ± 4.8*
	t½ (hr	*15.6 ± 2.8*	*16.9 ± 4.4*	*15.2 ± 2.2*

** Day 14 or Day 21*

13.3.2 Rationale Based on Efficacy

The efficacy of a 50 mg micafungin dose for the treatment of invasive fungal infections was evaluated in two dose-finding trials in patients with esophageal candidiasis (Studies FG-463-21-09 and 97-7-03) and in a large trial of patients with invasive candidiasis and candidemia (Study 98-0-047).

Clinical Reviewer's Comment: Studies FG-463-21-09 and 97-7-03 were reviewed in detail by Mary Singer, M.D. in the review of NDA 21-754. Study 98-0-047 was reviewed by the Medical Officer in the original review of NDA 21-506.

13.3.2.1 Esophageal candidiasis (Studies FG-463-21-09 and 97-7-03)

A total of 365 patients with esophageal candidiasis were enrolled and received at least one dose of study drug in the two dose-finding studies (Studies 97-7-003 and FG-463-21-09). A total of 305 patients received micafungin at doses ranging from 12.5 mg to 150 mg per day; 90 (29.5%) patients received micafungin at 50 mg per day. Clinical success was defined as clearing or improvement at the end of therapy for the chief presenting characteristics of esophageal candidiasis: dysphagia, odynophagia and retrosternal pain. A summary of clinical success rates by dose level for the two combined studies is presented in Table 1. The clinical success rate was 93.3% for patients treated with 50 mg per day, which was identical to the success rate in patients treated with 200 mg of fluconazole and comparable to the success rates achieved with higher doses of micafungin.

TABLE 1
Clinical Success Rates at End of Therapy in Patients with Esophageal Candidiasis in Studies 97-7-003 and FG-463-21-09 Combined by Daily Dose

	Micafungin (FK463) Daily Dose						Fluconazole
	12.5 mg	25 mg	50 mg	75 mg	100 mg	150 mg	200 mg
FAS	*(n=26)*	*(n=22)*	*(n=90)*	*(n=22)*	*(n=86)*	*(n=59)*	*(n=60)*
	61.5%	86.4%	93.3%	100.0%	91.9%	93.2%	93.3%
mFAS	*(n=19)*	*(n=15)*	*(n=75)*	*(n=20)*	*(n=82)*	*(n=56)*	*(n=53)*
	63.2%	80.0%	94.7%	100.0%	91.5%	92.9%	94.3%
PPS	*(n=18)*	*(n=13)*	*(n=67)*	*(n=19)*	*(n=67)*	*(n=51)*	*(n=48)*
	66.7%	92.3%	98.5%	100.0%	98.5%	100.0%	100.0%

Population base: Full analysis set (FAS), patients who received at least 1 dose of study drug. Modified FAS (mFAS), patients who received at least 1 dose of study drug and had a confirmed esophageal candidiasis infection at baseline. Per protocol set (PPS), patients who were deemed evaluable in their respective study. Combined data from Studies FG-463-21-09 and 97-7-003.
Clinical Success: Clinical response of cleared/improved at the end of therapy.
Source: Table 7 in the applicant's submission

While clinical response rates were similar between 50 mg of micafungin and higher doses, endoscopic cure was achieved in only 58.9% of patients treated with 50 mg and rates were higher in patients treated with 75 mg, 100 mg and 150 mg.

13.3.2.2 Candidemia (Study 98-0-047/FG-463-21-02)

The results from patients with confirmed candidemia in Study 98-0-047/FG-463-21-02 (an uncontrolled study) provide additional evidence of the efficacy of micafungin 50 mg per day in *Candida* infections. The overall success rate for all monotherapy patients (non-efficacy failure plus efficacy failure) with candidemia receiving a *maximum dose* of 50 mg per day was 73.8%

(48/65, Full Analysis Set) and 86.3% (44/51, Per Protocol Set). The overall response rates for candidemia monotherapy are provided in Table 2.

TABLE 2
Efficacy Rates for 50 mg Dose† Regimen (Monotherapy) in Candidemia from Study 98-0-047/FG-463-21-02

	Candidemia Patients		
	De Novo	**Efficacy Failure Micafungin Alone**	**Monotherapy Total**
Full Analysis Set			
Overall Success‡	39/51 (76.5%)	9/14 (64.3%)	48/65 (73.8%)
Per Protocol Set			
Overall Success‡	35/40 (87.5%)	9/11 (81.8%)	44/51 (86.3%)

Patient base: Full analysis set - patients who received at least 1 dose of study drug.
Per protocol set - patients who received at least 5 doses of study drug and had proven or probable (liver, spleen or disseminated only) invasive candidiasis at baseline.
† Patients received a maximum of 50 mg/day.
‡ Includes cured or improved at the end of therapy.
Source: Table 8 in applicant's submission

Clinical Reviewer's Comment: The overall success rate in the study, using the full analysis set and including daily doses of 1 mg/kg mg and higher, was 84.0% (157/187) in adults compared to 72.7% (16/22) in pediatric patients < 16 years of age. These results suggest that micafungin may have less efficacy in pediatric patients compared to adults.

13.3.3 Rationale Based on Exposure-Response

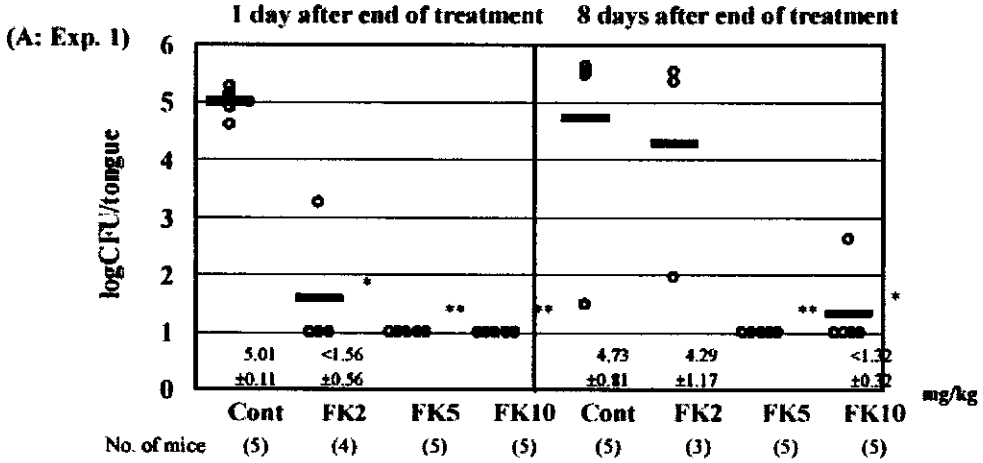
Candidemia and disseminated candidiasis can be prevented by relatively lower doses of micafungin because *Candida* species infect the blood or interstitial fluid of the target organ where micafungin is readily available at target concentrations. In esophageal candidiasis, *Candida* species colonize the keratinized mucosal layer, which is more difficult for micafungin to penetrate due to its high molecular mass (1292 daltons) and amphiphilicity. Taking this into account, higher doses of micafungin may be needed in mucosal infections in order to have sufficient drug levels in mucosa/skin compared to systemic fungal infections.

This was demonstrated in a pharmacokinetic study of the metabolism and distribution of radio-labeled micafungin (1 mg/kg) administered intravenously in male rats (Company Report CRR970275) where the ratio of the concentration of radioactivity in the skin compared to plasma was 0.17 ± 0.01 (mean ± standard error).

In two separate murine studies, a higher dose was effective in reducing fungal cell counts in mucosal candidiasis whereas a lower dose was effective in disseminated candidiasis. Micafungin doses of $\geq$ 2 mg/kg for 10 days (doses tested included 2, 5, and 10 mg/kg) were effective in significantly reducing viable cell counts compared with the control group in a mouse

model of oropharyngeal and esophageal candidiasis (Company Report CRE010074), see Figure 2.

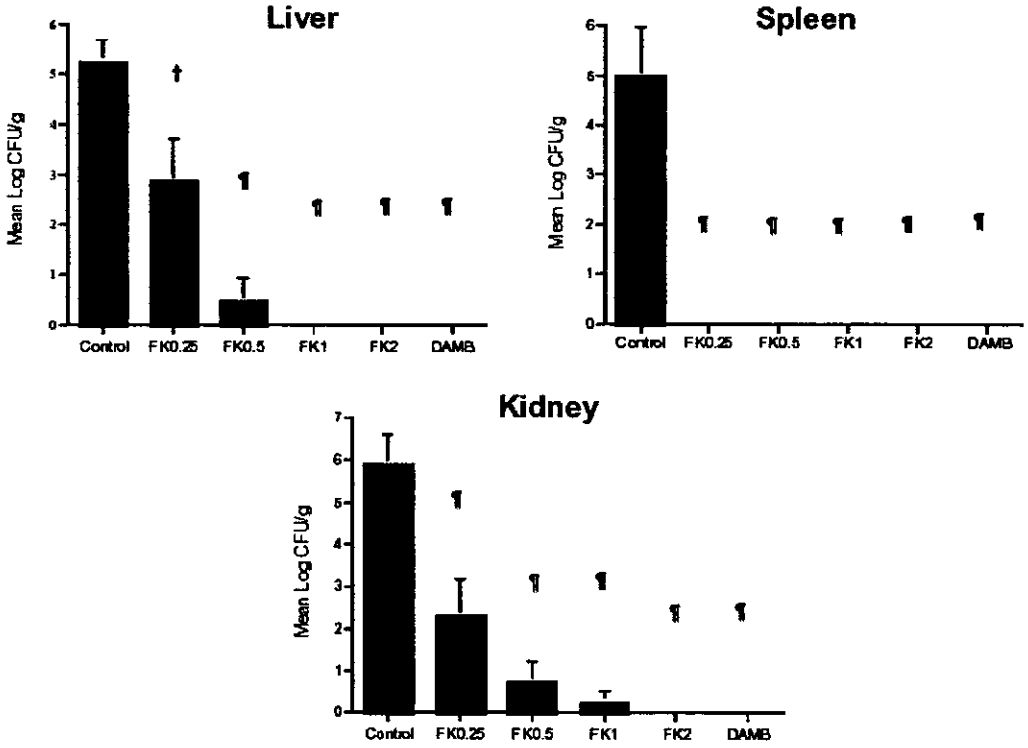
FIGURE 2
Effects of Micafungin on Viable Colony Counts of *Candida albicans* in Tongue



Infection: Male 3- to 5-week old mice were orally challenged with $0.1\sim1\times10^7$ CFU of *C. albicans* 19002 for 4 days.
Treatment: Intravenous administration of micafungin or control from 13 to 23 days after initial challenge, twice daily.
*, **: Significantly different from the control group by non-parametric Dunnett's multiple comparison ($p<0.05$, 0.01, respectively).
Mean ± SE of each group was presented, unless all individuals of the group were below or equal to the detection limit.
Source: Figure 3 in the applicant's submission

Micafungin was effective in reducing viable yeast cell counts in the kidney in a mouse model of disseminated candidiasis at doses of ≥ 0.5 mg/kg (doses tested included 0.25, 0.5, and 1.0 mg/kg) [Company Report CRE010071]. Additionally, Petraitis et al [2002] demonstrated that micafungin doses ≤ 1 mg/kg were effective in clearing the liver, spleen and kidney in a model of disseminated candidiasis in persistently neutropenic rabbits as shown in Figure 3.

FIGURE 3
Efficacy of Echinocandins in Subacute Disseminated Candidiasis in Persistently Neutropenic Rabbits [Petraitis et al 2002]



Measured by determination of the mean concentrations (in log CFU per gram) of the organism in the liver, spleen, and kidney of untreated controls (n=11) and rabbits treated with micafungin at concentrations of 0.25 (FK0.25, n=8), 0.5 (FK0.5, n=8), 1 (FK1, n=8) and 2 (FK2, n=6) mg/kg per day intravenously and desoxycholate amphotericin B at 1 mg/kg per day (DAMB, n=6).
Values are means ± SEMs. † $p<0.01$; ¶ $p<0.001$. P-values are for the results for treated rabbits in comparison to those for the untreated controls, as determined by ANOVA with Bonferroni's correction for multiple comparisons.

Source: Figure 4 in the applicant's submission

These findings with micafungin in animal models of esophageal candidiasis were confirmed in a model of fluconazole-resistant oropharyngeal and esophageal candidiasis with another echinocandin, anidulafungin. Petraitis et al [2001] measured fungal burden and tissue concentrations of anidulafungin in immunocompromised rabbits. Esophageal concentrations were dose-proportional and exceeded minimum inhibitory concentration (MIC) at all doses. Gastric and duodenal tissues demonstrated complete clearance at 2.5 mg/kg, whereas complete clearance in the tongue, oropharynx, and esophagus was achieved at 5.0 mg/kg. The echinocandin appeared to penetrate relatively well into the capillary bed of esophageal tissue. In contrast, the echinocandin was not excreted well into salvia. The authors speculate that the relatively large molecule may not transport well from the capillaries through the basement membrane and into the epithelial cells of the salivary glands. Micafungin and anidulafungin are

similar-sized molecules, 1292 and 1140 daltons, respectively. These findings suggest that while concentrations exceeding MIC are achieved in mucosal tissues, relatively higher doses of an echinocandin may be required to affect a complete cure.

In summary, micafungin was found to have efficacy in treating in treating established non-mucosal *Candida* infections (Study 98-0-047) at a dose of 50 mg per day. The applicant has postulated that in a prophylaxis setting there may be a lower burden of organisms than in the case of an established infection. In addition, they state, it was anticipated a lower dose would be associated with less toxicity and lower costs compared to a higher dose. Therefore, they conclude, a 50 mg dose was reasonable to study for a prophylaxis indication.

13.4 Reviewer's Conclusions

It is evident from published literature that neutropenic patients continue to be at risk of invasive fungal infections. In addition, there is a substantial evidence to conclude that antifungal prophylaxis reduces morbidity and continues to improve patient survival in this at-risk patient population. However, it is possible that the risk of developing a fungal infection is lower today than 10 years ago, as evidenced by the lower rate of empirical therapy in Study 98-0-50 compared to the Goodman and Slavin studies (See Section 11: *"Appendix II: Comparison of Study 98-0-050; Goodman et al. and Slavin et al trials"*). Since Study 98-0-050 did not contain a placebo arm, this question of risk remains theoretical.

The Reviewer agrees with the appropriateness of a 50 mg dose of micafungin for prophylaxis of *Candida* infections and accepts the rationale provided by the applicant as to why higher doses of micafungin are necessary to treat esophageal candidiasis. Unlike the azole class of antifungals (including fluconazole) the echinocandins (including micafungin) have limited penetration into mucosal tissues. Therefore, demonstration of the efficacy of an echinocandin in esophageal candidiasis is felt by the Agency to be a robust test of efficacy. Upon review of NDA 21-754 (micafungin for the treatment of esophageal candidiasis), the Agency believes that the efficacy of micafungin at a dose of 150 mg, which is three times the prophylaxis dose, has established the efficacy of micafungin for the treatment of esophageal candidiasis.

Other supportive evidence demonstrating the efficacy of micafungin in the treatment of *Candida* infections was included by the applicant in this amendment, including an open-label study of micafungin for the treatment of candidemia (Study 98-0-047, submitted to the original NDA 21-506). In this study, the dose of micafungin was initiated at 75 mg, which is higher than the prophylaxis dose and one-half the dose for esophageal candidiasis.

It should also be noted that the efficacy of a 50 mg dose of micafungin against fungal organisms, other than *Candida* species, has not been established.

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DIVISION OF SPECIAL PATHOGENS AND IMMUNOLOGIC DRUG PRODUCTS HFD-590
MEDICAL OFFICER REVIEW OF NDA 21-506, —
(MICAFUNGIN)

Name of Reviewer: Ekopimo Ibia, M.D., M.P.H.
Sponsor: Fujisawa Healthcare, Inc., Three Parkway North, Deerfield, IL 60015-2548. Telephone: 847 317 7286
Date of Submission: April 29, 2002
Date of Receipt: May 2, 2002
Date Assigned: May 13, 2002
Date Completed: January 15, 2003

EXECUTIVE SUMMARY

1. RECOMMENDATIONS

1.1 Recommendation on Approvability
NDA 21-506 Indication: Prophylaxis of — , in patients undergoing hematopoietic stem cell transplantation (HSCT).

To support this indication, the applicant submitted a large randomized, double-blind and actively controlled study (Study 98-0-050). The result of Study 98-0-050 is marginal and does not provide adequately robust statistical evidence of superiority to fluconazole when subjected to sensitivity analyses. In addition, as noted below, efficacy of micafungin against target infections is uncertain, given the relatively small number of patients with invasive infections due to *Aspergillus* species and *Candida* species who were treated with micafungin monotherapy. Consequently, the medical officer is unable to make a conclusive determination of the efficacy of micafungin as a drug for fungal prophylaxis in the setting it was studied. However, the findings of Study 98-0-050 are sufficiently encouraging to support the medical officer's conclusion that micafungin is not inferior to fluconazole as prophylaxis against invasive fungal infections in patients undergoing HSCT. Accordingly, from a clinical perspective, the medical officer recommends that micafungin is approvable for the indication of prophylaxis of — in patients undergoing HSCT. Approval for this indication will require data from adequate and well-controlled studies demonstrating the efficacy of micafungin in the treatment of patients with invasive infections due to — *Candida* species. —

2. SUMMARY OF CLINICAL FINDINGS

2.1 Brief Overview of Clinical program
Product name: Micafungin sodium (code name: FK463)
Product Class: Echinocandin antifungal agent
Route of Administration: Intravenous infusion
Requested Indications:

a. Prophylaxis o' _ , in patients undergoing hematopoietic stem cell transplantation (HSCT).
b.

c.

Population (s) studied: Children and adults undergoing hematopoietic stem cell transplantation and/or patients with candidemia/invasive candidiasis and invasive aspergillosis.

To support the proposed indications, the applicant conducted three pivotal (one for each indication) and five supportive trials. Including the additional patient data in the 120-Day Safety Update, a total of 1516 patients (prophylaxis study 882, candidemia/invasive candidiasis study 351, and invasive aspergillosis study 283) in the three pivotal trials received study drug. Of these 1516, 1059 (70%) received micafungin. The safety database comprises 1581 human subjects exposed to micafungin during the entire clinical development program.

2.2 Efficacy

Indication #1: Prophylaxis of [redacted] in HSCT Recipients

The pivotal study for this indication, Study 98-0-050, was a large randomized, double blind, multicenter, international trial of micafungin versus fluconazole for the prevention of invasive fungal infections in patients undergoing hematopoietic stem cell transplantation.

The primary efficacy endpoint was treatment success at the end of the study. This was defined as the absence of a proven, probable, or suspected systemic fungal infection through the end of therapy and the absence of a proven or probable systemic fungal infection through the end of the study. Both of the criteria had to be met in order for the patient to be considered a treatment success. Patients had a suspected fungal infection if they were neutropenic (defined as absoulte neutrophil count [ANC] < 500cells/mm^3), had a fever and received broad-spectrum antibiotics for at least 96 hours, and required initiation of empirical systemic antifungal therapy. This primary endpoint was to be obtained from the Full Analysis Set population, which the protocol defined as "all randomized patients who received at least one dose of study drug." Using the protocol-specified diagnostic criteria and in a blinded manner, a panel of independent reviewers evaluated all investigator-diagnosed breakthrough proven or probable invasive fungal infections.

It should be noted that the original protocol required that to be a successful outcome, a patient should not have discontinued study drug due to an adverse event related to study drug, and should be alive at the end of the study (4 weeks posttreatment). The protocol was amended about six weeks prior to study commencement to allow patients who died or discontinued study drug for reasons other than lack of efficacy to be considered treatment success so long as there was no proven, probable or suspected fungal infection.

The efficacy of FK463 and fluconazole was compared using a combination of tests of non-inferiority and superiority. First, a test of non-inferiority was performed followed by a test of superiority if FK463 was found to be statistically non-inferior to fluconazole.

A two-sided 95% confidence interval (CI) for the difference of the true success rates was constructed. If the lower bound of the CI was $\geq$-10% then FK463 was considered to be statistically non-inferior to fluconazole. Also, if the lower bound of the CI exceeded 0%, then FK463 was said to be statistically superior to fluconazole.

By the applicant's analysis, overall successful outcomes were documented for 80.0% and 73.5% of patients on the micafungin and fluconazole arms, respectively with a difference of 6.5% (95% confidence interval around the difference 0.9, 12.0%) in favor of micafungin. However, even in the applicant's original analysis, no other endpoint demonstrated superiority of micafungin over fluconazole, although nearly all point estimates were consistently in a direction favoring micafungin.

A total of 18 breakthrough proven or probable invasive fungal infections were documented by the independent review panel, 7 and 11 on the micafungin and fluconazole arms, respectively. Of the 7 proven/probable breathrough infections on the micafungin arm, 4 were due to *Candida* species and 1 due to *Aspergillus* species. The corresponding numbers of infections due to *Candida* and *Aspergillus* on the fluconazole arm were 2 and 7 respectively.

It should be mentioned that the design of Study 98-0-050 was based on the expectation of a larger proportion of breakthrough proven or probable fungal infections than observed in this study. Because of the lower than expected rate of breakthrough fungal infections, the outcome is almost entirely driven by the need for empiric parenteral antifungal therapy in patients suspected to have fungal infections, the lesser of the three types of failures.

To minimize subjectivity in ascertaining this endpoint, a rigid adherence to protocol-specified endpoint for empiric antifungal therapy was adopted in the review. Sensitivity analyses adjusting for protocol violations with respect to definition of suspected fungal infection failed to support a robust superiority of micafungin over fluconazole.

Nevertheless, the findings of this pivotal prophylaxis study remain sufficiently encouraging to support the medical officer's conclusion that micafungin is not inferior to fluconazole as prophylaxis [redacted] in patients undergoing hematopoietic stem cell transplantation.

Indication #2: [redacted]

Reader should refer to the review by Sary Beidas, M.D. In summary, the applicant sought indication number 2 based on a single open-label non-comparative study (Study 98-0-046) plus additional data from13 patients from another open-label non-

comparative study conducted in [redacted] study [redacted]

[redacted]. The reviewer of this indication, Dr. Beidas, concluded that the number of efficacy failure patients on micafungin monotherapy were insufficient to allow assessment of micafungin in the patient population targeted by the proposed indication.

Indication #3: [redacted]

The pivotal study (Study 98-0-047) to support indication number 2 was a phase 2, open-label, noncomparative, multinational study conducted in adult and pediatric patients who were diagnosed with candidemia or invasive candidiasis. Data included in the NDA from this study were derived from two separate protocols, the Non-European protocol and the European protocols. The Non-European and the European protocols were identical in all aspects except that while the former allowed De Novo patients and patients < 18 years to be enrolled, the latter did not allow enrollment of such patients. The bulk of the data in the NDA came from the Non-European protocol.

The objective of the study was to evaluate the safety and efficacy of FK463 in the treatment of patients with confirmed candidemia or invasive candidiasis caused by both *C. albicans* and non-*C. albicans* organisms.

Male and females children and adult patients were enrolled. The patients were divided into two groups: de novo and efficacy failure. The following is excerpted from the applicant's submission:

De Novo Patients

De Novo patients were newly diagnosed patients with candidiasis who received no more than 48 hours of systemic antifungal therapy prior to their first dose of FK463.

Efficacy Failure Patients

Efficacy failure patients must have had documented clinical and microbiological evidence of continuing disease despite therapy with systemic antifungal agents and must have received 5 or more days of systemic antifungal therapy with no response. The efficacy failure patients were further divided into subgroups of patients depending on their regimen in this study: those who received FK463 alone (i.e., FK463 replacing current systemic antifungal agent) and those who received FK463 along with their current antifungal regimen (i.e., FK463 added to current systemic antifungal agent). Efficacy failure patients on combination therapy who responded to treatment could have had their antifungal medications tapered to FK463 alone.

The findings from Study 98-0-047 were reviewed by an independent reviewer appointed by the sponsor.

The primary efficacy endpoint was the investigator's global assessment of treatment success (defined as complete or partial response) in the per protocol set. The per protocol set was defined as those patients who received at least 5 days of micafungin therapy and had a confirmed diagnosis of candidemia or invasive candidiasis at baseline.

Of the 250 patients from this study submitted initially in the NDA, 202 (81%) met the Per Protocol Set as assessed by the independent review panel. Of these 202 per protocol patients, 141 (70%) were enrolled in the De Novo group, 35 (17%) in the micafungin plus other systemic antifungal group, and 26 (13%) in the micafungin alone group. It should be noted that the most relevant patient group for the proposed indication is the group that received micafungin alone since the contribution of micafungin in a combination regimen is difficult to discern. One could argue that the De Novo patient group provided data that might demonstrate the activity of micafungin in patients with candidemia/invasive candidiasis. However, in the original NDA, 65.2% of per-protocol patients in the De Novo group in Study 98-0-047 (as aseessed by the independent review panel) were patients with esophageal candidiasis, a condition that should only be properly evaluated with a randomized active controlled trial. In addition, at the recent Bacterial and Mycosis Study Group (BAMSG) meeting, esophageal candidiasis and oropharyngeal candidiasis were considered in a risk group distinct from invasive candidiasis.

Moreover, the independent review panel noted that 47.5% of the patients they reviewed had what could best be called breakthrough rather than truly refractory or intolerant fungal infections. Generally, such breakthrough infections occurred in patients diagnosed with fungal infections while on systemic antifungal agents for prophylaxis or empiric treatment. Some of the patients on systemic antifungal prohylaxis received doses lower than required for treatment of established systemic fungal infections. In the opinion of the medical officer, therapy in such patients might not have been optimized to allow them to be regarded as refractory or intolerant. Indeed, the bulk of such patients had candidemia and it is unclear how many of them had their intravascular catheters removed or replaced as part of the overall management of the candidemia.

The per protocol dataset increased to 271 patients in the 120-Day safety Update. Of these, 179 (66%) were De Novo patients, 55 (20%) were efficacy failure patients who received micafungin plus other systemic antifungal agent (17 of these were breakthrough infections), 37 (14%) were efficacy failure patients treated with micafungin alone (18 patients had breakthrough infections). Of the remaining 19 efficacy failure patients treated with micafungin alone, 6 had esophageal candidiasis, 9 candidemia, and 4 invasive candidiasis.

Study 98-0-047 provides some evidence supportive of activity of micafungin in patients with candidemia/invasive candidiasis. The absence of a control arm and the uncertain contribution of micafungin in those treated wth combination antifungal agents mitigate an overall response of 81.2% obtained from all available data in study 98-0-047. Moreover, the quantity of data submitted for patients who received micafungin monotherapy preclude adequate determination of the activity of micafungin in the treatment of patients with candidemia/invasive candidiasis who are refractory to or intolerant of their current antifungal therapy.

The applicant's Medline review of medical literature published in English has limited utility in attempting to place the efficacy of micafungin in perspective. Although, response rates obtained in Study 98-0-047 are comparable with those in published literature, differences in trial design and patient population as well as temporal changes in clinical practice make a direct comparison unfeasible.

2.3 Safety

Micafungin acts to inhibit synthesis of fungal cell wall glucan, a structure absent from mammalian cell walls. Therefore, adverse events based on mechanism of action are unlikely. However, based on literature and labeling for an approved echinocandin, potential safety concerns for the echinocandin class of drugs include hepatic dysfunction, hemolysis, events associated with histamine release, injection site reactions, drug interactions, and embryopathy. Review of safety of micafungin emphasized these potential safety concerns.

In studies of micafungin in rats and dogs, the primary target of toxicity was the liver. Both biochemical and histologic changes were noted in the liver in these animals (at doses $\geq$ 32 mg/kg). In addition, in rats micafungin increased plasma histamine and heart rate (at doses $\geq$ 32 mg/kg) and decreased blood pressure (at a dose of 100 mg/kg). Although toxicities occurred at doses relatively higher than used in the clinical development program, findings from animals are still relevant as some of the patients who may use micafungin may have underlying liver impairment. Moreover, in some of the animals studied, the liver changes did not reverse at the end of the recovery period. Other effects observed in rats include effects related to histamine release, hemolysis, and injections site reactions. In addition, *in vitro*, micafungin induced platelet aggregation and hemolysis.

As noted earlier, a total of 1581 human subjects have been treated with micafungin. Of these 1421 subjects have been treated with 50-100 mg of micafungin for a mean duration of about 20 days. Additional 160 subjects have been treated with 150-200 mg of micafungin for a mean duration of 46 days. The duration of exposure is typical of the duration of treatment for the proposed indications. In all studies, monitoring and follow up were adequate. Entry criteria into the pivotal studies allowed enrollment of patients typical of those that will use micafungin.

Review of postmarketing spontaneous adverse event reports for an approved echinocandin conducted by the Office of Drug Safety was limited by the small size of

the utilization database. However, the review noted that the particular echinocandin might play a role in the development of hyperbilirubinemia and possibly clinical liver disorders (including liver failure) as well. In addition, that echiniocandin had been reported as a suspect drug in other concerning events (coronary vasospasm, hypercalcemia, myocardial infarction, multi-organ failure, pancreatitis, pancytopenia, renal failure / insufficiency, respiratory alkalosis, stroke, sudden death), but its role was not clear from the cases reviewed.

The typical patient enrolled in the studies presented with complex comorbid conditions and/or received multiple concomitant medications, some potentially more toxic than micafungin. Generally, investigators considered very few adverse events to be at least possibly related to micafungin. In the large pivotal prophylaxis study, the rates of adverse events by body organ systems were similar between the two arms.

Deaths

The NDA documents death in a total of 217/1156 (18.8%) patients across all studies. The highest mortality rate occurred in the invasive aspergillosis and candiasis studies (Studies 98-0-046 and 98-0-047, respectively) with overall mortality of 58.6% in Study 046 and 28.8% in Study 047. Not surprisingly, patients with these infections are seriously sick and the mortality rate in this patient population is generally high. The mortality rate in the large randomized prophylaxis study was similar across the two arms. Only one death in the database was considered by the investigator to be related to micafungin. The investigator could not exclude the possibility that this immunosuppressed patient (secondary to steroid therapy) with invasive aspergillosis died of pancytopenia resulting in pulmonary hemoprrhage possibly related to micafungin.

Withdrawal and Abuse potential

There has been no known or documented evidence of either withdrawal or rebound effects with micafungin. Similarly, there has been no evidence of psychological or physical dependence with micafungin and the drug is not known to impair metal ability. In clinical trials repeated daily doses of micafungin up to a maximum of 5.9 mg/kg in children and up to 8 mg/kg in adults were administered with no dose-limiting toxicity. No overdose with micafungin has been reported.

Potential Targets of Toxicity Based on Animal Data

Findings in the application show that micafungin does not present any major safety concerns and that the drug can be safely administered in patients with moderate hepatic and severe renal dysfunction. Nevertheless, there is a potential for hepatotoxicity and hemolysis, given the animal data. Moreover, there appears to be a trend towards mildly-moderately-increased liver dysfunction in patients receiving concomitant calcineurin inhibitors or corticosteroid. In addition, patients might be expected to develop asthenia when infused with micafungin.

2.4 Dosing, Regimen, and Administration

For prophylaxis and for — y
— he proposed dose in adults is 50 mg once daily · —
—

. Micafungin is intended to be marketed in and 50 mg vials, to be given as intravenous infusion. Lyophilized micafungin powder is to be reconstituted with — or 5% dextrose and further diluted with any of the two solutions.

The micafungin vial is overfilled by — during the filling process to compensate for the amount of drug product retained in vial following withdrawal since micafungin foams when reconstituted. The overfill is to ensure the withdrawal of the labeled amount from the vial.

2.5 Drug-Drug Interactions

Using *in vitro* systems, the effect of micafungin on cytochrome P [CYP] enzymes, P-glycoprotein, and other metabolic/transporte pathways were evaluated in the cause of micafungin development. There appears to be neither potentially significant drug-drug interactions nor induction/inhibition of the major metabolic pathway (cytochrome P [CYP] 450 system) at clinically relevant concentrations of micafungin. However, at a concentration of 50 μM (63.5 μg/mL), micafungin reduced metabolic activity of CYP3A isoform to 21.4% of control but inhibition of other isoforms was relatively minor. Multiple CYP isoforms are involved in the formation of micafungin metabolites, M5 and M13 as assessed using human liver microsomes. Among compounds tested, ketoconazole (a CYP3A4 inhibitor) at a concentration of 2.5 μM, had the most potent inhibitory effect on micafungin metabolism, decreasing the rate of M5 and M13 formation in human liver microsomal enzyme system to 57.4% and 40.7% of control.

In studies in healthy volunteers, single doses of either cyclosporine or tacrolimus had no pharmacokinetic interaction with single and repeated doses of micafungin. However, it is uncertain whether potential toxicities could occur with concomitant use of repeated doses of these immunosuppressants in a sick population.

2.6 Special Populations

Pediatrics

A total of 187/1156 patients in the safety database were children (< 16 years of age). Of the 187 patients < 16 years old, 113 (60.4%) were recipients of a hematopoietic stem cell transplant, primarily an allogeneic transplant or underwent intensive chemotherapy due to a hematologic malignancy, 26 (13.9%) received chemotherapy for solid tumor, and 42 (22.5%) had diverse other underlying conditions. Only 6 (3.2%) were HIV infected. This distribution was identical to the overall population with the exception of the proportion of patients who were HIV infected (13.2%) in the full patient safety database. Overall, rates of adverse events in children were similar to those of adults. Adverse events that were reported more frequently in

pediatric than adult patients were hepatomegaly (9.1% versus 0.7%), hypoproteinemia (12.8% versus 6.9%), hypertension (19.8% versus 13.3%), pruritus (16.6%versus 10.3%), and urticaria (6.4% versus 2.2%).

Geriatrics
Patients 65 years of age or older comprised 75 of the total of 1156 patients in the safety database. Adverse events were generally similar in the elderly patients compared to those 16 to 64 years old. Adverse events reported more frequently among the elderly patients were asthenia (33.3% versus 23.3%), peripheral edema (24.0% versus 15.1%), hypophosphatemia (24.0% versus 10.3%), ecchymosis (12.0% versus 4.4%), skin disorder (12.0% versus 6.2%), oliguria (14.7% versus 4.5%), urinary tract infection (12.0% versus 4.4%), and accidental injury (9.3% versus 1.7%)

Gender
Of the total patient population of 1156 in the safety database, males comprise 57.3% and females 42.7%. No gender differences in the incidence or type of adverse events are apparent.

Race
Overall, adverse events were less frequent among black patients. As noted by the sponsor, the difference in rate of adverse events likely reflects the differences in the patient populations and the underlying conditions. White patients were predominantly enrolled from North America and Europe and were recipients of hematopoietic stem cell transplant or were undergoing chemotherapy for a malignancy. On the other hand, most of the black patients were HIV-infected patients with esophageal candidiasis enrolled from South Africa.

In summary, no major differences were found to require micafungin dose adjustments based on in age, gender, or race.

Pregnancy and Lactation
Micafungin has not been adequately studied in pregnant human subjects. Not unexpectedly, there is no information in this patient database on use of micafungin in pregnant women. In animal (rats and rabbits) reproductive studies given 2.6 times the expected upper human dose (100 mg) of micafungin, there was no evidence of impaired fertility or harm to the fetus due to micafungin. The Segment I study showed that the nontoxic dose for fertility was 32 mg/kg per day. In males vacuolation of epithelial cells of the epididymis was seen at doses of 10 mg/kg or higher and at 32 mg/kg, there was a 14% decrease in the number of sperm in the cauda epididymis compared to the control group. From the Segment II studies, micafungin has no teratogenic potential in the species studied. In rats and rabbits, the respective maternal non-toxic dose is estimated to be equivalent to 1.6 to 0.8 and 5.2 to 2.6 times the recommended human clinical dose range of 1 to 2 mg/kg based on surface area correction. In both rats and rabbits, the NOEL for embryo-fetal developmental toxicity is 32 mg/kg. Animal studies also show that labeled micafungin and/or its metabolites are excreted into the breast milk.

The sponsor seeks a designation of — for micafungin. It should be mentioned here that caspofungin, the first marketed echinocandin, is labeled pregnancy category C due to embryonic toxicity observed in rats and rabbits at exposures similar to those in clinical trials of caspofungin.

1. INTRODUCTION AND BACKGROUND

1.1 Drug Product Identification

Established Name: Micafungin sodium
Proposed Trade Name: — for injection
Medical Officer's Comment: *The proposed trade name — was reviewed and rejected by the Division of Drug Marketing, Advertising, and Communications (DDMAC). An alternative trade name "Mycamime" was proposed by DDMAC and accepted by the sponsor.*
Code Name: FK 463
Drug Class: Echinocandin antifungal agent
Proposed Indications:

d. Prophylaxis of — in patients undergoing hematopoietic stem cell transplantation (HSCT).
e. —

f.

Proposed Dose and Regimens: Prophylaxis —
— (adults 50 mg once daily, —
—). Micafungin will be marketed in — . 50 mg vials, to be given as intravenous infusion.
Age Groups: Adults —

1.2 State of Armamentarium for Indications

Epidemiology of invasive fungal infections
Invasive fungal infections (IFI) remain a major source of morbidity and mortality, particularly among the immunocompromised host. Infections due to *Candida* and *Aspergillus* species constitute the most prevalent of the invasive fungal infections. More recently, *Fusarium* species, *Acremonium* species, *Scedosporium* species, *Scopulariopsis* species, *Paecilomyces* species, *Trichoderma* species, and the zygomycetes are reported to cause an increasing number of invasive fungal infections. Further, endemic mycoses,

such as those caused by *Penicillium marneffei*, *Coccidioides immitis*, and *Histoplasma capsulatum* are being reported more frequently.

According to data from the Centers for Disease Control and Prevention (CDC), candidemia occurs in 8 of every 100,000 persons per year (ref: CDC web site). In the National Nosocomial Infection Surveillance Program, the incidence of nosocomial fungal infections doubled between 1980 and 1990, the largest increase occurring among surgical patients. Candidemia now constitutes the fourth most common nosocomial bloodstream infection among hospitalized patients in the United States.

The exact incidence of invasive aspergillosis in the United States is unknown; however, population-based data available for San Francisco suggest a rate of 1-2 per 100,000 per year (ref: CDC web site). Further, the overall increase in incidence of invasive fungal infections seems to be driven by an increase in the incidence of invasive aspergillosis and other molds. Mortality remains very high in patients with invasive aspergillosis.

Experts suggest variables that may account for the current trends in the epidemiology of opportunistic fungal infections to include (Singh N. Trends in the epidemiology of opportunistic fungal infections: predisposing factors and the impact of antimicrobial use practices. Clin Infect Dis. 2001 Nov 15;33(10):1692-6):

- Increasing number of susceptible hosts
- Greater laboratory expertise in the detection and identification of fungi
- Use of new transplantation modalities for hematopoietic stem cell transplantation (e.g., CD34+ selected autografts and peripheral blood stem cell transplantation)
- Evolution in organ transplantation practices
  - Advances in surgical technology
  - Use of corticosteroid-sparing regimens and an overall conservative approach to immunosuppression
- Use of novel immunosuppressive agents
- Use of antimicrobial prophylactice practices, e.g., use of fluconazole for antifungal prophylaxis and quinolones for gram-negative bacterial prophylaxis

A further source of concern regarding invasive candidiasis is the increasing incidence of infections due to non-albicans *Candida* species. Factors contributing to this recent trend in the epidemiology of invasive candidiasis are thought to include (Singh N. Clin Microbiol Infect 2001;7 Suppl 2:1-7):

- An increasing number of immunocompromised patients at risk from fungal infections
- An overall greater acuity of illness in the hospitalized patients, particularly those in the critical care units
- Escalating rates of utilization of broad-spectrum antibiotic
- Wide use of azoles as prophylaxis

Following HSCT, patients often have disruption of their mucosal barriers from several factors such as mucositis, insertion of central vascular catheters, and/or from dermal injuries due to toxic substances or infusates. These factors all favor the development of

systemic fungal infections in a population with net immunosuppression. Such net immunosuppression is caused by neutropenia, graft-versus-host disease (GVHD) and its treatment, immunomodulating viral infections including human cytomegalovirus disease (CMV), and metabolic factors such as protein-energy malnutrition and uremia. On balance, patients receiving allogeneic HSCT are at higher risk of IFIs compared to those given autologous HSCT. Mortality from IFIs is particularly high in patients following allogeneic HSCT. Several factors contribute to such high mortality in HSCT patient population including (Sullivan et al. Preventing opportunistic infections after hematopoietic stem cell transplantation: The Centers for Disease Control and Prevention, Infectious Disease Society of America, and American Society for Blood and Marrow Transplantation Practice Guidelines and Beyond. Hematology 2001; :392-421

- difficulty in diagnosing IFIs,
- impaired inflammatory response occurring during the neutropenic phase preengraftment and during the treatment of GVHD during the postengraftment period,
- delayed institution of effective antifungal therapy,
- utility of currently available antifungal agents because of limited spectra of activity and frequent treatment-limiting toxicities
- need for prolonged treatment of IFIs, which further increases toxicity potential

Strategies to mitigate the impact of IFIs must take into consideration certain host factors and peculiarities of the infecting fungal agent while simultaneously dealing with sources of environmental exposure to the pathogen. Medications play a role in both prevention and therapy of IFIs. In the HSCT patient population, experts classify medication strategies for the prevention of established IFIs into primary prophylaxis, empiric treatment, and pre-emptive treatment

Primary Prophylactic Treatment
Medication is administered at time of HSCT and continued at least till engraftment. There is evidence from literature that fluconazole 400 mg administered orally or intravenously once daily is protective against IFIs in HSCT patient population. However, fluconazole has a relatively narrow indication as prophylaxis "to decrease the incidence of candidiasis in patients undergoing bone marrow transplantation who receive cytotoxic chemotherapy and/or radiation therapy." Further, increasing reports of cases of IFIs due to azole-resistant *Candida* species are concerning.

Empiric treatment
With this approach, antifungal therapy is administered to neutropenic HSCT patients who remain febrile for more than 3-4 days despite adequate therapy with broad-spectrum antibiotics. Drugs approved for such indication include amphotericin B deoxycholate, liposomal amphotericin B, and itraconazole.

Pre-emptive treatment
This strategy allows early treatment of patients at high-risk for life-threatening fungal infection before the onset of clinically recognizable disease. Scenarios for pre-emptive

antifungal therapy in the HSCT patient population include colonization of the respiratory tract by *Aspergillus,* finding of "halo sign" on computerized tomogram of the chest, and /or detection of fungal antigens or fungal metabolites that could signify early fungal infection. From a regulatory perspective, pre-emptive treatment is not a recognized indication. However, literature recommends use of amphotericin B or liposomal amphotericin B for such pre-emptive therapy (Sullivan et al. Hematology 2001).

Invasive infections by *Aspergillus* and other molds

Without treatment, invasive infections caused by *Aspergillus* and other molds are almost uniformly fatal. Notable recent trend in epidemiology is the increasing prevalence of amphotericin B-resistant mold infections. Although approved drugs are available for the treatment of invasive mold infections, clinical outcome in invasive mold infection depends on numerous factors, efficacy of the antifungal agent notwithstanding. Such factors include persistence of neutropenia, anatomic site involved, the specific infecting mold, delay in initiation of therapy, and treatment-limiting toxicity of the drug. Further compounding the problem is the fact that the optimal duration of therapy and the precise role of surgery remain unclear.

Until recently, amphotericin B deoxycholate was the only drug for primary treatment of invasive mold infections. However, *Aspergillus flavus*, *Aspergillus terreus*, *Scedosporium* species, and *Fusarium* species are resistant to amphotericin B. Even in the absence of a resistant mold infection, toxicities from amphotericin B deoxycholate often limit treatment options in these infections. In patients with refractory mold infection or who are intolerant of amphotericin B deoxycholate, approved salvage therapy include the lipid formulations of amphotericin B (amphotericin B colloidal dispersion a.k.a. amphotericin B cholesteryl sulfate [Amphotec®], amphotericin B lipid complex [Abelcet®], and liposomal amphotericin B [Ambisome®]), itraconazole (Sporonox®), and caspofungin (Cancidas®). Very recently, voriconazole (Vfend™), one of the newer triazole antifungal agents, was approved for primary therapy of invasive aspergillosis and for salvage therapy of invasive fungal infections caused by the pathogens *Scedosporium apiospermum* and *Fusarium spp.*

Although in recent years there has been an increase in available options for the medical treatment of invasive mold infections, many challenges persist. Only modest efficacy has been achieved with the agents recently approved for salvage therapy of invasive mold infections. In addition, the choice and optimal dose of the lipid formulations of amphotericin B remain uncertain. Further, often the costs of these LFAB are prohibitive. Indeed to optimize therapy for these patients, investigators are starting to explore the potentials for combination antifungal therapy.

Candidemia and invasive candidiasis

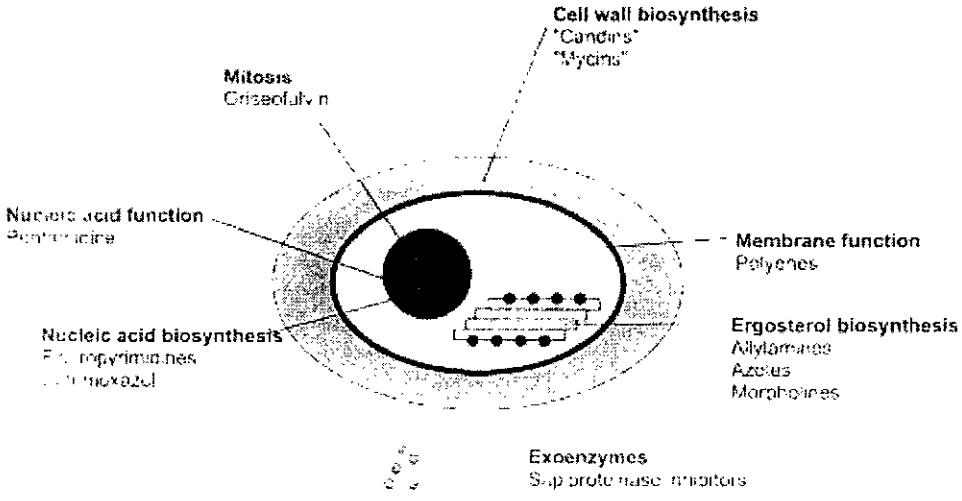
Experts express concern regarding the apparent shift in the etiology of candidemia. While *Candida albicans* remains the predominant isolate in many studies, increasingly non-albicans *Candida* species such as *C. parapsilosis*, *C. krusei*, *C. tropicalis*, and *C. glabrata* are being isolated. *C. krusei* and *C. glabrata* are inherently less susceptible to fluconazole. In the International Surveillance of Bloodstream Infections due to *Candida*

species (SENTRY Antimicrobial Surveillance Program) revealed that in the U.S. in 1997, based on NCCLS interpretive criteria, 97.5% and 88.7% of *Candida spp.* isolates from bloodstream infections were either susceptible to or susceptible-dependent upon dose of fluconazole and itraconazole, respectively. (Pfaller MA et al. J Clin Microbiol 1998;36:1886-1889). While resistance to these triazoles was neither prominent nor increasing when compared to earlier longitudinal studies by same authors, they note the consistent increase in the frequency of BSI caused by *C. glabrata* in all three regions studied.

Drugs approved for primary treatment of systemic candidiasis include amphotericin B deoxycholate and fluconazole. Ketoconazole is also approved for treatment of sytemic candidal infections except candidal meningitis because of the drug's poor penetration of the cerebrospinal fluid. As with invasive mold infections, treatment of candidemia and/or invasive candidiasis might be refractory or limited by drug toxicity. Further, although fluconazole is generally safe, its potential for drug-drug interactions could limit its use in the intended population. Approved products indicated for patients with invasive candidal infections who are refractory to or intolerant of primary therapy are liposomal amphotericin B and amphotericin B lipid complex. Given the limited treatment options and the high morbidity and mortality, there is need for further drug development for the treatment of these serious infections.

Current Approaches to Antifungal Treatment

Figure 1 summarizes mechanistic targets for antifungal drugs including novel drugs in development.



Adapted from Baster J, Schaller M, Korting HC, Evans EGV. Current and future approaches to antimycotic treatment in the era of resistant fungi and immunocompromised hosts. Int J Antimicrob Agents 2001;17:81-91
Two other cell wall acting drugs currently in early phases of development are chitin synthase (nikkomycins) and mannoproteins (pradimicins/benanomicins).

Potential niche for micafungin
If approved, micafungin would be the second marketed echinocandin. Its mechanism of action precludes development of mechanistic-based adverse events since human cell walls lack glucan. In addition, the mechanism of action of echinocandins provides a potential role for combination therapy with antifungal drugs of a different class.

1.3 Important Milestones in Micafungin Development
Clinical development of micafungin was initiated on February 26, 1998 with the submission of an original IND (IND#55,322). Starting from that time, Fujisawa received several advisories from the Agency, which culminated in an End-of-Phase 2 (EOP2) meeting on September 10, 1999. Key discussion points at the EOP2 meeting were as follows:

- Approach to be taken to deal with —

  Medical Officer's Comment: *A consult on this issue was to be addressed to OPDRA and remained unresolved at the time of NDA filing.*

- Discussions of changes to drug substance — and drug product that were to take place during the ongoing trial. The applicant was to submit all relevant drug substance data with the drug master file (DMF) amendment and drug product information was to be submitted with the NDA.
- Clinical development plan to support efficacy and safety of micafungin was considered adequate for filing of the NDA.
- Agreement on fluconazole dose of 12 mg/kg/day for subjects weighing < 40 Kg in Study 98-0-050.

  Medical Officer's Comment: *The dose of fluconazole used in Study 98-0-050 was 8 mg/kg/day for patients <50 kg. It is unclear if the agreed dose of 12 mg/kg/day in patients <40 kg would have made any difference to the outcome of the study.*

- Agreement on definitions of primary efficacy endpoint and primary efficacy populations in Study 98-0-050.
- Lowering of the lower age limit to 6 months and size of pediatric population in Study 98-0-050.
- Agreement on conduct of drug-drug interaction studies.

Also discussed at the EOP2 meeting was Fujisawa's plan to

Medical Officer's Comment: *The Agency has received no further submissions on this*

The Agency held a Pre-NDA meeting with the applicant on June 8, 2001. After the applicant presented preliminary data from the primary clinical studies, the following points were raised and agreed to:

- The need for sufficient information in the NDA to allow adqeuate assessment of the patient's underlying condition.
- The NDA should contain a written report documenting the Independent Reviewers' assessments of study 046 and 047.
- At the minimum, the applicant should provide a summary of information available in the literature to support the results in the open label, noncomparative studies 046 and 047.
- On study 050, the applicant proposed an independent review of suspected cases of fungal infection.
- Although the applicant presented data suggesting micafungin to be superior to fluconazole in study 050, the Agency

  . This issue was to be further discussed.
- The applicant agreed to provide the Agency with patient exposure to micafungin prior to NDA submission. Specifically, the applicant was to submit a compilation of human exposure to over 50 mg/day of micafungin.
- The Agency also agreed that a

  was no longer necessary given the fact that the applicant had conducted a pediatric PK study and the NDA database had a large pediatric safety data.
- The applicant agreed to include two PK studies in the NDA, one in patients with mild-moderate hepatic impairment and the other study in those with severe renal impairment. In addition, the Agency asked the applicant to consider conducting an in vivo study to assess the potential displacement of an albumin-bound drug after the administration of micafungin. Further, the Agency requested evaluation of the effects of race, age, and gender on the PK of micafungin as well as more information on the M5 metabolite and the nature of the elimination of all metabolites.

- The Agency also agreed to the applicant's proposal to submit safety data on 30 long-term patients from Study 98-0-046 no later than the 120-day safety update.

Medical Officer's Comment: *The 120-Day safety Update was submitted on August 28, 2002. The Update includes safety data from additional 179 patients (97 from Study 98-0-046 and 82 from Study 98-0-047) as well as safety and PK data on 34 subjects from the renal*
and hepatic impairment studies. These studies were ongoing at the time of NDA submission. Finally, the Update contains data from 3 additional PK drug-drug interaction studies conducted in Europe in 24 healthy male volunteers.

On June 28, 2001, the CMC team of the DSPIDP held a separate Pre-NDA meeting with the applicant to further discuss changes to drug substance and drug product as well as plans for pre-approval facility inspection at the time of NDA submission. The overage issue was again discussed but was to be addressed in the NDA.

A major concern raised by the Agency during the Pre-NDA meeting was the lack of a comparative trial data that demonstrates the activity of the drug against specific fungal infections.

1.4 Other Relevant Information: Foreign Marketing/Regulatory Status
At the time of NDA filing, Micafungin has not been approved in any other country and is currently not being evaluated by any other regulatory authority.

Medical Officer's Comments: *During teleconferences held with the applicant in the course of this review, the applicant*

1.5 Important Class Related Issues
Micafungin is the second in a new class of antinfungals known as echinocandins. Echinocandins are semisynthetic lipopeptides with potent and broad-spectrum antifungal activity. This activity is mediated by non-competitive inhibition of (1,3)-β-D-glucan synthase, which synthesizes (1,3)-β-D-glucan, a major component of fungal cell wall. Many pathogenic fungi possess (1,3)-β-D-glucan, an essential cell wall homopolysaccharide. This essential glucose polymer provides rigidity and osmotic/structural integrity to the cell wall of susceptible fungi. Inhibition of cell wall synthesis results in cell wall damage by osmotic lysis and eventual fungal death. (1,3)-β-D-glucan target is not a known component mammalian hosts. Thus, a mechanism-based toxicity is potentially unlikely, which could be a major attraction of the echinocandins.

In the 1980s, poor spectrum of activity and nephrotoxicity led to discontinuation of development of the first member of the class, cilofungin. In 2001, caspofungin (Cancidas®) was approved for marketing in the United States. A third member of the class, anidulafungin, is in advanced stages of development. One characteristic of this class of drugs is their uniformly poor oral bioavailability, which precludes development of oral formulations. The drugs can only be administered intravenously. This could be

considered a disadvantage among this class of drugs compared to the azoles. Nonetheless, intravenous administration ensures compliance in a setting of sick patients that these products are to be used.

There have been no major unexpected safety concerns since marketing approval of caspofungin. A common safety issue shared by members of the echinocandin class is histamine release effect following infusion. Such infusion reaction includes rash, facial swelling, pruritus, and a sensation of warmth. This adverse event is easily controlled with reduction in rate of infusion. Injection site reactions appear also to be common with the echinocandins.

In vitro, hemolysis seems to be a safety concern with all echinocandins. The exact mechanism remains unknown. Fortunately, so far hemolysis has not been a major safety problem with clinical use of caspofungin.

The liver is the primary target for toxicity in animal studies. Such hepatic toxicity include changes in liver function tests (alanaine aminotransferase [ALT], aspartate aminotransferase [AST], and alkaline phosphatase) and histopathological changes (single cell necrosis, acidophilic bodies, nuclear hypertrophy, and hepatocellular hypertrophy.

There has been controversy with concomitant use of echinocandins with corticosteroids in rats. A study by Clemmons et al, suggested co-administration of anidulafungin with corticosteroids results in excess mortality. This study is yet to be replicated in any other laboratory.

Another concerning safety issue is the potential for drug-drug interactions. Caspofungin is contraindicated in patients on cyclosporine because of the risk for hepatotoxicity.

Cross-resistance to azole antifungal agents appears to be a rapidly emerging problem globally (Arathoon E. Clinical efficacy of echinocandin antifungals. Curr Opin Infect Dis 2001; 14:685-91). To what extent and how rapidly this would impact the utility of the echinocandins is uncertain.

Echinocandins are generally fungicidal against *Candida* species, including strains resistant to azoles and amphotericin B; however, the distinction in activity is blurred with *Aspergillus* species because it is neither classically fungicidal nor fungistatic. Partial growth inhibition is seen with *Aspergillus* species, which presents as short, stubby, and highly branched hyphae on microscopy. The drug concentration at which this growth inhibition occurs is called the minimum effective concentration (MEC), the clinical and microbiologic relevance of which is yet to be fully defined.

2 SIGNIFICANT FINDINGS FROM CHEMISTRY, ANIMAL PHARMACOLOGY AND TOXICOLOGY, AND MICROBIOLOGY

2.1 Chemistry, Manufacturing, and Controls

This section reviews aspects of the Chemistry, Manufacturing, and Controls (CMC) of micafungin that have immediate clinical implications. For more details on CMC in this application, the reader should please refer to the review by the Chemistry reviewer.

Micafungin Drug Substance

Micafungin is a semi-synthetic white powder derived from *Coleophoma empetri*

. The drug substance is freely soluble in water

. Because the parent compound of FK463

There are , in the manufacturing process that, theoretically, constitute impurities for the drug substance. The chemical structures of the major degradation products have been elucidated. substances are consistently detected at levels over in the micafungin drug substance. Toxicology studies performed in rats using high levels of these substances showed that the no observable adverse effect levels (NOAEL) were three times higher than the amount of substances in the maximum therapeutic dose of micafungin (6mg/kg/dose) used in clinical trials (excluding the MTD studies).

During the course of development, the manufacturing method was changed. Impurity profiles of the drug substance obtained from the new manufacturing method were equivalent and/or improved in quality compared to the old manufacturing method. A study to was performed with process validation performed in the 4th quarter of 2001. The results of batch analyses on lots tested met the specifications of the NDA. In addition, there were no differences in results of stability studies obtained from both manufacturing methods. Further, the applicant commits to performing post-approval stability studies with the first three commercial batches of micafungin, according to the protocol shown in Table---

Storage Condition	Containers	Testing Stations
Long-term Testing 5°C		Month
Accelerated Testing 25°C/60% relative humidity		Month

Source: Adapted from Table 12, Vol 2.47 CTD Module 2.3, Quality Overall Summary p33

Micafungin drug substance test items to be performed at each testing station are:

The storage condition and retest date of micafungin drug substance are proposed as "

Micafungin Drug Product

The drug product is the sodium salt of micafungin. Micafungin for Injection is a lyophilized product for injection [redacted] 50 mg potency). It is administered by intravenous infusion after reconstitution with 5 mL [redacted] or 5% dextrose and further dilution with [redacted] or 5% dextrose. All excipients in micafungin for injection are compendial.

Medical Officer's Comment: *the reader should recall that the compounded solution is overfilled by [redacted] during the filling process to compensate for the amount of drug product retained in the vial following withdrawal. This is to ensure the withdrawal of the labeled amount from the vials.*

The stability of micafungin drug product is affected by pH and in aqueous solution. After storage at 70°C for [redacted], lyophilized micafungin drug product formulated at pH of ≥ [redacted] maintained its stability but had a higher amount of related substances compared with formulation at pH of [redacted] which also remained stable but with [redacted] increase in amount of total related substances. In aqueous solution at 50°C for [redacted] micafungin drug product loses [redacted] of its initial potency even at the most stable pH of [redacted] hence its formulation as a lyophilized powder. Vials of micafungin drug product lose potency with an increase in degradation product if unprotected from UV light. However, vials with UV-resistant film cover showed no decrease in potency following light exposure for [redacted]. Similarly, to prevent photo-degradation for up to 24 hours, the reconstituted solution in the vials should also be covered with UV-resistant film. Further, infusion bags containing the reconstituted drug product should be protected from light exposure using a light-resistant sleeve.

Animal Pharmacology and Toxicology

The NDA contains data from a total of 33 toxicology studies performed in the course of micafungin development. These studies were done in mice, rats, guinea pigs, rabbits, dogs, cynomolgus monkeys, cultured cells, and bacteria. Doses up to 32 mg/kg in repeated dose studies were evaluated in toxicology studies in rats and dogs. Among these

studies, seven are toxicologic and toxicokinetic studies with up to 26 week (rat) and 39-week (dog) treatment periods.

Medical Officer's Comment: *As noted by the applicant, patients with invasive aspergillosis could require prolonged antifungal therapy. Although the global mean ± standard deviation of duration of treatment in the NDA was 22.7 ± 28.3 days, the mean ± standard deviation in invasive aspergillosis (Study 98-0-046) was 50.0 ± 59.35 days with a median of 29 days. Indeed, the maximum duration of treatment was 470 days (67 weeks). Although there appears to be no safety concerns noted for the subject who received such prolonged exposure to micafungin, available animal toxicology data do not allow exposure beyond 39 weeks.*

3 HUMAN PHARMACOKINETICS AND PHARMACODYNAMICS

This section summarizes the key pharmacokinetic and pharmacodynamic characteristics of micafungin. A total of 20 human pharmacology studies were performed in the course of micafungin development. Thirteen (9 in healthy and 4 in patients) of these were pharmacokinetic studies, which show that the pharmacokinetic of micafungin is linear over a wide range of doses tested. Steady state is achieved rapidly, generally within 4-5 days. There is no systemic accumulation. Micafungin is rapidly and extensively distributed into tissues following intravenous injection. The highest concentrations occur in the lungs with minimal distribution into erythrocytes. In healthy volunteers and among different patient populations at clinically relevant doses, AUC0-24 ranged from approximately 50 to110 mcg.h/mL, Cmax 6.4 to 16.8 mcg/mL, and t1/2 12.5 to 15 hours.

Micafungin is >99% protein bound, primarily to albumin and to a lesser extent to α_1-acid-glycoprotein and other plasma proteins. The drug is not an inducer, inhibitor, or a substrate for cytochrome P450 enzyme system. Similarly, it is not an inhibitor of P-glycoprotein.

Although the metabolism of micafungin is yet to be fully elucidated, at least 12 metabolites have been identified by HPLC in animals and 5 in humans. The main metabolite in human plasma (M-5) has negligible in vitro fungal activity. M-1 and M-2 have potent in vitro activity but detected only in trace amounts in plasma. Enzymes thought to be involved in micafungin metabolism include aryl sulfatase, which metabolizes the parent compound to M-1, and catechol-O-methyl transferase (COMT), which converts M-1 to M-2.

Micafungin is primarily excreted via biliary pathway with only a mean of 7.4% of administered dose eliminated in urine. Because micafungin is highly protein bound, it is not dialyzable. Therefore, additional dosing may not be required in patients undergoing hemodialysis.

Medical Officer's Comment: *Preclinical studies showed little or no placental transfer of micafungin. However, the drug is secreted into milk and, therefore, potentially could be secreted into human breast milk.*

No dosing adjustments are needed based on race, age, gender, renal or hepatic status. However, it should be noted that relative to normal subjects, exposure (Cmax, AUC) was significantly decreased in subjects with moderate hepatic dysfunction. The applicant reasons that because micafungin is a capacity-limited (poorly extracted) drug with a low intrinsic total clearance, free drug could increase in hepatic dysfunction, due to the decreased synthesis of the binding proteins. This increased free drug could result in increased clearance with a concomitant decrease in AUC as was observed in micafungin studies in subjects with poor liver function. It is reassuring that studies in the context of actual clinical use showed that the PK parameters in patients with moderate hepatic dysfunction were not significantly different from those obtained in adult bone marrow and peripheral stem cell transplant recipients (Study 97-0-041). It should also be pointed out that micafungin has not been studied in patients with severe liver dysfunction

Pharmacodynamics and Microbiology

Studies on mechanism of action: Several applicant-sponsored and published studies demonstrate the in vitro and in vivo spectrum of activity of micafungin against the targeted pathogenic fungi. Micafungin acts to inhibit 1,3-beta-D-glucan synthesis, a mechanism of action distinct from other antifungal drug classes. Potential for cross-resistance might therefore be minimal. Further, additive or synergistic activities have been demonstrated when used with other classes of antifungal drugs.

Studies on dosing: A once daily dosing interval is based on the terminal elimination half life of 10-17 hours. The minimum effective plasma concentrations of micafungin in mouse models of disseminated fungal infections and the results of Phase 1 PK studies in healthy volunteers were used in the selection of doses for early clinical trials. In subsequent clinical development, initial daily doses were increased in Studies 98-0-046 and 98-0-047. At clinically relevant daily dosages (50-100 mg adults or 1-2 mg/kg pediatric patients), mean minimum plasma concentrations at 24 hours exceed the determined inhibitory concentrations of several species of *Candida* and *Aspergillus*.

Medical Officer's Comment: *MIC50 and MIC90 of micafungin against Candida parapsilosis is >8 μg/mL but shows reasonable activity against other species including azole resistant isolates (Laverdiere M, Hoban D, Restieri C, Habel F. In vitro activity of three new triazoles and one echinocandin against Candida bloodstream isolates from cancer patients. J Antimicrob Chemother 2002;50:119-23). In a study comparing the activity of micafungin versus amphotericin B deoxycholate or liposomal amphotericin B in experimental persistently neutropenic rabbit model, micafungin failed to clear galactomannan antigenemia or to reduce pulmonary tissue burden of Aspergillus fumigatus. However, there was significant reduction in mortality and level of pulmonary infarction in the micafungin treated rabbits. In contrast, rabbits treated with both formulations of amphotericin had significant reductions in galactomanna antigenemia and tissue burden of Aspergillus fumigatus. (Petraitis V, Petraitiene R, Groll AH, Roussillon K, Hemmings M, Lyman CA, Sein T, Bacher J, Bekersky I, Walsh TJ. Comparative antifungal activities and plasma pharmacokinetics of micafungin (FK463) against disseminated candidiasis and invasive pulmonary aspergillosis in persistently neutropenic rabbits. Antimicrob Agents Chemother 2002;46:1857-69). However, In vitro studies show FK463 exhibited potent activity against Aspergillus species, which was*

superior to amphotericin B, itraconazole and fluconazole and FK463 was also active against the dematiaceous fungi Cladosporium trichoides, Exophiala spinifera, Fonsecaea pedrosoi, and Exophiala dermatitidis except for certain clinical isolates. (Nakai T, Uno J, Otomo K, Ikeda F, Tawara S, Goto T, Nishimura K, Miyaji M. In vitro activity of FK463, a novel lipopeptide antifungal agent, against a variety of clinically important molds. Chemotherapy 2002;48:78-81).

Studies related to potential safety concerns: From preclinical studies, the liver is the primary toxicity target for micafungin. There is sufficient data in the NDA to address liver tocicity and this will be discussed in relevant sections of this review (See Section---). Hemolysis, histamine release, and injection site reactions are among other potential safety issues that will be addressed in this review. No study specifically addresses the potential for micafungin to prolong the QT interval.

Studies on interactions: Adequate studies were done to evaluate potential interactions with cyclosporine and tacrolimus, drugs frequently used in the context of patients likely to require antifungal therapy. In these studies the primary PK parameters showed no evidence of interaction of micafungin with these drugs. Therefore, no dose adjustment is needed when micafungin is co-administered with cyclosporine, or tacrolimus. Similarly, dose adjustment is not required when micafungin is used concomitantly with fluconazole. Drug-drug interactions are further addressed in the review (See Section---)

4 DESCRIPTION OF CLINICAL DATA AND SOURCES

4.1 Sources of Clinical Data

The clinical data in this NDA are derived primarily from clinical trials sponsored by the applicant. One of the studies (Study 98-0-050) was conducted under the auspices of the National Institute of Allergy and Infectious Diseases (NIAID) Mycosis Study Group (MSG 46).

4.2 Overview of Clinical Trials

Appendix--- summarizes all the clinical trials conducted to support this NDA for the three indications of:

1. Prophylaxis of , in patients undergoing hematopoietic stem cell transplantation (HSCT).
2.
3.

Tables--- and --- present a summary of human exposure to micafungin

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Table---: Overall Exposure to Micafungin-Patient Drug Exposure by Study and Patient Days for All Micafungin Treated Patients

	97-7-003 (N=120)	97-0-041 (N=62)	FG463-21-03 (N=36)	98-0-043 (N=77)	FG463-21-01 (N=186)	98-0-047/ FG463-21-02 (N=250)	98-0-050 (N=425)	TOTAL (N=1156)
PATIENT DAYS								
1 – 14	98(81.7%)	56(90.3%)	9(25.0%)	73(94.8%)		50(26.9%)	100(40.0%)	90(21.2%) 476(41
15 – 28	22(18.3%)	6(9.7%)	27(75.0%)	4(5.2%)	43(23.1%)	97(38.8%)	303(71.3%)	502(43.4%)
29 – 60					47(25.3%)	49(19.6%)	32(7.5%)	128(11.1%)
> 60					46(24.7%)	4(1.6%)		50(4.3%)
TOTAL PATIENT DAYS	1541	664	700	511	8091	5140	8093	24740
RANGE OF PATIENT DAYS	1 - 21	1 - 27	8 - 28	1 - 27	1 - 346	1 - 95	1 - 51	1 - 346
MEAN OF PATIENT DAYS	12.8	10.7	19.4	6.6	43.5	20.6	19.0	21.4

Taken from Appendix 6 of applicant's submission

Table---: Overall Drug Exposure by Age Group

Parameter		Patients (N=1156)			All Subjects (N=1368)
		< 16 Years	> 16 Years	All Patients	
Categorized Treatment Duration (Days)					
	1-14	97 (51.9)	360 (37.2)	457 (39.5)	619 (42.2)
	15-28	39 (20.9)	474 (48.9)	513 (44.4)	540 (39.5)
	29-60	33 (17.6)	97 (10.0)	130 (11.2)	153 (11.2)
	>60	18 (9.6)	38 (3.9)	56 (4.8)	56 (4.1)
Categorized Mean Daily Dose (mg/kg)					
	<1.0	33 (17.6)	578 (59.6)	611 (52.9)	697 (51.0)
	1.0-1.9	110 (58.8)	284 (29.3)	394 (34.1)	499 (36.5)
	2.0-2.9	24 (12.8)	54 (5.6)	78 (6.7)	92 (6.7)
	3.0-3.9	12 (6.4)	22 (2.3)	34 (2.9)	40 (2.9)
	≥ 4	8 (4.3)	27 (2.8)	35 (3.0)	35 (2.6)
	Missing	-	4 (0.4)	4 (0.3)	5 (0.4)
Categorized Mean Daily Dose (mg)					
	50	145 (77.5)	632 (65.2)	777 (67.2)	886 (64.8)
	75	22 (11.8)	153 (15.8)	175 (15.1)	205 (15.0)
	100	10 (5.3)	87 (9.0)	97 (8.4)	153 (11.2)
	150	9 (4.8)	39 (4.0)	48 (4.2)	65 (4.8)
	200	1 (0.5)	58 (6.0)	59 (5.1)	59 (4.3)
Treatment Duration (Days)		29.4	21.4	22.7	21.1
Mean Daily Dose (mg) [a]		45.8	75.8	71.0	70.2
Mean Daily Dose (mg/kg)		1.5	1.1	1.2	1.2
Cumulative Dose (mg)		1881.3	1842.8	1849.0	1703.1
Cumulative Dose (mg/kg)		51.4	27.0	30.9	28.9
Maximum Dose (mg)		50.9	83.1	77.9	76.4
Maximum Dose (mg/kg)		1.7	1.2	1.3	1.3

Summarized from Appendix 2.1, 3.1, 3.2, and 3.3 of the applicant's submission

[a] 50 = ≤ 62.5; 75 = > 62.5 - ≤ 87.5; 100 = > 87.5 - ≤ 125; 150 = >125 - ≤ 175; 200 = >175

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4.3 Postmarketing Experience

Micafungin has not been marketed in any country, therefore, no postmarketing data were reviewed for this submission.

4.4 Literature Review

The applicant has conducted an extensive review of the literature spanning 1988 to 2001. Electronic copies of the cited literature are also provided with the submission. The bulk of the cited literature discuss diagnose and treatment of systemic fungal infections in the immunocompromised host with particular emphasis on candidiasis and aspergillosis. However, given the fact that the echinocadins are relatively new molecular entities, only few of the cited literature address safety and efficacy issues directly relevant to micafungin. On August 31, 2002, an additional literature search was conducted using PubMed and Embase. The search covered the period starting from January 2002.

5 CLINICAL REVIEW METHODS

5.1 Description of Review Method

For efficacy, this review focuses on trials supporting the indication of prophylaxis [redacted] in recipients of hematopoietic stem cell transplant. Trials to support this indication include the pivotal trial 98-0-050 and three supporting trials 97-0-041, 98-0-043, FG463-21-03. These studies are reviewed separately with a significant portion of the review devoted to Study 98-0-050. In addition, the pivotal studies supporting the other two indications Studies 98-0-046 and 98-0-047, and all trials involving patients are reviewed. For safety, the studies listed for efficacy are also reviewed. The safety review is then integrated across all studies. Finally, a review of post-marketing adverse event reports for caspofungin (Cancidas®) provides a perspective to the safety of yet another echinocandin, micafungin.

5.2 Overview of Materials Consulted in Review

The archival copy of this NDA was submitted in an electronic format. Sections of the NDA were also submitted as hard copies. Both formats provided the main source of material for this review. Supplementary sources of material for this review include medical officers' reviews of micafungin protocols and NDAs for the following approved products Cancidas® (caspofungin), V-fend® (voriconazole), Ambisome® (liposomal amphotericin B), Sporonox® (itraconazole), and Abelcet® (amphotericin B colloidal dispersion). Further, the detailed review of the post-marketing safety of Cancidas® conducted by Sarah Singer, R.Ph. Safety Evaluator, Office of Drug Safety (ODS) was consulted. In addition, more literature review was conducted to supplement the literature cited by the applicant. Finally, written reviews from the Division of Scientific Investigation, Division of Drug Marketing, Advertising, and Communications, and the Office of Post-Marketing Drug Risk Assessment were considered in the overall assessment of this NDA.

5.3 Overview of Methods Used to Evaluate Data Quality and Integrity

Three criteria were considered in the assessment of data quality and choice of sites for auditing, inappropriate breaking of blind in Study 98-0-050, excessively high response

rates, and excessively low response rates for the three pivotal studies (98-0-050, — — and 98-0-047). In addition, the sites should have enrolled a relatively substantial number of subjects. Using these criteria, six sites were selected for inspection by the Division of Scientific Investigations (DSI). Three of the sites were domestic (Voravit Ratanatharathorn [Ann Arbor, MI], Elias Anaissie [Little Rock, AR], and Joseph McGuirk [Kansa City, KS]) while two were foreign (Marinella Della Negra and Jamal Suleiman both in Sao Paulo, Brazil). DSI concluded that no major deficiencies were noted at any of the sites inspected, all subjects consented to the study, and that the data appear acceptable for review purposes. A sixth site, Leonard Sender (Orange, CA) was later inspected, again relatively minor violations were found.

5.4 Assessment of Ethical Standards and Related Issues

For all trials reviewed in this NDA submission, the applicant affirms that the protocols were reviewed and approved by the Institutional Review Board (IRB)/Ethics Committee (EC) of participating institutions. The applicant also affirms that the studies were conducted in accordance with the Declaration of Helsinki and Good Clinical Practice (GCP) and that written informed consent was obtained from each patient or legal guardian prior to enrollment. Further, the NDA contains a copy each of debarment certification, field copy certification, current Good Manufacturing Practices (cGMP) certification, and certificate of quality assurance. Finally, the applicant has provided justification for categorical exclusion from the requirement to submit an environmental assessment for micafungin for injection as analysis indicates that environmental effects associated with the release of micafungin drug substance to the environment due to patient use are expected to be negligible.

5.5 Evaluation of Financial Disclosures

There are no financial disclosures in this application. The review finds no potential financial conflicts that could cast doubt on the findings of this application.

6 Integrated Review of Efficacy

6.1 Brief Statement of Conclusions

6.2 General approach to Review of the Efficacy of Micafungin

The efficacy database for the indication of prophylaxis of — in patients undergoing hemotopoietic stem cell transplant is summarized in Table---

Table---: Summary of Studies in Support of Efficacy of Micafungin for the Prophylaxis Indication

98-0-050	Efficacy, safety of FK463 vs fluconazole	Double-blind randomized/ active control	1-hr infusion 1x daily FK463: 50 mg/day (1 mg/kg/day <50 kg); fluconazole: 400 mg/day (8 mg/kg/day <50 kg)	FK463 426 Fluconazole 463	Adult & pediatric patients undergoing hematopoietic stem cell transplant	Treatment started at time transplant-conditioning regimen was initiated or within 48 hours post-initiation; treated until neutrophil recovery + 0 to 5 days to max of 42 days posttransplantion
98-0-043	MTD, safety in age groups 2-12 and 13-17	Open-label, sequential dose escalation	1-hr infusion 1x daily, 0.5 mg/kg/day; escalation to 1.0, 1.5 2.0, 3.0, and 4.0 mg/kg/day; because of slow enrollment highest dose for 13-17 year olds was 1.5 mg/kg/day	78	Febrile, neutropenic pediatric patients with 1 of the following: leukemia or lymphoma (except patients on maintenance therapy); bone marrow or peripheral stem cell transplant; chemotherapy inducing >10 days of neutropenia; aplastic anemia; or myelodysplastic syndrome	Treatment at onset of fever while neutropenic for min of 3 days to max of 4 weeks or until neutrophil recovery
97-0-041	MTD of FK463 in combination with fluconazole	Double-blind, randomized, sequential dose escalation/active control	FK463/saline: 1-hr infusion 1x daily; fluconazole: PO 1x daily (1-hr infusion if PO not possible); FK463 at 12.5, 25, 50, 75, 100, 150, or 200 mg/day; fluconazole at 400 mg/day; saline at 100 mL	FK463 + fluconazole 65 Fluconazole + saline 14	Adult patients undergoing bone marrow or peripheral stem cell transplant	Treatment from 48 hrs prior to transplant to 24 hrs after transplant initiation; dosing continued until neutrophil recovery, up to 5 days post recovery or max of 4 weeks
FG463-21-03	MTD, safety	Open-label, sequential dose escalation	1-hr infusion, 1x daily, at 3.0, 4.0, 6.0, or 8.0 mg/kg/day	36	Adult patients scheduled to undergo bone marrow or peripheral stem cell transplant	Treatment from 2 or 3 days before transplantation for min of 7 days to max of 28 days or until recovery of neutropenia

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6.3 Detailed Review of Trials by Indication

6.3.1 Indication

Prophylaxis of — in patients undergoing hematopoietic stem cell transplantation (HSCT).

6.3.1.1 Protocol Number: 98-0-050 Conducted November 23, 1999 to December 12, 2000

Title: A Phase 3, randomized, double-blind, comparative trial of FK463 versus fluconazole for prophylaxis of fungal infections in patients undergoing a hematopoietic stem cell transplant [Conducted from November 23, 1999 to December 12, 2000]

6.3.1.1.1 Protocol

6.3.1.1.1.1 Objective/Rationale

The study sought to determine the efficacy and safety of FK463 versus fluconazole in preventing fungal infections in patients undergoing an autologous (for hematologic malignancies) or allogeneic hematopoietic stem cell transplant. Fluconazole, the only drug currently approved for prophylaxis against invasive fungal infections, is not active against *Aspergillus* and fluconazole-resistant *Candida* species have emerged. Given FK463's *in vitro* activity against *Candida* species and *Aspergillus* species, the applicant reasons that FK463 is potentially an attractive agent for antifungal prophylaxis in patients at risk for invasive fungal infections.

6.3.1.1.1.2 Overall Design

Protocol 98-0-050 was a multicenter, randomized 1:1, stratified by center, age, type of transplant, and risk for transplant-related mortality, double-blind study in adult and pediatric patients.

Medical Officer's Comment: *The design of this trial is the most appropriate to answer the trial question. However, a major limitation of the design is the need for consistent interpretation and application of the protocol across the many study sites.*

6.3.1.1.1.3 Population and Procedures

Study participants were adult and pediatric patients scheduled for hematopoietic stem cell transplant. Notable inclusion criteria were as follows:

- Patients were required to be ≥ 6 months old
- Patients were required to be at risk for systemic fungal infections as a result of their immunocompromised state due to one of the following:
  - Patients with a hematologic malignancy undergoing an autologous hematopoietic stem cell transplant, or
  - Any patient undergoing an allogeneic hematopoietic stem cell transplant

Relevant exclusion criteria were:

- Patient had evidence of liver disease, defined as:
  - AST/SGOT or ALT/SGPT >5 times ULN
  - Total bilirubin >2.5 times ULN

- Patient had evidence of an active deep or disseminated fungal infection prior to enrollment or had received systemic antifungal agents within 72 hours prior to the first dose of study drug
- Patient was receiving an autologous transplant for nonhematologic malignancies
- Patient was known to be infected with HIV

Medical Officer's Comment: *The entry criteria were fairly non-restrictive. In addition, an analysis of subjects who were screened but not randomized shows that subjects who were ultimately enrolled were typical of those who were eligible. Thus the enrolled population is generalizable to the target population.*

The sponsor made only one amendment to this protocol. That amendment was dated October 12, 1999, which was approximately six weeks prior to initiation of the study. The purpose of the amendment was to:

1. Change the weight criteria for mg/kg dosing to < 50 kg
2. Change the fluconazole dose for patients weighing < 50 kg to 8 mg/kg/day
3. Modify the entry age to a lower limit of 6 months old
4. Modify the exclusion criteria for liver disease
5. Modify the timing of initiation of study drug
6. Modify the definition of suspected fungal infection
7. Clarify the length of therapy of study drug
8. Clarify method of blinding the study drugs
9. Clarify dose adjustments for renal impairment
10. Modify the definition of successful therapy
11. Remove the interim analysis and adjustment of sample size
12. Replace Southwest Oncology Group Toxicity Criteria with National Cancer Institute's Common Toxicity Criteria
13. Incorporate additional administrative clarifications

Amendment items 4, 5, 6, and 10 were notable and warrant further elaboration.

Modify the exclusion criteria for liver disease
In the original protocol, evidence of liver disease for the purpose of exclusion from the study was defined as "1. AST or ALT > 10 times upper limit of normal (ULN) 2. Total bilirubin > 5 times ULN and 3. Alkaline phosphatase > 5 times ULN." This was amended to "1. AST or ALT > 5 times upper limit of normal (ULN) 2. Total bilirubin > 2.5 times ULN."

Modify the timing of initiation of study drug
Study drug was originally to be "initiated no later than 24 hours after the first infusion of stem cells." This section was later modified to read "Study drug will be initiated at the time the transplant-conditioning regimen is initiated or within 48 hours of initiating the transplant-conditioning regimen."

Modify the definition of suspected fungal infection

In the original protocol, a suspected fungal infection was to be established if a patient:

- is neutropenic (ANC < 500 cells/mm^3)
- has a persistent fever of ≥100.4°F (≥ 38°C) for which there is no known etiology or a recurrent fever of >100.4°F (38°C) on two measurements of temperature at least 3 hours apart or a single measurement of ≥ 101.3°F (≥ 38.5° C).
- has failed to respond to at least 96 hours of adequate broad-spectrum antibacterial therapy.

The protocol was amended to read:

A suspected fungal infection will be established if a patient meets the following criteria for at least 96 hours:

- is neutropenic (ANC < 500 cells/mm^3), AND
- has a persistent or recurrent fever of ≥100.4°F (≥ 38°C) for which there is no known etiology, AND
- has failed to respond to at least 96 hours of broad-spectrum antibacterial therapy.

Modify the definition of successful therapy

Treatment success was originally defined as:

> "...the absence of a proven, probable or suspected fungal infection through the end of therapy, absence of a proven or probable fungal infection through the end of study, did not discontinue study drug due to an adverse event related to study drug, and alive at the end of the study (4 weeks posttreatment)." "All four criteria must be met to be considered a treatment success."

This was amended to read:

> "...the absence of a proven, probable or suspected fungal infection during the treatment phase of the study" and "absence of a proven or probable fungal infection during the 4 week posttreatment phase of the study." "Both criteria must be met to be considered a treatment success."

Medical Officer's Comment: *This amendment allowed patients who died or discontinued study drug for reasons other than lack of efficacy to be considered treatment success so long as there was no proven, probable or suspected fungal infection.*

Study Drug Administration

Treatment was administered in an inpatient or outpatient setting. Patients on the test drug arm received FK463 at 50 mg per day (approximately 1 mg/kg/day for patients weighing < 50 kg) while those on the active comparator arm received fluconazole at 400 mg per day (approximately 8 mg/kg/day for patients weighing < 50 kg). ***(Medical Officer's Comment:*** *The reader should recall that at the EOP2 meeting, the applicant agreed to use flucoanzole at a dose of 12 mg/kg/day for patients < 40 kg.)* These products were infused intravenously over a period of one hour, once daily. Given the need for dose adjustment in patients with renal dysfunction who receive fluconazole and because FK463 requires no such dose adjustment, volume of FK463 was adjusted during the study to mimic the volume the patient with renal dysfunction would have received had they been randomized to fluconazole. Such adjustment also allowed the blind to be

maintained. Patients undergoing dialysis received 100% of the fluconazole dose on days when dialysis was done and 200 mL 0.9% sodium chloride (normal saline) on days they were not dialyzed. Dialysis patients randomized to FK463 received their appropriate doses but volume was adjusted to mimic the volume that would have been used had they been randomized to the fluconazole arm.

Medical Officer's Comment: *Volume adjustments for renal impairment as described above seems rather complex and may have potentially compromised blinding. A simpler strategy could have been to use a double dummy but this may not have been feasible, given the medical complexity of the study population and the potential dangers of fluid overload.*

6.3.1.1.1.4 Evaluations/Endpoints

Study Procedures and Assessments
Eligible patients underwent a physical examination (including body weight and height) and pregnancy test (baseline only); a chest x-ray or computerized tomography (CT) scan (baseline, and during treatment, and at the end of therapy if clinically indicated); an evaluation of vital signs; blood collection for determination of absolute neutrophil count (ANC) and fungal surveillance cultures (baseline, at scheduled times during treatment, and at the end of therapy); and blood collection for determination of hematology, serum chemistry and an assessment of fungal infection (baseline, at scheduled times during treatment, at the end of therapy, and at 4 weeks posttreatment). Adverse events with onset during the study through 72 hours posttreatment were recorded. Concomitant medications were recorded from baseline through the end of therapy; the use of antifungal agents was recorded through 4 weeks posttreatment.

Primary Efficacy Endpoint
The primary efficacy endpoint was treatment success at the end of the study. This was defined as the absence of a proven, probable, or suspected systemic fungal infection through the end of therapy AND the absence of a proven or probable systemic fungal infection through the end of the study. Both of the criteria had to be met in order for the patient to be considered a treatment success. Patients had a suspected fungal infection if they were neutropenic, had a fever and received broad-spectrum antibiotics for at least 96 hours, and required initiation of empirical systemic antifungal therapy.

Medical Officer's Comment: *It should be noted that the protocol provided for a blinded review of the proven and probable fungal infections as the basis for definitive diagnosis of proven and probable fungal infections.*

Secondary Efficacy Endpoint
Secondary endpoints included the following:

- Incidence of proven or probable systemic fungal infections during the study (treatment plus posttreatment periods)
- Incidence of proven, probable, or suspected systemic fungal infections through the end of therapy

- Incidence of proven or probable systemic fungal infection during the posttreatment period for patients who did not have a systemic fungal infection through the end of therapy
- Incidence of systemic (proven, probable, or suspected) fungal infections during the posttreatment period for patients who did not have a systemic fungal infection through the end of therapy
- Incidence of proven or probable systemic fungal infections during the study by organism
- Incidence of suspected fungal infections during the study
- Incidence of the use of systemic antifungal agents during posttreatment
- Time to treatment failure during the study
- Time to suspected fungal infection
  Medical Officer's Comment: *Time to suspected fungal infection was added to the secondary analysis variables post-hoc.*
- Incidence of superficial fungal infections through the end of therapy
- Incidence of fungal colonization at baseline and at the end of therapy

Medical Officer's Comment: *Candida infection occurs in about 11% of this population with a mortality rate of about 39% for candidemia and up to 90% for invasive candidiasis. The rate of invasive Aspergillosis is about 4.5% with mortality rate of about 80%. The primary endpoint is a composite endpoint. In the target population, use of antifungal therapy is often empiric. It is expected that this composite primary endpoint would be driven by the incidence of suspected fungal infection during the therapy phase of the study. Because several factors could potentially affect the decision to start empiric antifungal therapy, this issue is explored in more detail in this review. As noted earlier in this review (Section 6.3.1.1.1.3), prior to the start of the study the definition of treatment success was amended to allow deaths and discontinuations for adverse events to qualify as treatment success if patient had no proven, probable or suspected fungal infection as stipulated in Section 6.3.1.1.1.3.*

6.3.1.1.1.5 Statistical Plan

This section is reproduced from the applicant's submission with minor editing for lucidity.

Planned Sample Size

The sample size estimation was based on the primary endpoint, treatment success at the end of the study. Based on prior multicenter, randomized prophylactic trials with fluconazole in adult bone marrow transplant patients, the rate of treatment success for fluconazole was estimated to be 40%. Therefore, 400 patients per treatment group would provide at least 80% power at a one-sided 2.5% significance level to demonstrate that FK463 is not inferior to fluconazole over a difference of 10%.

Medical Officer's Comment: *This study was powered based on an expected failure rate of 60% on the control arm. In other words, 60% of patients on fluconazole arm were expected to develop proven, probable, or suspected fungal infections up to end of therapy or proven or probable fungal infection at end f study. As discussed later in the review, the failure rate for the active control arm was far lower than expected. In particular, the rate*

of breakthrough proven or probable fungal infections was quite small, the outcome almost entirely driven by the rate of use of empiric antifungal therapy.

Populations for Analysis
Statistical analyses were performed on the following data sets, as appropriate: full analysis set, defined as "all randomized patients who received at least one dose of study drug"; and per protocol set, defined as "all randomized patients who received at least one dose of study drug and who were deemed evaluable following patient classification". The full analysis set was the primary data set used for efficacy analyses. Patient classification was carried out prior to breaking the blind based on pre-specified patient classification criteria determined by the sponsor.

Statistical Methodology
Definitions, Data Conversions, and Handling of Missing Data
Missing information was to be handled by carrying the last recorded observation forward.

Medical Officer's Comment: *Carrying the last observation forward presents analytical challenges, especially if there is an imbalance between the two arms in the proportions and types of missing data. This issue is further addressed in the review by the Statistician.*

Demographics, Other Baseline Characteristics, and Prior and Concomitant Medications
Demographic variables were summarized by treatment arm, type of transplant, and age group. The treatment arms were compared for discrete variables using the Chi-squared test and for continuous variables using an ANOVA. Descriptive statistics were used to summarize continuous variables and frequency counts were used to summarize discrete variables. The applicant used Anatomical and Therapeutic Classification (ATC) grouping to summarize medications taken during treatment.

Efficacy Analyses
Efficacy analyses were performed on the full analysis set and the per protocol set. Efficacy data were summarized by treatment arm. For the efficacy analysis, all treatment centers were combined. The efficacy of FK463 and fluconazole was compared using a combination of tests of non-inferiority and superiority. First, a test of non-inferiority was performed followed by a test of superiority if FK463 was found to be statistically non-inferior to fluconazole.

A two-sided 95% confidence interval (CI) for the difference of the true success rates was constructed. If the lower bound of the CI was $\geq$-10% then FK463 was considered to be statistically non-inferior to fluconazole. Also, if the lower bound of the CI exceeded 0%, then FK463 was said to be statistically superior to fluconazole.

In the secondary analysis of the primary endpoint, treatment success was analyzed using the Cochran-Mantel-Hanszel (CMH) test adjusting for center and strata. Centers were pooled due to markedly different sample sizes. The treatment by center interaction was assessed using the Breslow-Day test for homogeneity of odds ratios. The estimated rates

of treatment success and their differences were tabulated by center and strata. The strata were age group. (≤12; >12 years of age); type of transplant and risk of transplant related mortality (autologous, allogeneic matched sibling low risk, allogeneic matched sibling high risk, allogeneic other donor low risk, and allogeneic other donor high risk).

For all secondary endpoints, except for time to treatment failure, the treatment arms were compared using the CMH or Fisher's exact test as appropriate. Time to treatment failure was analyzed using the Log Rank Test and the Cox's proportional hazards models. All comparisons were 2-sided with a 5% significance level.

Safety Analyses
Safety analyses were performed on all randomized patients who received at least one dose of study drug. Safety analyses were performed on the following data: adverse events AEs, clinical laboratory test results, and vital signs. The AEs were coded by body system using a modified COSTART dictionary. Treatment emergent AEs were defined as any AE that occurred during the treatment period through 72 hours after the last dose of study drug or any pre-existing condition that worsened during the treatment period. Treatment emergent AEs were summarized by treatment arm, age group, relationship to study drug, and intensity. The applicant also summarized treatment emergent serious AEs (SAEs) and AEs leading to study drug discontinuation by treatment arm, age group, and relationship to study drug. Finally, the applicant summarized the primary cause of death by treatment arm and age group. Clinical laboratory test results, hematology, serum chemistry, and vital signs were assessed at baseline, and at various times throughout the study.

Interim Analysis
Planned interim analysis of safety and efficacy data by Data Safety Monitoring Board (DSMB) was not done due to faster than expected patient accrual. It should be pointed out that the Mycoses Study Group (MSG) participated in the study design and data review. However, an independent MSG Data Safety Monitoring Board (DSMB) performed an unblinded monthly review of serious adverse events occurring during the conduct of the study.

Medical Officer's Comment: *It is unclear if the independent DSMB members were different from MSG study participants*

6.3.1.1.2 Results

Enrollment by investigator site and treatment group is presented on Table--- and further summarized in Table---.

Table---Patient Enrollment by Site and Treatment Group

Site Code	FK463 Arm	Fluconazole Arm	Site Code	FK463 Arm	Fluconazole Arm	Site Code	FK463 Arm	Fluconazole Arm	Site Code	FK463 Arm	Fluconazole Arm
1	1	4	*38*	6	3	*84*	28	26	*266*	1	1
5	14	12	*42*	22	22	*89*	12	12	*274*	1	1
7	1	1	*50*	10	8	*93*	4	3	*290*	1	2
8	7	7	*51*	14	19	*114*	4	2	*342*	13	14
9	2	2	*52*	4	2	*123*	9	12	*404*	2	2
11	3	2	*57*	22	22	*125*	6	8	*405*	5	6
12	21	19	*59*	3	4	*126*	4	3	*416*	1	1
13	8	9	*62*	6	7	*132*	0	1	*418*	2	2
16	3	5	*63*	2	4	*141*	7	7	*419*	3	3
20	25	30	*64*	5	6	*181*	0	1	*420*	4	3
21	3	3	*65*	1	0	*205*	13	13	*421*	1	1
31	11	13	*70*	4	6	*241*	7	7	*422*	1	1
32	12	11	*71*	1	0	*242*	7	8	*428*	1	1
33	5	10	*73*	2	7	*245*	1	3	*464*	2	5
34	3	1	*75*	9	8	*247*	0	2	*488*	3	5
35	8	8	*76*	12	11	*249*	1	1	*519*	0	2
36	4	3	*78*	2	1	*253*	3	3	-	-	-
37	15	18	*79*	6	10	*262*	2	3	-	-	-

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Table---Summary of Patient Enrollment by Site

Number of Patients Enrolled	Number of Sites
≤ 5	24
6-10	17
11-15	9
16-20	5
21-25	5
26-30	3
31-35	2
36-40	1
≥ 41	4 (with 44, 44, 54, 55 Patients)
Mean Number of Patients Enrolled	13
Median Number of Patients Enrolled	7
Range of Number of Patients Enrolled	1-55

Medical Officer's Comment: *Overall, enrollment was balanced between the treatment groups. Fifteen of the largest sites (enrollment ≥ 20 patients), enrolled 496 (55.8%) of the 889 patients. Protocol-defined successful outcome ranged from 44.4% to 96.3% at these sites.*

6.3.1.1.2.1 Subject Disposition

A total of 1267 patients were screened from 70 sites (2 sites were initiated but never enrolled patients), and 889 were randomized into the study. Table--- summarizes the demographic characteristics of those who were randomized and those who were screened but not randomized (screen failures).

Table---: Demography of Randomized Patients and Screen Failures

	Screen Failures N=380	**FK 463 N=425**	**Fluconazole N=457**
Gender			
Male	217 (57.1%)	253 (59.5%)	274 (60.0%)
Female	159 (41.8%)	172 (40.5%)	183 (40.0%)
Not Stated	4 (1.1%)	-	-
Race			
Caucasian	294 (77.4%)	387 (91.1%)	411 (89.9%)
Black	28 (7.4%)	30 (7.1%)	37 (8.1%)
Oriental	5 (1.3%)	5 (1.2%)	8 (1.8%)
American Indian	2 (0.5%)	2 (0.5%)	0 (0.0%)
Other or not stated	51 (13.4%)	1 (0.2%)	1 (0.2%)
Age (years)			
Mean (SD)	39.3 (17.5)	43.2 (17.1)	41.9 (17.1)
Range	1.0 - 68.0	0.6 - 73.0	0.6 - 71.0

Source: Adapted from applicant's Study 98-0-050 report Table 5 and Appendix 14.4.29 (Listing of Screen Failures)

Of the 354 screen failures with age specified, 45 (12.7%) were < 16 years and 309 (87.3%) were ≥ 16 years.

Subjects randomized were similar in demographic characteristics to those screened but not randomized. Of those randomized who received at least one dose of study drug (full analysis set), 84/882 (9.5%) were < 16 years and 56/882 (6.3%) were ≥ 65 years the study comprised. The distribution of demographic characteristics was balanced between the two study arms. This balance in demographic characteristics between the two treatment arms was maintained in those ≥ 16 years and in those <16 years except for gender distribution among those < 16 years (M/F 51.3%/48.7% FK463 and 62.2%/37.8% fluconazole). Demographic characteristics in the per protocol set remained balanced between the two treatment arms.

Reasons for screen failure

The main reasons for not randomizing patients who were screened included:

- patient refusal
- autologous transplant for a non-hematologic malignancy
- receiving an alternative systemic antifungal therapy
- participation in another study
- presence of a systemic fungal infection
- postponement of transplant, concomitant medical condition
- increased liver laboratory parameters
- receiving a non-myeloablative transplant which would not cause significant neutropenia
- allergy to fluconazole, and patient not meeting age criteria

The following tables present additional information on study population.

Table-- Full analysis and Per Protocol Sets

	FK463	Fluconazole	Total
All Randomized Patients	426	463	889
Full Analysis Set	425 (99.8%)	457 (98.7%)	882 (99.2%)
Per Protocol Set	397 (93.2%)	433 (93.5%)	830 (93.4%)

Source: Applicant's Study 98-0-050 Report Table 1

Table---Patient Status at End of Study

Status	FK463 N=426	Fluconazole N=463
Completed Study	402 (94.4%)	428 (92.4%)
Death	18 (4.2%)	27 (5.8%)*
Lost to follow-up	5 (1.2%)	3 (0.6%)
Other	1 (0.2%)	5 (1.1%)

Source: Applicant's Study 98-0-050 Report Table 3

Patient base: all randomized patients irrespective of whether study drug was administered (all randomized patients)

*Patient Number 0203614 died prior to receiving study drug.

Other: None of these 6 patients received study drug.

Table--Summary of Exclusions from Per Protocol Set

Criteria for Exclusion From Per Protocol Set	FK463 N=425	Fluconazole N=457
Any Criteria	28	24
Absolute Neutrophil Count Never < 200 cells/mm3	12	16
Baseline Systemic Fungal Infection	1	1
Systemic Antifungal Therapy Prior to Enrollment	9	5
Missing End of Therapy or End of Study Fungal Infection Assessment	6	5
Did Not Receive Hematopoietic Stem Cell Transplant	2	0
Blind Broken Prior to Efficacy Assessments	1	0

Table---Risk group and types of transplant

	FK N=425	Fluconazole N=457
Autologous or Syngeneic	203 (47.8%)	201 (44.0%)
Allogeneic	220 (51.8%)	256 (56.0%)
Matched Sibling	131 (30.8%)	160 (35.0%)
Other Donor	89 (20.9%)	96 (21.0%)
None	2 (0.5%)	0 (0.0%)

Table--- Underlying Disease Study 98-0-050

Primary Diagnosis	FK463	Fluconazole
Adults Patients (≥ 16 Years of Age)		
n	386	412
Non-Hodgkin's Lymphoma	104 (26.9%)	104 (25.2%)
Multiple Myeloma	83 (21.5%)	90 (21.8%)
Chronic Myelogenous Leukemia	48 (12.4%)	54 (13.1%)
Acute Myelogenous Leukemia	46 (11.9%)	62 (15.0%)
Hodgkin's Disease	37 (9.6%)	35 (8.5%)
Acute Lymphocytic Leukemia	18 (4.7%)	19 (4.6%)
Myelodysplasia RAEB	10 (2.6%)	18 (4.4%)
Myelodysplasia RAEB-T	9 (2.3%)	3 (0.7%)
Chronic Lymphocytic Leukemia	8 (2.1%)	12 (2.9%)
Renal Cell Carcinoma	7 (1.8%)	4 (1.0%)
Aplastic Anemia	5 (1.3%)	2 (0.5%)
Leukemia NOS	5 (1.3%)	2 (0.5%)
Other Diseases	3 (0.7%)	3 (0.7%)
Breast Carcinoma	2 (0.5%)	0 (0.0%)
Other Solid Tumor	2 (0.5%)	4 (1.0%)
Fanconi s Anemia	1 (0.2%)	1 (0.2%)

Testicular Carcinoma	0 (0.0%)	1 (0.2%)
Pediatric Patients (<16 years of age)		
n	39	45
Acute Lymphocytic Leukemia	15 (38.5%)	11 (24.4%)
Acute Myelogenous Leukemia	7 (17.9%)	12 (26.7%)
Other Diseases	6 (15.4%)	10 (22.2%)
Aplastic Anemia	4 (10.3%)	4 (8.9%)
Fanconi s Anemia	3 (7.7%)	2 (4.4%)
Non-Hodgkin's Lymphoma	2 (5.1%)	1 (2.2%)
Myelodysplasia RAEB	1 (2.6%)	2 (4.4%)
Chronic Myelogenous Leukemia	1 (2.6%)	2 (4.4%)
Hodgkin's Disease	0 (0.0%)	1 (2.2%)

Source: Applicant's Study 98-0-050 Report Table 9

Primary diagnoses in adults and children (Table---), development of graft versus host disease (GVHD), maximum grade of GVHD and time to GVHD (Table---) were balanced between the two treatment arms. Similarly, neutrophil recovery and time to recovery, receipt of and time to second HSCT, receipt and duration of growth factors were all similar between the two arms (Table---).

Table--- Summary of GVHD, Neutrophil Recovery, Second Transplant, and Use of Growth Factors

Parameter	**Class**	**FK463 N=397**	**Fluconazole N=433**
Development of GVHD			
	Yes	94 (23.7%)	97 (22.4%)
	No	303 (76.3%)	336 (77.6%)
Maximum Grade of GVHD			
	Absent	303 (76.3%))	336 (77.6%))
	I	27 (6.8%)	30 (6.9%)
	II	40 (10.1%)	42 (9.7%)
	III	19 (4.8%)	21 (4.8%)
	IV	8 (2.0%)	4 (0.9%)
Time to GVHD (Day)			
	Median	20	20 (
	Range	3-49	1-66
Neutrophil Recovery			
	Yes	386 (97.2%)	412 (95.2%)
	No	11 (2.8%)	21 (4.8%)
Time to Neutrophil Recovery (Day)			
	Median	13	13
	Range	8-54	7-44
Second HSCT			
	Yes	8 (2.0%)	11 (2.5%)
	No	389 (98.0%)	422 (97.5%)
Time to Second HSCT (Day)			

	Median	34	22
	Range	15-65	1-52
Received Growth Factor During Therapy			
	Yes	309 (77.8%)	325 (75.1%)
	No	88 (22.2%)	108 (24.9%)
Duration of Growth Factor Use (Day)			
	Median	9.6	9.2
	Range	1.0-33.0	1.0-44.0

Source: Applicant's Study 98-0-050 Report End-of-Text Table 13.4.1.2

Use of systemic antifungal therapy prior to study drug administration was similar between the two arms. On both arms, fluconazole was the predominant systemic antufungal agent patients received prior to study drug administration as shown on Table---

Table--- Summary of Patients Receiving Systemic Antifungal Therapy Prior to Study Drug Administration

Prior Antifungal Therapy	FK463 (n=425)	Fluconazole (n-457)
Any Antifungal	34 (8.0%)	35 (7.7%)
Abelcet	0 (0.0%)	1 (0.2%)
Amphotericin B	1 (0.2%)	2 (0.4%)
Itraconazole	2 (0.5%)	3 (0.7%)
Fluconazole	32 (7.5%)	31 (6.8%)

Source: Table 10 page 48 of sponsor's Study Report for Study 050

Overall, use of concomitant systemic antifungal therapy was limited. A total of 17 (9 FK463 and 8 Fluconazole) patients received at least one dose of systemic antifungal therapy during the treatment period other than the study drug. However, use of systemic antifungal therapy was very extensive in the posttreatment phase of the study, predominantly fluconazole for prophylaxis or maintenance.

Study Drug Exposure

Overall, the mean duration of study drug was similar between the two treatment arms and both had a median duration of study drug exposure of 18 days. As expected, on both treatment arms the median treatment duration for autologous or syngeneic transplant patients was shorter than for allogeneic transplant patients (16 days on both arms for autologous/syngeneic and 21 days and 20 days, respectively for FK463 and Fluconazole patients who received allogeneic transplant). Compared to adult patients, pediatric patients had somewhat longer duration of treatment but this was comparable between the two arms (a median of 22 days and 21 days for the FK463 and the fluconazole arms, respectively). Finally, the interval from patient's first dose to transplant date was comparable between the two arms (a mean of 6.6 days and a median of 7 days for each arm).

Medical Officer's Comment: *14.3% of FK463 and 15.3% of fluconazole patients were admitted to ICU. The median duration of ICU stay for the two groups was 18.0 and 21.5 days, respectively. Thus, fluconazole patients may have been sicker than those on FK.*

Unblinding

Two FK463 patients were unblinded during study drug administration: Patient Number 2051012 developed a rash and required further fungal prophylaxis and Patient Number 2422501 experienced a serious adverse event (SAE) (diffuse white matter changes in the brain), which the investigator determined might be related to study drug. Three fluconazole patients were unblinded during study drug administration: Patient Numbers 0511007 and 0511009 were unblinded due to infusion-related reactions on Day 1, and required further fungal prophylaxis. Patient Number 0732001 was unblinded when a fax containing randomization information was inadvertently sent to the study coordinator instead of the pharmacy. (The study drug assignment was revealed to the study coordinator and not the investigator.)

Five patients at a single site (1 FK463 and 4 fluconazole patients) were unblinded after completion of the study and preparation of the CRFs, but prior to monitoring the CRFs. An administrative support staff member inadvertently obtained faxes containing the treatment assignment and placed them in the patient's CRF.

Two FK463 pediatric patients at a single site (Patient Numbers 0523101 and 0523501) were unblinded after the completion of the study, preparation of the CRFs, and monitoring of the CRFs. The institution's IRB became aware of a potential pharmacy error (under-dosing of those patients due to misunderstanding of the preparation of study drug) and requested that treatment assignment for those patients be revealed. Since the unblinding took place after monitoring of the site, these events are not recorded in the CRFs.

Only 1/12 patients (Patient Number 2051012) who had their randomization unblinded was excluded from the per protocol set analysis since the unblinding occurred prior to the assessment of efficacy.

Medical Officer Comment: *Using ACCT.xpt datase in Study 98-0-050 CRTt, the medical officer assessed the risk group stratification assignment by center and treatment group. At each center sufficient balance was maintained in assigning patients with various risk groups to the two treatment arms.*

6.3.1.1.2.2 Efficacy Endpoint Out comes

Because the primary efficacy endpoint is derived from the full analysis set population, discussion of efficacy endpoint in the review of this study focuses on the full analysis set with appropriate mention of the per protocol set as the need arises.

Primary Efficacy Endpoint

Table---Overall success (Full Analysis Set) Per Applicant's Analysis

	FK463 N=425	Fluconazole N=457	Treatment Difference	95% CI

Overall	340 (80.0%)	336 (73.5%)	+6.5%	(0.9, 12.0%)
Type of Transplant				
Allogeneic	157/220 (71.4%)	175/256 (68.4%)	+3.0%	
Autologous or Syngeneic	181/203 (89.2)	161/201 (80.1%)	+9.1%	
None	2/2 (100.0%)	0 (0.0%)	N/A	

Source: Applicant's Study 98-0-050 Report Table

Difference in outcome (FK463 minus Fluconazole) was larger under the following situations:

- GVHD present +10.8%
- <16 years old +15.9%
- ≥ 65 years +27.4%

The success rate was not affected by gender and was consistently higher for the FK463 treatment arm (80.2% vs. 74.8% among males and 79.7% vs. 71.6% among females). These results were replicated in the per protocol dataset.

Medical Officer's Review of a Random Sample of Case Report Forms for Study 050

A 10% random sample of CRFs for Study 050 was thoroughly assessed in the course of this NDA review. The main objectives of the assessment of these CRFs were to:

- Examine the quality of the data entry and thereby validate the data submitted
- Ascertain that enrolled patients met the entry criteria
- Ascertain the accuracy of risk group assignments
- Evaluate protocol violations between the two treatment arms
- Compare success rate in this sample with the overall success rate
- Assess relatedness of treatment-emergent adverse events to study drug as assigned by the investigator
- Corroborate applicant's assessment of outcome

The review statistician, Qian Li, Ph.D. generated a 10% random sample from Study 050 using the unique patient identification number. On August 1, 2002, the review Division e-mailed the resulting list containing identification numbers for 88 patients to the applicant. In a submission to the NDA dated August 9, 2002, the applicant supplied 84 CRFs, all blinded to the treatment arm assignment. The remaining four CRFs had earlier been submitted in the original NDA. The medical officer independently reviewed all 88 CRFs while blinded to treatment group assignment. The results of this blinded review is attached in Appendix--- Following the review, the treatment group assignment was obtained. Results were tabulated using the protocol-defined full analysis and per protocol sets. Finally, the applicant's assessment of outcome for each patient was obtained and compared with those in the blinded review.

Data Quality

Deletions and additions to the CRF gave a measure of the quality of records. Given the complexity of the underlying condition and the patient population, errors were not unexpected in the CRFs. Overall, the quality of data entry to the CRF was satisfactory.

The CRFs were clearly legible and corrections to the CRFs were appropriately signed and dated. Moreover, the coordinator's logs provided lucid explanation of events, where appropriate. Further, the sponsor's 'Request for Information' log excellently tracked inconsistencies in the CRFs and provided various study sites the opportunity to correct those inconsistencies.

Ascertainment of Entry Criteria

All of the 88 patients met the entry criteria except three. Patient 383501 was randomized on [redacted] to the fluconazole treatment arm and had AST of 492 and ALT of 757 on day of randomization. The coordinator's log documents the following

> *Liver enzymes done on [redacted] were within normal range. The patient does not have a history of liver disease. Liver enzymes drawn at baseline were elevated due to conditioning regimen that started on [redacted] consisting of ATG, solumedrol, and benadryl.*

Although both liver enzymes normalized in the course of the study ([AST by [redacted] and [ALT by [redacted], and the patient received 21 days of assigned treatment, this patient should not have been enrolled. Indeed, the treatment-emergent nausea (from [redacted] that was attributed to the study drug by the investigator may have been related to this baseline derangement in liver function.

Similarly, Patient 893501 was randomized to fluconazole treatment arm with a baseline ALT and AST of 223 and 71, respectively. On Day 12 following randomization, these indices peaked at 578 and 268, respectively. The day before these peaks in liver enzymes the patient had been discontinued from the study for hepatotoxicity. Thus conferring some disadvantage to the comparator arm, albeit small.

Finally, Patient 421026 was randomized on [redacted] also to the fluconazole treatment arm. Unlike the other two, this patient had chronic renal failure at baseline with blood urea nitrogen (BUN) of 60 and creatinine of 3.4. The patient received 20 days of assigned treatment with BUN and creatinine peaking at 64 and 3.7, respectively. Although the protocol did not specify the entry criteria for these indices, one could consider that degree of renal insufficiency to constitute additional safety risk in a drug trial of this nature.

Accuracy of Risk Group Assignments

Five patients in the random sample were assigned wrong risk group classifications. All five were in the fluconazole treatment arm. Four of the five were originally labeled as low risk but later corrected to high risk while one was reclassified from high to low risk. It is reassuring that the review of the random sample is consistent with the applicant's corrected risk group classifications in the case report tabulation (CRT). Of note, three of the five risk group reclassifications occurred at one study site (20). The entire study contained 64 cases of risk reclassifications, 26 and 38 from the FK463 and fluconazole treatment arms, respectively. Twenty-two (34%) of the 64 reclassifications occurred at site 84 that enrolled 54 patients. However, such reclassification was balanced between the two treatment arms at that site (10 FK 463 and 12 fluconazole).

Evaluate protocol violations between the two treatment arms

Protocol deviations were common as expected for a relatively sick and complex patient population. Indeed, of the 88 patients reviewed in the random sample, 58 (66%) had at least one protocol violation. However, the protocol violations were generally trivial, involving mostly omission of surveillance cultures, assessments and tests done outside protocol-specified windows, and minor medication errors. More reassuring is the fact that there was no hint of imbalance between the treatment arms in the types or significance of protocol violations.

Success Rate in the Random Sample Versus Overall Success Rate

In this relatively small random sample, 28 (90%) of 31 patients in FK463 arm in the full analysis set were successful compared to 44 (77%) of 57 patients in the fluconazole arm. When patients considered unevaluable are excluded the response rates for the FK 463 and fluocnazole arms are 89% and 78%, respectively. The following patients considered unevaluable were excluded:

Fluconazole arm

- Patient 383501 Did not meet enrollment criteria with a baseline AST and ALT of 492 and 757, respectively
- Patient 731004 Empiric antifungal therapy was started prior to 96 hours of fever with neutropenia
- Patient 841007 Empiric fluconazole therapy was started when patient was no longer neutropenic
- Patient 891006 Empiric antifungal therapy started when no longer neutropenic
- Patient 1411001 Met criteria for suspected fungal infection for several days but not given such therapy
- Patient 893501 Did not meet enrollment criteria with a baseline ALT of 223

FK463

- Patient 511015 Patient left against medical advise after receiving 7 days of study medication. Patient was neutropenic (ANC<500) only on the day the patient left.
- Patient 701003 There is no documented evidence of neutropenia in the CRF
- Patient 3421012 Was taken off study when patient had not met study stoppage criteria

Assessment of relatedness of treatment-emergent adverse events to study drug as assigned by the investigator

All patients in the random sample had treatment-emergent adverse events as would be expected for this kind of study population. However, only very few of these adverse events were considered by the investigators to be related to the study drug as shown in the list below:

- Patient 132005 Rash and elevated cyclosporine A level
- Patient 383501 Nausea
- Patient 512002 Worsened liver function tests
- Patient 731004 Abdominal pain, nausea, hand swelling, pruritus, and neutropenia
- Patient 891005 Elevated liver function tests
- Patient 891006 Dizziness, hypotension, and phenytoin toxicity
- Patient 2411101 Vomiting

- Patient 3421014 Vomiting, fatigue, abdominal tenderness
- Patient 893501 Icterus, hepatotoxicity

Finally, anemia was a very common baseline condition and during treatment all patients had some degree of anemia.

Corroboration of applicant's assessment of outcome
In the full analysis set there was concordance between the medical reviewer's assessment of protocol-defined successful outcome and that of the applicant for all 88 patients in the random sample, except for six patients.

Patient 511015 was randomized to FK463 arm. This patient underwent transplantation five days following randomization. Study drug was started on the day following randomization and the patient received 7 days of study drug. This patient left the hospital against medical advice without receiving Day 7 of study medication. Patient was neutropenic (ANC<500) only on the day the patient left the hospital. Study coordinator later discussed with the patient's physician and was informed that the patient did well and that the neutropenia had resolved 19 days since the patient left the hospital. No fungal infection was documented or suspected at any stage. The applicant considered this patient unevaluable. The medical reviewer, however, considers the patient a success in the full analysis set.

Patient 762502 was randomized on — to the FK463 arm. On — the patient underwent transplant. Study drug was administered from —). The patient became neutropenic on — and recovered on — Prophylactic oral fluconazole was given in error on — . However, the patient received empiric Amphotericin B from — . There was no proven or probable fungal infection at any stage in the study. Moreover, while there were spikes of fever, there was no documented neutropenia with sustained fever lasting up to 72 hours. Further, blood cultures obtained on — grew *Streptococcuss* group D and *Enterococcus*, respectively. The applicant assessed this patient as a failure. However, the medical reviewer considers the patient a success in the full analysis set.

Patient 891006 was randomized on —) the fluconazole arm and underwent transplant on — The patient received study drug from —) and from — The patient was neutopenic from —) and the last absolute neutrophil count was recorded on — as <600. Amphotericin B was administered from — for empiric treatment of suspected fungal infection while oral prophylactic fluocnazole was given from —). At the start of the empiric therapy the absolute neutrophil count was recorded as being less than 600. The CRF documents suspected fungal infection on — (On-study assessment) and also suspected fungal infection on — (End of Study assessment). However, on — the coordinator's log documents the following:

"Clinic visit note refers to "possible yeast infection just after discharge."

It should be noted that by this patient was no longer neutropenic. The applicant assessed this patient as a failure but the medical reviewer considers the patient a success.

Patient 1233502 was randomized on the FK463 arm and receieved transplant on . Study drug was administered from and from . Patient was neutropenic from From the patient received prophylactic Abelcet followed by itraconzole and on , Abelcet was re-administered but this time as empiric therapy of suspected fungal infection. This patient died on from what was suspected on MRI scan to be central nervous system infection although brain biopsy failed to show any infection. It should be noted that from onward, this patient was no longer neutropenic (one of the protocol-defined endpoint) or febrile. The applicant assessed this patient as a failure while the medical officer considers the patient a success.

Patient 1411001 was randomized on , fluconazole arm and underwent transplantation the following day. The patient received study drug from through and was neutropenic from . The patient developed fever with neutropenia from During this time the patient was treated with piperacillin) and metronidazole (,. The applicant assessed this patient as a success but the medical reviewer considers this patient a failure as the patient met criteria for empiric antifungal therapy for several days.

Patient 202602 was randomized on to fluconazole arm and had transplantation on Study drug was given from while the patient was neutropenic from The patient had a brief period of fever with neutropenia (out never required empiric antifungal therapy. The patient died on from the underlying disease. Although no autopsy was done, the CRF does not document any proven, probable, or suspected fungal infection. The applicant considers this patient unevaluable with outcome left blank. However, the medical reviewer considers the patient a success in the full analysis set.

Conclusions from Review of 10% Random Sample

Overall, findings from review of the 10% random sample are consistent with the findings of the applicant. Indeed, it appears the applicant was rather conservative in assessment of success, given the discordance between the medical officer and the investigators, although such assessment is based on a small subset of patients.

Secondary Efficacy Endpoint

Proven and Probable Fungal Infections

As mentioned earlier, using the protocol-specified diagnostic criteria, a panel of three (one physician and two nurses) blindly reviewed CRFs for all investigator-reported proven a probable fungal infections. It should be pointed out that the physician on this review panel is one of the investigators that conducted Study 98-0-050. It is, however, unlikely that there is any conflict of interest arising from this situation, given the prominence and integrity of this physician. Table --- summarizes the frequency of proven and probable breakthrough systemic fungal infections based on the results obtained by the blinded independent review panel.

Table— Proven or Probable Breakthrough Systemic Fungal Infections During Study Based on Protocol-Specified Diagnostic Criteria

Organism	FK463 N=425	Fluconazole N=457
Proven	6 (1.4%)	8 (1.8%)
Aspergillus species	0 (0.0%)	4 (0.9%)
Candida species	4 (0.9%)	2 (0.4%)
Fusarium species	1 (0.2%)	2 (0.4%)
Zygomyces species	1 (0.2%)	0 (0.0%)
Probable	1 (0.2%)	3 (0.7%)
Aspergillus species	1 (0.2%)	3 (0.7%)

Source: Applicant's Study 98-0-050 Report Table

All Documented Breakthrough Fungal Infections by Site

Site*	FK463	Fluconazole
Lungs	10	10
Blood	4	2
CNS/Brain	2	2
Sinus	1	1
Oropharyngeal	33	14
Skin	11	7
Vaginal	4	5
Other**	4	16

*Some patients had multiple sites involved

**Other - 8 Toe/toe nails/Tinea pedis, 6 Groin, 1 each of the following sites: skin, bone, sputum, urine, colon, and left eye.

Medical Officer's Review of Case Report Forms for Breakthrough Invasive Fungal Infections

The medical officer blindly reviewed CRFs for all twenty-eight investigator-diagnosed proven and probable breakthrough fungal infections. Coordinator's log and applicant's manual request for information form at the end of each CRF were carefully scrutinized for information that may not have been captured in the CRF or that corrected data previously entered in the CRF. Criteria for assessment of fungal infections were as

specified in the applicant's protocol. The CRFs were also assessed to be sure patients with potential invasive fungal infections at baseline were not enrolled. The randomized treatments were revealed at the end of the review. Finally, findings from the MO review were compared to the review conducted by the blinded independent review panel employed by the applicant.

Overall, there was concordance between the MO review and that by the applicant's independent panel of reviewers. However in three instances, the MO's assessment differed somewhat from that of the independent reviewers. In two of these instances, the patients had baseline conditions that suggested potential invasive fungal infection.

Patient #005-2505 was a 42 year old Caucasian female with biphenotypic acute leukemia diagnosed in . This patient was in relapse at time of study. She was randomized on to receive FK463. On she underwent allogeneic matched sibling HSCT using peripheral stem cells. She met criteria for high risk of mortality. Significant baseline conditions included right buttock lesion, productive cough, right chest pain, right base rales, and neutropenia among others. The cough and neutropenia resolved on respectively while others were ongoing. She had been on intravenous amphotericin B from and oral itraconazole from for undisclosed reasons. She received blinded study drug from and was discontinued for lack of efficacy. Her chest x-ray on showed "moderate atelectasis within the right mid and lower lobes with increasing bands of subsegment collapse." Chest CT scan on showed "density and confluence of the peripheral base consolidation within the right middle lobe." All subsequent chest x-rays remained abnormal. Culture of bronchoalveolar lavage (BAL) on yielded *Candida albicans* that was considered a contaminant. However, fungal stain of BAL obtained the same day showed septate hyphae. The patient was started on intravenous amphotericin B from Posaconazole (SCH56592) suspension was given from and beyond.

The independent review panel confirmed this patient to have met the criteria for probable lung aspergillosis. The MO agrees with the independent reviewers' evaluation relative to diagnosis of probable lung aspergillosis. However, the MO believes this patient should not have been enrolled as her baseline conditions suggested underlying invasive fungal infection and, indeed, her drug treatment history seems supportive of that view.

Patient #013-3502 was a 50 year old Caucasian female with acute myelogenous leukemia diagnosed in She was randomized on to receive fluconazole and was in relapse at the time of enrollment. Patient received only one dose of blinded study drug on which was stopped to allow enrollment in the She received additional unblinded intravenous fluconazole on and from as prophylaxis. It should be noted that this patient had been treated with intravenous fluconazole from for unclear reasons. Her baseline conditions included left pleural effusion, fever with neutropenia, and sinusitis among several others. Indeed, chest x-ray

on _ _ was reported to show "left pleural effusion with bilateral diffuse parenchymal opacities which could be due to pulmonary edema of cardiac or non-cardiac origin, pneumonia, or ARDS." A repeat chest x-ray on _ revealed "increased area of consolidation surrounding right and left heart borders..." These baseline conditions were documented to continue till _

On _ , she received allogeneic HSCT using bone marrow cells and was considered to have high risk of mortality. This patient expired on _ from multiorgan system failure with Gram positive (VRE) thrombus in the subclavian vein as a contributory condition. There were no positive fungal cultures but autopsy revealed focal aspergilloma in the left upper lobe of the lung.

As with Patient #005-2505, the independent review panel confirmed this patient to have met protocol criteria for proven lung aspergillosis. The MO agrees with the independent reviewers' evaluation relative to diagnosis of proven lung aspergillosis. However, the MO believes this patient should not have been enrolled as her baseline conditions suggested underlying invasive fungal infection and, indeed, her drug treatment history is quite supportive of that view.

Patient 057-2528 was a 33 year old Black female with acute myelogenous leukemia diagnosed in _ , and still active at enrollment. She was randomized to receive micafungin on _ and underwent allogeneic matched sibling HSCT on _ using peripheral stem cells. She was considered to be at high risk for transplant related mortality. Blinded study drug was administered from _ through _ when it was discontinued for lack of efficacy. MRI scan of "right big toe" on _ showed "extensive multifocal bone abnormalities involving the left distal tibia including distal metaphysis left ankle and posterior half of the calcaneous." No report is documented in the Histology section of the CRF but coordinator's log notes that "patientt had fusariosis of the great toe. The initial biopsy was from the skin tissue. However, the MRI also demonstrated disease consistent with the bone" The patient received formulations of amphotericin B from _ for emirical therapy of fungal infection followed by Ambisome® from _ to _ and from _ onwards for treatment. Applicant's request for information form later documented that the patient has *Fusarium* from skin culture. On _ patient was suspected to have fungal infection. On _ the applicant's request for information notes as follows "Fungal Culture DATE OF TEST = _, yet no corresponding Fungal Culture listed on CRF#16. Please review and correct as appropriate. On _, the site added the following information: date of culture _, source code skin (5), result code 1-positive, organism Fusarium, surveillance culture No (1)." No histology report is documented in the appropriate section of CRF. On _, the final applicant's request for information corrects end-of-study assessment of fungal infection from proven to probable.

The applicant's independent reviewer considered this a confirmed proven Fusarium infection of the bone. The MO considers this a probable Fusarium infection of bone, which may even be regarded as superficial infection since no bone biopsy was done.

The MO is quite satisfied with the independent review of the breakthrough infections, which appears to have been very conservative. The few differences between the MO review and the independent review do not confer any disadvantage on the test drug rather if the three cases are excluded the test drug gains some advantage over the comparator.

This review uncovers two additional deaths not included in the earlier submissions. Patient #035-2504 was a 33 year old Caucasian female relapsed Hodgkin's disease who was randomized to the micafungin arm on —. She received allogeneic matched sibling transplant on — and was considered to have high risk of transplant related mortality. Blinded study drug was administered from day of randomization through — when it was discontinued and empiric treatment given for suspected fungal infection. Patient completed study and was last evaluated on —. However, Coordinator's log also report that on — this patient died following alveolar hemorrhage, acute heart failure, and secondary multiorgan failure. Although this patient was captured as being a protocol failure, the death was not included in the list of deaths or discontinuations and there is no evidence that autopsy was done.

Patient #123-3502 was a 42 year old Caucasian female with active chronic myelogenous leukemia randomized to micafungin arm on —. She had allogeneic other HSCT on —, and was considered at high risk for transplant related mortality. She receieved blinded drug therapy from — to — except for a dose missed on — due to weekend interruption. She completed study and was last evaluated on —, — Although the investigator diagnosed her with probable fungal infection of the brain/central nervous system, the independent reviewer and the MO considered that the protocol-specified criteria for such diagnosis were not met. Coordinator's log reports that this patient died on — from "suspected CNS infection..." Also this patient was captured as being a protocol failure; however the death was not included in the list of deaths or discontinuations and there is no evidence that autopsy was done. (Details of the Medical Officer's review of investigator-diagnosed breakthrough infections are on Appendix---)

Impact of Systemic Antifungal Therapy on Outcome in Patients Who Received < 14 Days of Study Drug Treatment

It was in the cause of the review that a substantial number of patients received randomized treatment for a relatively short period of time. Many of these patients were almost immediately transitioned to fluconazole yet they were classified as success outcomes. To fully assess this cohort of patients, the medical and statistical reviewers requested additional analyses from the applicant to assess the impact of use of other systemic antifungal therapies in patients who received less than 14 days of study drugs. Specifically, the applicant was requested to:

1. Provide a SAS dataset that includes the following information for one patient per record:
   - patient ID,

- treatment indicator,
- strata
- first dose date,
- second dose date,
- transplant date,
- discontinue date,
- death date,
- discontinuation indicator,
- duration on therapy,
- outcome (success, failure, N/A),
- indicator for other systemic antifungal use,
- date start on other systemic antifungal use,
- date stopped using other systemic antifungal,
- duration of other antifungal use,
- type of fungal drug,
- period when other systemic antifungal was used (concomitant use with study drugs, used after therapy, used in both periods, or used after the discontinuation of study drugs).

2. Make sure to provide all the formats associated with these data sets.
3. Provide subgroup analyses by classifying patients who were on therapy < 14 days and >=14 days.
   - Provide the rates of success in the two arms, difference and two-sided 95%CIs.
   - Perform subgroup by treatment interaction analysis.
   - Exclude the two patients who did not undertake transplant.

Applicant's Response

Table--- Treatment Success[a] by Duration of Treatment
Patients that Received ≥ 1 Dose of Study Drug and Had Transplant

Treatment Duration (Days)	Treatment Group		Treatment Difference	95% CI for Difference[b]	P-value	
	FK463 (N=423)	Fluconazole (N=457)				
<14	33/60 (55.0%)	42/75 (56.0%)	-1.0%	-17.9%, 15.9%	0.908[c]	0.211[d]
≥ 14	305/363 (84.0%)	294/382 (77.0%)	7.1%	1.4%, 12.7%	0.015[c]	

[a] Defined as absence of proven, probable or suspected systemic fungal infection through the end of therapy and absence of proven or probable systemic fungal infection through the end of study.
[b] 95% confidence interval (CI) for the difference in overall success rate based on large sample normal approximation test.
[c] From the Cochran-Mantel-Haenszel test
[d] From the Breslow-Day test

4. Provide summary statistics on therapy duration for the subgroup of patients who were on therapy for <14 days by treatment groups. The summary statistics should include number of patients, mean, median, and range.

Applicant's Response

Table--- Summary of Study Drug Exposure for Patients with the Length of Treatment < 14 Days in the Full Analysis Set

Parameter	Class	Treatment Group	
		FK463 (N=60)	Fluconazole (N=75)
Days on Treatment	N	60	75
	Mean	9.9	10.3
	Standard Deviation	3.46	3.33
	Minimum	1.0	1.0
	Median	11.5	11.0
	Maximum	13.0	13.0

Analysis excludes patients without transplant

5. Provide similar subgroup analyses to Request 2 by classifying patients who used other systemic antifungal therapy during the 28 days post-therapy period and who did not.

Applicant's Response

Table--- Treatment Success[a] by Other Systemic Antifungal Therapy During Posttreatment (Yes/No)
Patients that Received ≥ 1 Dose of Study Drug and Had Transplant

Received Other Systemic Antinfungal Therapy During Posttreatment	Treatment Group		Treatment Difference	95% CI for Difference[b]	P-value	
	FK463 (N=423)	Fluconazole (N=457)				
No	166/171 (97.1%)	154/159(96.9%)	0.2%	-3.5%, 3.9%	0.907[c]	0.719[d]
Yes	172/252 (68.3%)	182/298 (61.1%)	7.2%	-0.8%, 15.2%	0.080[c]	

[a] Defined as absence of proven, probable or suspected systemic fungal infection through the end of therapy and absence of proven or probable systemic fungal infection through the end of study.

[b] 95% confidence interval (CI) for the difference in overall success rate based on large sample normal approximation test.

[c] From the Cochran-Mantel-Haenszel test

[d] From the Breslow-Day test

6. Provide summary statistics on duration of other systemic antifungal therapy use during the 28 days post-therapy period by treatment.

Applicant's Response

Table--- Summary of Duration of Other Systemic Antifungal Medications During Post Treatment Period in the Full Analysis Set

Parameter	Class	Treatment Group	
		FK463 (N=252)	Fluconazole (N=298)
Days on Treatment	N	252	298
	Mean	22.6	23.1
	Standard Deviation	11.26	14.77

	Minimum	1.0	1.0
	Median	27.5	27.0
	Maximum	75.0	195.0

Analysis excludes patients without transplant

7. Provide similar summary statistics to Request 5 by further dividing the type of antifungal drugs.

Applicant's Response

Table--- Summary of Duration of Other Systemic Antifungal Medications During Post Treatment Period in the Full Analysis Set

Parameter	Type of Antifungal Drug	Class	Treatment Group	
			FK463 (N=252)	Fluconazole (N=298)
Days on Treatment	Amphotericin B	N	101	137
		Mean	13.0	12.1
		Standard Deviation	9.50	10.07
		Minimum	1.0	1.0
		Median	10.0	9.0
		Maximum	32.0	47.0
Days on Treatment	Azole	N	209	238
		Mean	21.2	22.3
		Standard Deviation	11.34	15.64
		Minimum	1.0	1.0
		Median	26.0	26.0
		Maximum	75.0	195.0
Days on Treatment	Other	N	1	1
		Mean	23.0	25.0
		Standard Deviation		
		Minimum	23.0	25.0
		Median	23.0	25.0
		Maximum	23.0	25.0

Patients may have had more than one type of antifungal drug.
Analysis excludes patients without transplant.

The applicant further summarized use of other systemic antifungal medications during the posttreatment by antifungal name and reason for use. Overall, the numbers were small and mean duration of use was somewhat similar between the two groups whenever substantial numbers of patients were treated with a particular agent.

Prior Use of Systemic Fluconazole in Study 98-0-050

There were also concerns that some patients did not discounted prior systemic antifungal therapy for a sufficient interval as specified in the protocol. Fluconazole was the predominant systemic antifungal agent involved. A quick inspection of applicant's

Appendix 14.4.9 (Listing of medications associated with underlying disease) shows that the vast majority of prior use of fluconazole was in association with other prophylactic drugs such as Bactrim, ganciclovir and acyclovir. Overall, the numbers are small and do not suggest an imbalance as shown on Table---.

Fluconazole Stop Day Prior to Study Randomization	FK463 N=16	FLUCONAZOLE N=13
Day 1	1	0
Day -1	5	4
Day -2	4	0
Day -3	6	9

Other Relevant Secondary Efficacy Endpoints

Suspected Fungal Infections and Use of Empiric Antifungal Therapy
Of the 882 randomized subjects in the full analysis set, 162 (18.4%) received empiric antifungal therapy for suspected fungal infection. Significantly more patients on the FK463 arm received empiric antifungal therapy compared to those on the fluconazole arm (64/425 [15.1%)] vs. 98/457 [21.4%], p=0.024). However, 40 of the 162 (24.7%) patients that received empiric antifungal therapy violated the protocol-specified criteria for empiric antifungal therapy. Of the 40 protocol violators, 16 were on FK arm and 24 on fluconazole arm as summarized in Table---

Table--- Protocol violations

Violation	FK463 N=425	Fluconazole N=457
Met all criteria but empiric therapy started between 72 and 96 hours	7	16
No fever $\geq$ 38°C	2	1
No longer neutropenic at initiation of therapy	2	4
Met criteria for < 72 hours	5	3
Total (%)	16 (3.8)	24 (5.3)

Medical Officer's Comment: *Patient 122502 was already classified as success in the overall analysis. Patient was randomized to FK463. Received randomized treatment from — Died with no neutrophil recovery. Autopsy showed no fungal infection. That leaves 39 patients that violated criteria for empiric fungal infection. Results of sensitivity analyses that exclude the 39 subjects and others are further discussed below.*

Per applicant's analyses, the rates of successful outcomes between the two arms by subgroups is shown on Table---

Table---Treatment Success Rates by Subgroup Full Analysis Set

Subgroup	Class	FK463 N=425	Fluconazole N=457

Neutropenic Status			
	ANC < 200	332/413 (80.4%)	325/442 (73.5%)
	ANC ≥ 200	8/12 (66.7%)	11/15 (73.3%)
Type of Transplant			
	Allogeneic	157/220 (71.4%)	175/256 (68.4%)
	Autologous or Syngeneic	181/203 (89.2%)	161/201 (80.1%)
GVHD			
	No	275/329 (83.6%)	278/355 (78.3%)
	Yes	65/96 (67.7%)	58/102 (56.9%)
Colonization During study			
	No	129/159 (81.1%)	153/216 (70.8%)
	Yes	211/266 (79.3%)	183/241 (75.9%)
Donor Type			
	Matched Sibling	102/131 (77.9%)	122/160 (76.3%)
	Other Donor	55/89 (61.8%)	53/96 (55.2%)
Risk Group			
	High	92/126 (73.0%)	97/152 (63.8%)
	Low	65/94 (69.1%)	78/104 (75.0%)

Source: Applicant's Study 98-0-050 Report End-of-Text Table 13.4.5.1

Medical officer's Comment: *Using the per protocol population, the statistical reviewer, Qian Li, Ph.D. conducted sensitivity analyses that excluded the following*

- *patients without transplant*
- *those who died during the study but were classified as success*
- *those who received 7 days or less of randomized therapy without meeting the criteria for successful stopping point*
- *those that violated criteria for empiric therapy*
- *one patient considered nonevaluable*

Following the sensitivity analyses, the 95% confidence interval for the difference in the overall success rate (mcafungin minus fluconazole = 5.3%) was -0.3%, 10.8%.

As shown in Table---, successful outcome rates tended to be lower in the following subgroups: allogeneic transplantation, presence of GVHD, non-matched sibling donors, and high risk of transplant mortality. Perhaps, an antifungal trial designed for study in one of these subgroups might show a higher rate of breakthrough infections and, possibly, allow demonstration of a more robust statistical superiority of micafungin over the comparator.

It should be noted that besides the primary efficacy endpoint of global success in the full analysis set, none of the applicant's other analyses showed superiority over fluconazole. For further details, the reader should refer to the review by the statistical reviewer, Qian Li, Ph.D.

6.3.1.1.3 Conclusions Regarding Efficacy Data in Study 98-0-050

Study 98-0-050 was a large, randomized, active controlled, double blind trial of micafungin versus fluconazole for the prevention of fungal infections in recipients of hematopoietic stem cell transplantation. The design of the study was based on a larger proportion of breakthrough proven or probable fungal infections than obtained from the study. Because of the lower than expected rate of breakthrough fungal infections, the

outcome is almost entirely driven by the need for empiric antifungal therapy in patients suspected to have fungal infections, a rather weak and subjective endpoint. Given that subjectivity, a rigid adherence to protocol-specified endpoint for empiric antifungal therapy is adopted in this review. As a consequence, micafungin fails to demonstrate superiority over fluconazole with the exclusion of the 39 patients that did not quite meet the endpoint for empiric antifungal therapy. Moreover, even in the applicant's original analysis, no other endpoint demonstrated superiority of micafungin over fluconazole although nearly all point estimates were consistently in a direction favoring micafungin. However, the findings of this pivotal prophylaxis study are sufficiently encouraging to support the medical officer's conclusion that micafungin is not inferior to fluconazole as prophylaxis against [redacted] in patients undergoing hematopoietic stem cell transplantation.

6.3.1.2 Sponsor's Protocol #97-0-041 Conducted June 10, 1998 to May 26, 1999

Title: A Phase I/II Study to determine the maximum tolerated dose and pharmacokinetics of FK463 in combination with fluconazole for prophylaxis of fungal infections in adult patients undergoing a bone marrow or peripheral stem cell transplant.

6.3.1.2.1 Protocol

6.3.1.2.1.1 Objective/Rationale

Primary Objective

- To determine the maximum tolerated dose (MTD) of FK463 with concomitant fluconazole administration that can be safely administered to adult cancer patients receiving a bone marrow or peripheral stem cell transplant

Medical Officer's Comment: *The sponsor defined the maximum tolerated dose as the highest intravenous dose of FK463 administered without development of the same grade 3 toxicity (considered at least possibly related to study drug) in three separate patients.*

Secondary objectives

- To ascertain the toxicities associated with FK463 at doses of 12.5 mg per day and higher and to evaluate the pharmacokinetics of FK463 at these doses
- To evaluate Day 7 pharmacokinetics of fluconazole

Sponsor's Rationale (excerpted from sponsor's submission)

- The results of preclinical pharmacology studies indicated that FK463 has clinical potential in the treatment of *Candida* and *Aspergillus* infections; preclinical toxicology studies supported safety and entry into man; and single and repeated dose studies in healthy volunteers suggested an acceptable safety profile at daily doses up to 50 mg. The current study is a Phase 1/Phase 2 trial of the safety and pharmacokinetics of FK463 in immunocompromised patients. Since FK463 efficacy data in immunocompromised patients was limited at the time this study was designed, the sponsor considered it prudent to administer FK463 in combination with another antifungal agent.

6.3.1.2.1.2 Overall Study Design

This was a randomized, double blind, sequential group, dose escalation, multicenter, tolerance study.

Medical Officer's Comments: *As discussed below, there are several differences in the design of this study when compared to the pivotal study presented above. These differences limit the value of this study to support the proposed indication. It should also be noted that four of the five sites/investigators in this study also participated in the pivotal study.*

6.3.1.2.1.3 Population and Procedures

Inclusion and Exclusion Criteria

Important inclusion criteria were as follow:

Patients were eligible for the study if they fulfilled all of the following criteria:

- 18-55 years of age
- Females with child bearing potential were required to have a negative pregnancy test
- Undergoing an autologous or allogeneic bone marrow or peripheral stem cell transplant

Key criteria for exclusion from the study were the following:

- Pregnant or nursing (females of child bearing potential were to avoid becoming pregnant while receiving antifungal therapy.)
- Abnormal liver test parameters defined as:
  (a) Transaminase (AST/SGOT or ALT/SGPT) > 2.5 times upper limit of normal (ULN)
  (b) Total bilirubin > 2.5 times ULN
  (c) Alkaline phosphatase > 2.5 times ULN
- Serum creatinine > 2.0 mg/dL
- Clinical or other evidence of a deep or disseminated fungal infection prior to enrollment
- Requirement for systemic antifungal agents other than fluconazole
- History of anaphylaxis attributed to azole compounds or echinocandins
- Presence of a concomitant condition that, in the opinion of the Investigator and/or Medical Monitor, could have created additional risk for the patient
- Receipt of an investigational drug other than those for the treatment of cancer or supportive care

Medical Officer's Comment: *The entry criteria is similar to that of the pivotal study. However, while this study allowed enrollment of patients receiving autologous hematopoeitic stem cell transplant transplant for solid tumor, the pivotal study limited such transplant to those with hematologic malignancies only. Additionally, this study used a combination design whereas in the pivotal study, FK463 was compared as a single agent to fluconazole.*

Amendments to Protocol 97-0-041
There were four amendments to this study's protocol as follow:

- Amendment #1 dated March 12, 1998 sought to clarify the collection and processing of blood samples for pharmacokinetic analysis
- Amendment #2 dated July 8, 1998 (about a month following commencement of enrollment) sought to open enrollment to patients receiving an ALLOGENEIC bone marrow or peripheral stem cell transplant and to clarify portions of the synopsis, objectives, assignment to treatment, and statistical sections of the protocol. Originally, the protocol was designed to determine the maximum tolerated dose and pharmacokinetics of FK463 in combination with fluconazole for prophylaxis of fungal infections in adult patients undergoing an AUTOLOGOUS bone marrow or peripheral stem cell transplant.
- Amendments #3 (October 12, 1998) and #4 (February 2, 1999) allowed dose of FK463 to be escalated to 100, 150, and 200 mg.

6.3.1.2.1.4 Evaluations/Endpoints
Patients were randomized 4:1 to receive either FK463 and fluconazole (FK463 treated patients) or fluconazole and normal saline (control patients). A total of 79 patients were randomized and 74 patients received at least one dose of assigned therapy (full analysis set). The full analysis set consisted of 12 patients as controls (on fluconazole 400 mg/day) and 62 FK463 treated patients (8 patients at 12.5 mg/day, 9 patients at 25 mg/day, 9 patients at 50 mg/day, 9 patients at 75 mg/day, 9 patients at 100 mg/day, 10 patients at 150 mg/day, and 8 patients at 200 mg/day).

Assessments
Patients underwent physical examination (baseline only), evaluation of vital signs, blood collection for determination of clinical laboratory profile, and assessment of fungal infection at baseline, at scheduled times during treatment, and at 1 and 4-weeks posttreatment. Adverse events (AE) with onset during the study through 72 hours posttreatment were recorded.

Study Drug Administration
FK463 was intravenously administered beginning between 48 hours prior to initiation of transplant and 24 hours after initiation of transplant. Treated patients received either FK463 and fluconazole (FK463 treatment group) or a normal saline infusion and fluconazole (control group). FK463 was administered at dosages of 12.5 mg/day, 25 mg/day, 50 mg/day, 75 mg/day, 100 mg/day, 150 mg/day, or 200 mg/day. Fluconazole (400 mg/day) was administered either orally (whenever clinically feasible) or intravenously. The control group received fluconazole and a 1-hour normal saline infusion (100 mL). Treatment could be administered in an outpatient setting.

Blinding
Investigators and patients were blinded to the identity of the randomized study drugs. The pharmacist at the study site and Fujisawa Healthcare, Inc. were aware of the randomized drug assignment. Study drug (FK463 or normal saline) was administered in identical 100 mL saline infusion bags. Each bag was labeled with the protocol number and patient number, and covered with a light-protectant bag.

Endpoints
As stated in the objectives, this study was primarily designed to assess safety and pharmacokinteics of micafungin. The sponsor presents the pharmacokinetic data in a separate report.

Efficacy assessment was based on the incidence of fungal infections through the 4 week posttreatment period, the incidence of mortality during the treatment and posttreatment periods, and the use of additional antifungal therapy.

Patients who developed a proven or suspected systemic fungal infection met the efficacy failure endpoint. A suspected fungal infection was empirically established if a patient was neutropenic (ANC<500 cells/mm^3), had a persistent or recurrent fever (>100.4°F, >38°C) for which there was no known etiology, and failed to respond to 96 hours of adequate broad spectrum antibacterial and/or antiviral therapy.

Medical Officer's Comments: *The criteria for diagnosis of proven fungal infection is not stated in the study report. With the inherent difficulties in diagnosis of systemic fungal infections, most trials use the EORTC and the MSG criteria as was used in Study 050. Further, it is unclear how long patients had to be febrile with neutropenia and to have received systemic antibacterial treatment before being considered for empiric antifungal therapy.*

Safety assessments included the incidence of adverse events and the evaluation of laboratory profiles, chest x-rays and other radiological procedures, and vital signs.

6.3.1.2.1.5 Statistical Plan

This section is excerpted from the applicant's submission

Populations for Analysis
All randomized patients who received at least one dose of assigned study drug were included in the safety analyses, including determination of the MTD, and in efficacy analyses (full analysis set). In addition, efficacy evaluable patients were defined as those who met protocol eligibility criteria and received at least 7 days of study.

Missing information was to be handled by carrying the last recorded observation forward, and data from control patients (i.e., those receiving fluconazole plus normal saline) at each dose level were combined for the safety and efficacy analyses.

Demographic variables were summarized by dose level. Descriptive statistics were used to summarize continuous variables and frequency counts were used to summarize discrete variables. Baseline characteristics such as disease status and type of transplant were summarized. Medications taken during treatment were summarized using Anatomical and Therapeutic Classification (ATC) grouping.

Efficacy analysis was performed on two data sets: a modified intent-to-treat set (called the full analysis set) and an efficacy evaluable set. Efficacy data were summarized by treatment group and dose level.

Safety analyses were performed on the following data: adverse events, clinical laboratory test results, and vital signs. The adverse events were coded by body system using modified Coding Symbols for Thesaurus of Adverse Reaction Terms (COSTART) dictionary. Treatment emergent adverse events were defined as any adverse events that occurred during the treatment period or any pre-existing condition that worsened during the treatment period. Treatment emergent adverse events were summarized by dose level, relationship to study drug, intensity, and seriousness. Clinical laboratory test results, hematology, serum chemistry, and vital signs were assessed at baseline, and at various times throughout the study.

There were no changes to planned analyses and interim analysis was neither planned nor performed.

6.3.1.2.2 Results

Patient Population and Disposition

Patient population and disposition are summarized in Table---

Table---: Patient Population and Disposition

	Control	FK463 Dose Levels (mg/day)						
		12.5	25	50	75	100	150	200
Randomized	14	8	10	10	9	10	10	8
Full Analysis Set	12	8	9	9	9	9	10	8
Efficacy Evaluable Set	11	7	8	8	8	9	9	8
Completed Therapy	7	5	6	6	6	7	8	6
Discontinued Therapy	7	3	4	4	3	3	2	2
Adverse Event	0	1	0	1	0	0	0	0
Lack of Efficacy[a]	5	2	3	2	3	2	1	2
Administrative	2[b]	0	1[b]	1[b]	0	1[b]	1[c]	0

Patient population: all randomized patients

FK463 treated patients received a regimen of both FK463 and fluconazole

Control patients received normal saline and fluconazo87le

[a] administration of FK463 was discontinued and empirical systemic antifungal therapy was initiated due to a suspected fungal infection

[b] randomized patients who never received study drug therapy

[c] Patient Number 071605 (150 mg/day): The patient received one treatment of FK463 and then withdrew his consent for further participation when he learned that the study required daily infusions of study drug.

Medical Officer's Comment: *Excluding patients younger than 16 years, the demographics of patients in studies 97-0-041 and 98-0-050 were similar. However, while 66.2% of patients in study 97-0-047 were females, only about 40% were females in study 98-0-050.*

Table--- demographic and Baseline Characteristics Study 97-0-041

	FK463 Dose Levels (mg/day)							
	Control	**12.5**	**25**	**50**	**75**	**100**	**150**	**200**
Sex								
Male	5(42%)	2(25%)	5(56%)	3(33%)	4(44%)	1(11%)	3(30%)	2(25%)
Female	7(58%)	6(75%)	4(44%)	6(67%)	5(56%)	8(89%)	7(70%)	6(75%)
Age (years)								
N	12	8	9	9	9	9	10	8
Mean	43.5	41.6	39.8	43.7	42.2	42.4	41.0	42.9
SD	11.63	6.65	11.51	11.84	13.51	11.07	10.61	15.97
Range	20-56	31-54	19-56	22-58	20-65	21-63	22-54	22-58
Underlying Disease								
Hematologic Malignancy	7(58%)	4(50%)	7(78%)	5(56%)	6(67%)	4(44%)	4(40%)	5(63%)
Solid Tumor	4(33%)	4(50%)	2(22%)	4(44%)	2(22%)	5(56%)	4(40%)	3(38%)
Other	1(8%)	0	0	0	1(11.1%)	0	2(20%)	0

Adapted from Applicants submission
Patient population: all randomized patients who met protocol eligibility and received at least 1 dose of study drug regimen (full analysis set)
FK463 treated patients received a regimen of both FK463 and fluconazole
Control patients received normal saline and fluconazole

Medical Officer's Comments: *Patients with solid tumors were enrolled in study 97-0-041 but were excluded from study 98-0-050.*

Study Drug Exposure

In the full analysis set, FK463 treated group had a mean of 10.7 ± 4.31 days of study drug therapy (maximum 27 days) while the control group had a mean of 11.2 ± 3.35 days of study drug therapy (maximum 18 days). The difference in duration of study drug therapy was therefore comparable between the two arms.

Medical Officer's Comment: *Compared with Study 98-0-050, duration of study drug therapy was relatively short. In study 98-0-050, patients on the FK463 and fluconazole arms received study drug for a mean duration of 19.2 ± 6.88 and 18.7 ± 6.32 days, respectively. Even among those who had allogeneic transplant, mean duration of study drug was 12.6 ± 5.43 days (maximum 27 days) in study 97-0-041 compared to 21.6 ± 7.66 and 20.7 ± 6.81 days for FK463 and fluconazole arms, respectively in study 98-0-050.*

Efficacy

The response rates of patients in study 97-0-041 is shown in Table---

Table—Response Rates by Dose Level

	Control (n=12)	Dose Levels (mg/day)						
		12.5 (n=8)	25 (n=9)	50 (n=9)	75 (n=9)	100 (n=9)	150 (n=10)	200 (n=8)
Infection Status at End of Treatment								
Absent	7(58%)	6(75%)	6(67%)	7(78%)	6(67%)	7(78%)	9(90%)	6(75%)
Suspected	5(42%)	2(25%)	3(33%)	2(22%)	2(22%)	2(22%)	1(10%)	2(25%)
Proven	0	0	0	0	1(11%)	0	0	0

Adapted from Applicants submission
Patient population: all randomized patients who met protocol eligibility and received at least 1 dose of study drug regimen (full analysis set)
FK463 treated patients received a regimen of both FK463 and fluconazole
Control patients received normal saline and fluconazole

6.3.1.2.1.5 Efficacy conclusion from Study 97-0-041

For doses of FK463 $\geq$ 50 mg, overall response was 77.8% (35/45). This response rate is lower than the response rate on the FK463 arm in study 98-0-050. Similarly, the response rate of 58% in the control arm in study 97-0-041 is lower than the response rate for patients in the fluconazole arm in study 98-0-050. The reasons for the lower response rates in study 041 are not clear but may be reflect a different patient population or reduced duration of treatment. In addition to the one subject with proven fungal function in the 75 mg dose cohort, three other patients in the FK463 arm had proven or probable fungal infections. One patient in the 12.5 mg dose cohort had probable histoplasmosis based on bone marrow biopsy on Day 20 and two patients in the 75 mg dose cohort had proven fungal infections in the posttreatment period, one from Cunninghamella bertholletia and the other intestinal Candidiasis that did not qualify as invasive Candidiasis.

6.3.1.3 Sponsor's Protocol #98-0-43 Conducted November 2, 1998 to August 15, 2000

Title: A Phase 1 Study to Determine the Safety and Pharmacokinetics of FK463 in Febrile Neutropenic Pediatric Patients.

6.3.1.3.1 Protocol

6.3.1.3.1.1 Objective/Rationale

The primary objective of the study was to determine the safety and pharmacokinetics of FK463 in neutropenic pediatric patients at doses of 0.5 mg/kg per day and higher.

Medical Officer's Comment: *As further evidence to support findings from Study 98-0-050, review of Study 98-0-043 focuses on efficacy outcomes. Safety will be discussed in the integrated review of safety for the entire NDA.*

6.3.1.3.1.2 Overall Study Design

This was an open-label, sequential group, dose-escalation, pharmacokinetic, and tolerance study in pediatric patients aged 2 to 17 years. The study was conducted at seven sites in the United States.

Medical Officer's Comment: *Given the known limitations of a non-randomized, non-comparative trial design, findings from this study must be interpreted with caution. The utility of such findings in supporting the proposed indication is uncertain.*

6.3.1.3.1.3 Population and Procedures

Inclusion Criteria

Patients were eligible for the study if they fulfilled all of the following criteria:

- Informed consent of the patient and/or legally authorized representative was provided prior to study entry,
- Females with child bearing potential were required to have a negative pregnancy test,
- 2 to 17 years of age with neutropenia (ANC <500/mm^3) and one or more of the following conditions:
  - Leukemia or lymphoma, except patients on maintenance chemotherapy
  - Bone marrow or peripheral stem cell transplant
  - High dose chemotherapy anticipated to induce >10 days of neutropenia
  - Aplastic anemia
  - Myelodysplastic syndrome,
- Neutropenic and febrile and undergoing broad-spectrum empiric antibacterial therapy due to this episode of fever with neutropenia, and
- Sufficient venous access to permit administration of study drug, collection of pharmacokinetic samples, and monitoring of safety variables.

Exclusion Criteria

Fulfillment of any of the following criteria resulted in exclusion from the study:

- Pregnant or nursing,
- Evidence of liver disease, defined as:
  - Transaminase (aspartate aminotransferase [AST]/serum glutamic oxaloacetic transaminase [SGOT] or alanine aminotransferase [ALT]/serum glutamic pyruvic transaminase [SGPT]) > 2.5 times upper limit of normal (ULN)
  - Total bilirubin > 2.5 times ULN,
- Presence of clinical or other evidence indicating a deep or disseminated fungal infection prior to enrollment,
- Receipt of intravenous formulations of amphotericin B administered within 72 hours of study entry or a requirement for treatment with systemic antifungal agents other than FK463. Patients receiving fluconazole prophylactically were permitted to continue to receive therapy (no more than 400 mg per day or 12 mg/kg per day) while on the study. Discontinuation of all other systemic antifungal agents prior to the first dose of FK463 was required.
- History of anaphylaxis attributed to the echinocandin class of antifungals.
- Previous enrollment in this study,
- Presence of a concomitant condition that, in the opinion of the investigator and/or medical monitor, created a risk for the patient, or

- Use of investigational drugs other than those for the treatment of cancer or supportive care.

Patients were enrolled into one of two age groups, 2 to 12 years or 13 to 17 years. Patients (or guardian) provided informed consent and a medical history (baseline only). Patients underwent physical examination including chest x-ray (baseline only), evaluation of vital signs, blood collection for determination of clinical laboratory profile, and clinical assessments of fungal infection at baseline, at scheduled intervals during treatment, and at 1 week posttreatment. Blood was collected for determination of pharmacokinetic parameters on days 1 and 4 of study drug dosing.

Approximately 8 patients in each age group (2-12 and 13-17) were to be studied per dose level. The first eight patients in each age group received 0.5 mg/kg per day. Escalation to higher dose levels of 1.0, 1.5, 2.0, 3.0, and 4.0 mg/kg per day continued until two patients in the same age group experience the same dose-limiting toxicity at that dose level. A dose-limiting toxicity was defined as any grade 3 or higher toxicity considered at least probably related to the study drug occurring in at least two patients at that dose level. Dose escalation within the age groups was carried out independently.

Medical Officer's Comment: *As with Study 97-0-041, patients with solid tumors were enrolled in contrast to Study 98-0-050. Further, the criteria for diagnosis of proven fungal infection is not stated in the study report as earlier noted for Study 97-0-041. With the inherent difficulties in diagnosis of systemic fungal infections, most trials use the EORTC and the MSG criteria as was used in Study 050. Further, it is unclear how long patients had to be febrile with neutropenia and had received systemic antibacterial treatment before being considered for empiric antifungal therapy.*

Unlike Study 97-0-041, patients were not receiving background antifungal therapy, although patients receiving fluconazole prophylactically were permitted to continue this medication (no more than 400 mg per day or 12 mg/kg per day).

6.3.1.3.1.4 Evaluations/Endpoints

Safety analyses were performed on all patients who received at least 1 dose of study drug. Efficacy analyses were performed on two data sets, the modified intention-to-treat (also called the full analysis set) and the per protocol set (evaluable patients). The full analysis set included all enrolled patients who received at least 1 dose of study drug. The per protocol set included all enrolled patients who received at least 3 doses of study drug. Because the study was designed primarily to assess safety and not efficacy, no primary efficacy endpoint was specified in the protocol. Pharmacokinetic analyses were to be performed on patients with the full panel of pharmacokinetic sampling through Day 4.

For efficacy outcomes, analyses were performed by dose cohort and included:

- Incidence of treatment-emergent proven, probable, or suspected systemic fungal infection.

- Proportion of patients with proven, probable, or suspected systemic fungal infection during posttreatment week 1
- Proportion of patients requiring additional systemic antifungal therapy during the posttreatment period.

A patient was to continue on study medication until:

- A minimum of 3 days of therapy was administered, even if neutrophil recovery occurred,
- Neutrophil recovered (post nadir ANC =250 cells/mm ^{3}),
- Empirical antifungal therapy was required,
- A proven or probable systemic fungal infection developed,
- Unacceptable toxicity developed,
- The investigator decided it was in the best interest of the patient to discontinue therapy,
- Further study participation was declined by the patient/guardian,
- Death occurred, or
- Patient had received 14 days of therapy.

The maximum duration of therapy could be increased to 4 weeks provided the investigator felt the patient was tolerating FK463 and would benefit from additional therapy. Both patients who had persistent neutropenia in the absence of an active proven deeply invasive fungal infection or had a need for empirical therapy were eligible to receive an additional 2 weeks of therapy.

Medical Officer's Comment: *Criteria for initiation of empiric therapy for suspected systemic fungal infection was not standardized but was based on institutional standard of care.*

6.3.1.3.1.5 Statistical Plan

The reader should please refer to review by the Statistical reviewer. Descriptive statistics were used to summarize continuous variables while the summary of discrete variables was limited to frequency counts. Protocol planned to construct 95% confidence interval around proportions but this was not done due to small number of patients enrolled per dose group. Missing data were handled by carrying forward last observation. No hypothesis was tested and no interim analysis was conducted.

6.3.1.3.2 Results

6.3.1.3.2.1 Subject Disposition

Study population and patient disposition at end of study are summarized in Table---

Table--- Study Population and Patient Disposition at End of Study

	FK463 Dose Level (mg/kg per day)

	0.5	1.0	1.5	2.0	3.0	4.0	Total
All Enrolled Patients							
Total	16	18	13	12	10	9	78
Full Analysis Set							
Total	16	18	13	12	10	8	77
2 to 12 Years	8	10	9	12	10	8	57
13 to 17 Years	8	8	4	N/A	N/A	N/A	20
Per Protocol Set							
Total	16	16	10	11	7	8	68
2 to 12 Years	8	9	8	11	7	8	51
13 to 17 Years	8	7	2	N/A	N/A	N/A	17
Completed Study	16	18	13	11	10	8	76
2 to 12 Years	8	10	9	11	10	8	56
13 to 17 Years	8	8	4	N/A	N/A	N/A	20
Discontinued Study	0	0	0	1	0	1	2
2 to 12 Years	0	0	0	1	0	1	2
13 to 17 Years	0	0	0	N/A	N/A	N/A	0

Adapted from applicant's submission

Demographics

Children enrolled in Study 98-0-043 (mean age 9.0 ± 4.49 years [range 2-17 years]) were generally older than those enrolled into the FK463 arm in Study 98-0-050 (mean age 7.4 ± 4.49 years [range 0.5-17 years]). Gender and racial distribution were similar.

Study Drug Exposure

As with Study 97-0-041, the mean duration of treatment in Study 98-0-043 is shorter than in Study 98-0-050. While mean duration of FK463 therapy in pediatric patients (patients < 16 years old) in Study 98-0-050 was 23.2 ± 9.97 days (range (4-51 days), the overall (for all age groups and at all dose cohorts) mean duration of FK463 therapy in Study 98-0-043 was 6.6 ± 4.81 days (range 1-27 days).

6.3.1.3.2.2 Efficacy Endpoint Outcomes

Table-- shows overall incidence of systemic fungal infections at the end of therapy while Table--- summarizes the data by age group.

Table---: Fungal Infections by Dose Cohort at End of Therapy

Fungal Infection	FK463 Dose Level (mg/kg per day)						
	0.5 (n=16)	1.0 (n=18)	1.5 (n=13)	2.0 (n=12)	3.0 (n=10)	4.0 (n=8)	Total (n=77)
Absent	9 (56.3%)	13 (72.2%)	11 (84.6%)	7 (58.3%)	8 (80.0%)	6 (75.0%)	54 (70.1%)
Suspected	7 (43.8%)	4 (22.2%)	2 (15.4%)	4 (33.3%)	2 (20.0%)	2 (25.0%)	21[a] (27.3%)
Not Evaluated	0 (0.0%)	1 (5.6%)	0 (0.0%)	1 (8.3%)	0 (0.0%)	0 (0.0%)	2[b] (2.6%)

Reproduced from applicant's submission

Patient base: all patients who received at least 1 dose of study drug (full analysis set)

[a] Two of these 21 patients, Patient Number 012336 (2 to 12 years, 1.0 mg/kg per day) and Patient Number 262335 (2 to 12 years, 1.0 mg/kg per day), completed therapy with FK463 but then developed a new fever within 3 days of the last dose of study drug for which amphotericin B therapy was initiated.
[b] Patient Number 059334 (2 to 12 years, 1.0 mg/kg per day) and Patient Number 226534 (2 to 12 years, 2.0 mg/kg per day) were not evaluated since they received only 1 dose of study drug.
Overall: both age groups combined.

Table---: Fungal Infections by Dose Cohort and Age Group at End of Therapy

Age Group	FK463 Dose Level (mg/kg per day)						
	0.5	**1.0**	**1.5**	**2.0**	**3.0**	**4.0**	**Total**
2 to 12 Years							
n	8	10	9	12	10	8	57
Absent	4 (50.0%)	6 (60.0%)	7 (77.8%)	7 (58.3%)	8 (80.0%)	6 (75.0%)	38 (66.7%)
Suspected	4 (50.0%)	3 (30.0%)	2 (22.2%)	4 (33.3%)	2 (20.0%)	2 (25.0%)	17 (29.8%)
Not Evaluated	0 (0.0%)	1 (10.0%)	0 (0.0%)	1 (8.3%)	0 (0.0%)	0 (0.0%)	2 (3.5%)
13 to 17 Years							
n	8	8	4	N/A	N/A	N/A	20
Absent	5 (62.5%)	7 (87.5%)	4 (100%)	N/A	N/A	N/A	16 (80.0%)
Suspected	3 (37.5%)	1 (12.5%)	0 (0.0%)	N/A	N/A	N/A	4 (20.0%)

Excerpted from applicant's submission
Patient base: all patients who received at least 1 dose of study drug (full analysis set).
The worst result of fungal infection assessment up to 3 days after last dose
N/A Due to slow enrollment in the age group 13 to 17 years, enrollment in this age group was terminated after enrollment was completed in the 4.0 mg/kg per day dose level of age group 2 to 12 years.

Medical Officer's Comment: *In Study 98-0-043, the overall successful response rate for patients who received ≥ 1 mg/kg per day dose of FK463 is 73.8% (45/61). This is comparable with the overall response rate of 77.8% for patients who received ≥ 50 mg of FK463 in Study 97-0-041 and 69.2% for patients < 16 years in Study 98-0-050. This finding is of interest given the much shorter duration of treatment with FK463 in both Studies 97-0-041 and 98-0-043 compared with Study 98-0-050. This raises the question of the role of FK463 as an antifungal prophylaxis in this clinical scenario.*

6.3.3 Indication Number 2

Reader should refer to the review by Sary Beidas, M.D. In summary, the applicant sought indication number 2 based on a single open-label non-comparative study (Study 98-0-046) plus additional data from13 patients from another open-label non-comparative study conducted — (Study ' —

6.3.4 Indication Number 3

6.3.4.1 Sponsor's Protocol # 98-0-047/FG463-21-02

Title: An open-label, non-comparative study of FK463 in the treatment of candidemia or invasive candidiasis

This study started on February 27, 1999. An interim study report was submitted in the original NDA. Additional data from protocol 98-0-047 was submitted during the 120-day safety update.

6.3.4.1.1 Protocol

6.3.4.1.1.1 Objective/Rationale

The objective of the study was to evaluate the safety and efficacy of FK463 in the treatment of patients with confirmed candidemia or invasive candidiasis caused by both *C. albicans* and non-*C. albicans* organisms. Given the findings from nonclinical and early clinical studies, the current study was designed to further explore the therapeutic potentials of micafungin in the treatment of candidemia and invasive candidiasis.

6.3.4.1.1.2 Overall Study Design

This Phase 2, open-label, noncomparative, multinational study was conducted in adult and pediatric patients who were diagnosed with candidemia or invasive candidiasis. Data included in the NDA from this study are derived from two separate protocols, the Non-European protocol and the European protocols. The Non-European and the European protocols were identical in all aspects except that while the former allowed de novo and patients < 18 years to be enrolled, the latter did not allow enrollment of such patients. The bulk of the data in the NDA comes from the Non-European protocol.

Medical Officer's Comment: *An unblinded, noncomparative study design is fraught with problems, perhaps the most critical being the difficulty of minimizing bias in patient assignment, outcome assessment, data analysis, and result interpretation. Moreover, this was an emergency use protocol and enrollment criteria might not have been rigidly applied.*

6.3.4.1.1.3 Population and Procedures

Male and females children and adult patients were enrolled. The patients were divided into two groups: de novo and efficacy failure. The following is excerpted from the applicant's submission:

De novo Patients
De novo patients were newly diagnosed patients with candidiasis who received no more than 48 hours of systemic antifungal therapy prior to their first dose of FK463.

Efficacy Failure Patients
Efficacy failure patients must have had documented clinical and microbiological evidence of continuing disease despite therapy with systemic antifungal agents and must have received 5 or more days of systemic antifungal therapy with no response. The efficacy failure patients were further divided into subgroups of patients depending on their regimen in this study: those who received FK463 alone (i.e., FK463 replacing current systemic antifungal agent) and those who received FK463 along with their current antifungal regimen (i.e., Fk463 added to current systemic antifungal agent). Efficacy failure patients on combination therapy who responded to treatment could have had their antifungal medications tapered to FK463 alone.

Inclusion Criteria
Patients were eligible for the study if they fulfilled all of the following criteria:

- Informed consent of the patient and/or legally authorized representative was provided prior to study entry (consent was to be obtained from minors capable of understanding)
- Females of childbearing potential must have had a negative pregnancy test
- Candidemia or invasive candidiasis documented by typical clinical signs and symptoms and confirmed by fungal culture or histology
    - De novo patients must have had a positive culture obtained no more than 4 days prior to the first dose of FK463.
    - Efficacy failure patients must have had documented clinical and microbiological evidence of continuing disease despite therapy with systemic antifungal agents. In addition, patients who experienced treatment-limiting toxicities and were unable to continue their current antifungal regimen in the presence of continued documented *Candida* species infection could be enrolled as an efficacy failure patient.
- Sufficient venous access to permit administration of FK463 and monitoring of safety variables

Exclusion Criteria
Fulfillment of any of the following criteria resulted in exclusion from the study:

- Pregnant or nursing (Females of childbearing potential were to avoid becoming pregnant while receiving antifungal therapy.)
- Abnormal liver test parameters defined as:

(a) transaminase >10 x upper limit of normal (ULN)
(b) total bilirubin >5 x ULN
(c) alkaline phosphatase >5 x ULN

- Life expectancy judged to be less than 5 days
- History of allergy, hypersensitivity, or any serious reaction to the echinocandin class of antifungals
- De novo patients who had received a systemic antifungal agent for the treatment of this episode of candidemia or invasive candidiasis for more than 48 hours prior to the first dose of FK463
- Efficacy failure patients who had received < 5 days of prior systemic antifungal therapy (stable dose and brand) for the treatment of this episode of candidemia or invasive candidiasis
- Requirement for systemic antifungal agents for conditions other than candidemia or invasive candidiasis
- Previous enrollment in this study
- Concomitant medical condition, in the opinion of the investigator and/or medical monitor that might have created an unacceptable additional risk for the patient.

Patients underwent physical examination and evaluation of vital signs (baseline only); blood collection for determination of clinical laboratory profile, and assessment of fungal infection at baseline, at scheduled times during treatment, and at week 6 posttreatment. Adverse events with onset during the study through 72 hours posttreatment were recorded.

FK463 was administered intravenously as a daily 1-hour infusion for at least 5 days and up to a maximum of 6 weeks. FK463 could have been administered intermittently (a minimum of 3 days a week) if daily therapy was no longer feasible, and the patient had responded to FK463.

Diagnosis of candidemia and invasive candidiasis were as follows:

1. Candidemia

    - One positive blood culture obtained within 96 hours prior to the first dose of study drug

2. Acute Disseminated Candidiasis

a. Organ involvement
    - Recovery of *Candida* species from culture or histologic confirmation from biopsy of at least one internal organ
    - Clinical, pathological or cultural evidence of *Candida* species infection in at least one other organ

b. Skin Lesions or Ophthalmitis
    - Biopsy of skin revealing *Candida* histologically ± culture
    - Recovery of *Candida* species from blood culture, or
    - In neutropenic patients, multiple biopsy-proven *Candida* skin lesions alone

3. Chronic Disseminated Candidiasis (Hepatosplenic Candidiasis)

a. Proven Chronic Disseminated Candidiasis
   - Persistent or intermittent fever for $\geq$ 2 weeks despite treatment with broad spectrum antibiotics, with fever persisting after recovery from neutropenia
   - Any abdominal signs and symptoms (such as upper abdominal pain or tenderness, jaundice, hepatomegaly, and/or splenomegaly)
   - Elevated liver function tests, especially serum alkaline phosphatase
   - Abnormal findings on abdominal imaging (ultrasound, computed tomography, or magnetic resonance imaging) consistent with the radiologic picture of chronic disseminated candidiasis
   - Recovery of *Candida* species from blood culture or culture or histologic confirmation from biopsy of an involved organ

b. Possible Chronic Disseminated Candidiasis
   - Persistent or intermittent fever for $\geq$ 2 weeks despite treatment with broad spectrum antibiotics, with fever persisting after recovery from neutropenia
   - Abnormal findings on abdominal imaging (ultrasound, computed tomography, or magnetic resonance imaging) consistent with the radiologic picture of chronic disseminated candidiasis

4. Abscess (including CNS)
   - Radiologic, nuclear medicine or nuclear magnetic resonance evidence of an inflammatory focus
   - Biopsy or aspiration from a sterile site positive histologically or culturally for *Candida*
5. Esophagitis, Tracheitis or Bronchitis
   - Endoscopically visualized plaques clinically suggestive of fungal infection
   - Hyphae or pseudohyphae noted by Gram or other appropriate stain or biospy demonstrating invasive fungal elements
6. Other Focus
   The investigator should specify site in detail and the diagnosis should be supported by biopsy from a sterile site showing invasive fungal elements or positive culture from a normally sterile site. Examples include pneumonia or pyelonephritis

Medical Officer's Comment: *The criteria for diagnosis of candidemia and invasive candidiasis as detailed above are widely used in other studies of this infection.*

6.3.4.1.1.4 Evaluations/Endpoints

All patients who received at least 1 dose of FK463 (full analysis set) were included in the safety analysis. The per protocol set was defined as those patients who received at least 5 days of FK463 therapy and had a confirmed diagnosis of candidemia or invasive candidiasis at baseline. The per protocol set was the primary efficacy data set.

The primary efficacy endpoint was the investigator's global assessment of treatment success, which was defined as complete or partial response.

Secondary endpoints were clinical response at the end of therapy (complete response, partial response, stabilization, or progression) and mycological response at the end of therapy (eradication, presumed eradication, or persistence). The incidence of relapse and the use of additional antifungal medications during the 6-week posttreatment period were also assessed.

Each endpoint evaluated outcome in the different patient groups (de novo, efficacy failure [FK463 plus other systemic antifungal] and efficacy failure [FK463 alone]) and all groups together.

Safety assessment was based upon adverse events and laboratory profiles. All adverse events through 72 hours after the last administration of study drug, whether ascertained through patient interview, physical examination, laboratory findings, or other means, were recorded. Ongoing adverse events were followed for as long as necessary to adequately evaluate the patient's safety or until the event stabilized.

Medical Officer's Comment: *The findings from Study 98-0-047 were reviewed by an independent reviewer appointed by the sponsor. The independent reviewer was ——— M.D., c ~ ~ ———*

— It should be mentioned that Dr. — was one of the investigators for this study. However, Dr. Rex is an internationally renowned clinical mycologist and there is no reason to doubt findings from his review.

6.3.4.1.2 Results

Description of database

Study population, patient status at end of study, and reasons for treatment discontinuation are shown on Table---

Table--- Study Population, Patient Status at End of Study, and Reasons for Treatment Discontinuation (Applicant's Analysis)

	De Novo	Efficacy Failure		Total
		FK463 & Other	FK463 Alone	
All Enrolled Patients*	169	48	37	254
Full Analysis Set	165/169 (97.6%)	48/48 (100.0%)	37/37 (100.0%)	250/254 (98.4%)
Per Protocol Set	146/169 (86.4%)	35/48 (72.9%)	28/37 (75.7%)	209/254 (82.3%)
Completed Study	111/169 (65.7%)	29/48 (60.4%)	19/37 (51.4%)	159/254 (62.6%)
Death †	41/169 (24.3%)	19/48 (39.6%)	13/37 (35.1%)	73/254 (28.7%)
Lost to Follow-up	11/169 (6.5%)	0/48 (0.0%)	2/37 (5.4%)	13/254 (5.1%)
Other	6/169 (3.6%)	0/48 (0.0%)	3/37 (8.1%)	9/254 (3.5%)
Completed Therapy	113/165 (68.5%)	25/48 (52.1%)	23/37 (62.2%)	161/250 (64.4%)
Discontinued Therapy	52/165 (31.5%)	23/48 (47.9%)	14/37 (37.8%)	89/250 (35.6%)
Adverse Event	28/165 (17.0%)	11/48 (22.9%)	8/37 (21.6%)	47/250 (18.8%)
Lack of Efficacy	14/165 (8.5%)	9/48 (18.8%)	3/37 (8.1%)	26/250 (10.4%)
Administrative	10/165 (6.1%)	3/48 (6.3%)	3/37 (8.1%)	16/250 (6.4%)

Patient base: all enrolled patients

*Includes death of one de novo patient who never received study drug (Patient Number 359485).
De novo: patients must have had less than 48 hours of systemic antifungal therapy.
Efficacy failure: patients must have had documented clinical and microbiological evidence of continuing disease despite >5 days of therapy with systemic antifungal agents prior to study entry; patients received either a regimen of FK463 alone or FK463 was added to their prior systemic antifungal regimen.
Other: 4 patients did not meet enrollment criteria (Patient Numbers 055880, 359474, 359481, 358473), 3 patients did not receive study medication (Patient Numbers 114871, 325472, 329476), 1 patient was non-compliant with follow-up (Patient Number 033873), and 1 patient was considered not evaluable (Patient Number 103871)

As shown in Table---, of the 254 patients in the study, only 37 (15.6%) patients enrolled as efficacy failure that received micafungin alone (based on applicant's analysis). Additional 48 efficacy failure patients had micafungin used concomitantly with another systemic antifungal medication.

A sample size of 37 patients that fits the target population is rather lean, especially given the non-comparative design of the study. The use of micafungin in combination with other systemic antifungal agents precludes adequate determination of the contribution of micafungin to patient outcome in the other 48 efficacy failure patients.

Review of the findings from this study will focus on the 37 efficacy failure patients who were treated with micafungin alone.

Case report forms for the 37 patients classified as efficacy failures were closely reviewed. The review focused on ascertainment of protocol-specified criteria for efficacy failure, nonuse of concomitant systemic antifungal treatment to qualify as "efficacy failure, micafungin replacing prior therapy", and outcomes (clinical and mycologic). In addition, attention was given to study coordinator's comments, investigator's comments, and sponsor's manual request for information. The reviewer made independent determination of status of patient at enrollment and study outcome. These were compared with those of the investigators and the sponsor's independent reviewers.

Of the 37 efficacy failure patients with micafungin replacing prior systemic antifungal therapy, the independent reviewer identified 35 that met the definition of full analysis set (had received at least one dose of study medication). Of the 35 patients in the full analysis set, 26 met the per protocol set (received at least five days of study medication and had proven or probable systemic fungal infection) in the independent reviewer's assessment.

In the medical officer's evaluation, all the 37 patients listed as efficacy failure micafungin replacing prior therapy met the above definition of full analysis set. The MO's evaluation was concordant with 27 of the independent reviewer's assessment relative to meeting protocol-defined criteria for efficacy failure, micafungin replacing prior therapy. However, the following discordant assessments between the MO and the independent reviewer occurred:

- 8 patients were classified by the independent reviewer as meeting protocol criteria but considered by the MO to not meet such criteria.
  The reasons for such patients failing to meet the specified criteria included: duration of prior systemic antifungal less than 5 days, use of prior systemic antifungal agent at low doses for prophylaxis with no clinically or microbiologically documented invasive fungal infection and the CRF clearly labels such a patient as "De Novo", and when features are inconsistent with invasive fungal infection.

- As noted above, 2 patients were classified by the independent reviewer as not meeting the criteria for full analysis set but considered by the MO to meet criteria for both full analysis and per protocol sets.

From the MO assessment, a total of 19 patients met the protocol-specified criteria for efficacy failure, micafungin replacing prior systemic antifungal agent. Table --- summarizes the independent reviewers' assessment of baseline fungal infections by primary site per protocol. The table also shows the Medical Officer's assessment of similar parameter but limited to efficacy failure patients whose treatments were replaced by micafungin.

Primary Site of Fungal Infection at Baseline
Independent Review and Medical Officer review

	Efficacy Failure			Non-Efficacy Failure	Total
	FK463 & Other	**FK463 Alone**			
	(n=35)	**Ind. Review (n=26)**	**MO Review (19)**	(n=141)	(n=202)
Site of Candida Species Infection					
Esophageal	1 (2.9%)	**5 (19.2%)**	**5**	***92 (65.2%)***	98 (48.5%)
Blood	16 (45.7%)	**17 (65.4%)**	**11**	***36 (25.5%)***	69 (34.2%)
Disseminated					
proven	7 (20.0%)	**2 (7.7%)**	**2**	3 (2.1%)	12 (5.9%)
probable	4 (11.4%)	**0 (0.0%)**	**0**	0 (0.0%)	4 (2.0%)
Abscess	2 (5.7%)	**1 (3.8%)**	**1**	2 (1.4%)	5(2.5%)
Peritoneal	1 (2.9%)	**0 (0.0%)**	**0**	2 (1.4%)	3 (1.5%)
Oropharyngeal	0 (0.0%)	**1 (3.8%)**	**N/A**	0 (0.0%)	1 (0.5%)
Other†	4 (11.4%)	**0 (0.0%)**	**0**	6 (4.3%)	10 (5.0%)

Patient Base: Patients who received at least 5 doses and had proven or probable (liver, spleen, or disseminated only) invasive candidiasis at baseline as assessed by the independent reviewer (per protocol set). N/A not applicable
Efficacy failure or non-efficacy failure, the independent reviewer's response to the following question on the single-page case report form: "Was the Patient an efficacy failure?".
Type of infection is proven unless otherwise noted.
† Other: Empyema (2 patients), endocarditis (3 patients), sternal osteomyelitis, wound infection, colon infection, cholangitis, and septic arthritis.

Analysis of Consistency between Medical Officer and Independent Reviewer

- 17 patients-Concordance, met protocol-specified criteria
- 10 patients-Concordance, not met protocol-specified criteria

- 8 patients-Discordance, not met protocol-specified criteria
- 2 patients-Discordance, met protocol-specified criteria

Table --- shows the MO's global assessment of the outcome at end of therapy compared to the independent reviewer's assessment.

Table--- Global Assessment of Outcome at End of Therapy for Efficacy Failure Patients who Received Micafungin Alone

	Independent Reviewer's Assessment N=26	**MO's Assessment N=19**
Success, n (%)	17 (65.4)	11 (57.8)
Complete Response, n (%)	17 (65.4)	7 (36.8)
Partial Response, n (%)	0 (0.0)	4 (21.0)
Failure, n (%)	7 (26.9)	6 (31.6)
Not Evaluable, n (%)	2 (7.7)	2 (10.5)

Table--- summarizes the MO's global assessment of outcome at end of therapy by primary site compared with the independent reviewer's assessment.

Table--- Global Assessment of Outcome at End of Therapy by Primary Site

	Independent Reviewer's Assessment N=26	MO's Assessment N=19
Blood*		
Complete Response	11/17 (64.7%)	5/11 (45.5%)
Partial Response	0/17 (0.0%)	0/11 (0.0%)
Failure*	4/17 (23.5%)	4/11 (36.4%)
Not Evaluable	2/17 (11.8%)	2/11 (18.2%)
Esophageal		
Complete Response	3/5 (60.0%)	2/5 (40.0%)
Partial Response	0/5 (0.0%)	1/5 (20.0%)
Failure	2/5 (40.0%)	2/5 (40.0%)
Not Evaluable	0/5 (0.0%)	0/5 (0.0%)
Disseminated		
Complete Response	1/2 (50.0%)	0/2 (0.0%)
Partial Response	0/2 (0.0%)	2/2 (100.0%)
Failure	1/2 (50.0%)	0/2 (0.0%)
Not Evaluable	0/2 (0.0%)	0/2 (0.0%)
Abdominal abscess		
Complete Response	1/1 (100.0%)	0/1 (0.0%)
Partial Response	0/1 (0.0%)	1/1 (100.0%)
Failure, n (%)	0/1 (0.0%)	0/1 (0.0%)

Not Evaluable	0/1 (0.0%)	0/1 (0.0%)

* Includes one patient with candidemia and endophthalmitis

6.3.4.1.3 Conclusions Regarding Efficacy in 98-0-047

Study 98-0-047 provides some evidence of activity of micafungin in patients with candidemia/invasive candidiasis. However, the quantity and quality of data submitted preclude adequate determination of the efficacy of micafungin for the proposed indication. Besides the small number of efficacy failures treated with micafungin alone, 84.2% (16/19) of patients in the MO's assessment are patients with candidemia and esophageal candidiasis. Indeed, even among the non-efficacy failure ("De Novo") database from the independent reviewer, candidemia and esophageal candidiasis constituted 65.2% and 25.5%, respectively with only 13 (9.2%) cases involving other deeper tissues. At the recent BAMSG meeting, esophageal candidiasis together with oropharyngeal candidiasis were considered in a risk group distinct from invasive candidiasis.

Similarly, it is doubtful that the supporting Study 97-7-003 has significant utility with regards to the proposed indication. Study 97-7-003 was a phase 2 non-comparative, dose de-escalation study of micafungin in the treatment of HIV infected adult patients with esophageal candidiasis. This study was conducted solely in South Africa. The design of the study did not clearly target efficacy failures and migafungin was used largely as primary therapy. Accordingly, the MO will not undertake a detailed review of this study.

Medical Officer's Comment: *At best findings from Study 98-0-047 and Study 97-7-003 provide a synopsis of the natural history of the condition and generate hypothesis that warrant further testing. In addition, these studies contributed that allowed fileability of the NDA. However, the studies by themselves are not sufficiently robust due to the small sample size in the relevant patient group and the trial design relevant to the proposed indication.*

Applicant's Review of Literature for a Perspective on the Efficacy of Micafungin

The objective of the literature review was to provide an estimate of outcomes in patients with newly diagnosed or refractory invasive candidiasis, including esophageal candidiasis, candidemia, and other manifestations of invasive candidiasis. The applicant conducted a Medline search of medical literature published in English from 1988 to November 1, 2001. These were supplemented with abstracts presented at the two major international infectious disease conferences, Infectious Disease Society of America (IDSA) or the Interscience Conference for Antimicrobial Agents and Chemotherapeutics (ICAAC) annual meetings during the three years, 1999 to 2001. A total of 55 articles and 3 abstracts were identified. From the literature, cure rates for esophageal candidiasis ranged from 73% to100% (clinical cure rates) and 38% to 100% (endoscopic cure rates) for azoles and other antifungal drug classes.

In 3 published randomized trials of fluconazole versus amhotericin B for the treatment of candidemia, efficacy rates in evaluable patients ranged from 57% to 75% for the fluconazole arm and 62% to 86% for amphotericin B. One of the trials included

immunocompromised patientrs and those with invasive candidiasis, similar to applicant's Study 98-0-047.

Published experience with invasive candidiasis largely derives from open-label studies. Nevertheless, among patients refractory to amphotericin B, response rate for fluconazole ranges from 67% to 100%. From one study, a resposne rate of 87.5% is reported for hepatospenic candidiasis in patients undergoing chemotherapy for acute leukemia receiving initial therapy of amphotericin with or without flucytosine.

Medical Officer's Comment: *Major differences in study design and study population preclude a direct comparison of the results in — with published data. In particular, too few patients with candidemia or invasive candidiasis got micafungin monotherapy. In addition, it was difficult to ascertain the contributions of micafungin in situations where micafungin was added to existing therapy. Furthermore, assessment of response in patients who received initial treatment with micafungin (majority of these patients had esophageal candidiasis) is arduous in the absence of a randomized controlled trial design.*

Early Discussion of Status of Review with Applicant

On December 6, 2002, the Agency held a teleconference with the sponsor to discuss the status of the review of the NDA. At the meeting, the Agency informed the sponsor of some of the deficiencies of the data presented in the NDA, which would not allow approval of the proposed indications. The sponsor offered to submit additional data from Studies 98-0-046 and 98-0-047 that would likely support the indications sought from these studies. On December 18, 2002, the sponsor provided additional data from the two studies using a tabular format suggested by the Agency.

With reference to Study 98-0-047, the sponsor submitted data from additional 101 patients, (De Novo 58, Efficacy Failure FK & Other 21, Efficacy Failure FK Alone 12, Breakthrough fungal infection FK & Other 7, and Breakthrough fungal infection FK Alone 3).

Tables --- and --- present a breakdown of the additional data in relation to the primary site of infection and global assessment of outcome at end-of therapy in the per-protocol set. It should be noted that in these Tables, breakthrough fungal infection refers to patients who developed fungal infection while receiving prophylactic or empiric systemic antifungal agent (s)

Table— Primary Site of Fungal Infection at Baseline
As Per Independent Reviewers' Assessment (Per Protocol Set)

		Efficacy Failure		Breakthrough Infection		Total
	De Novo N=179	FK463 & Other N=38	FK463 Alone N=19	FK463 & Other N=17	FK463 Alone N=18	N=271
Site of *Candida* Species Infection						
Esophageal	92	1	6	0	1	100
Blood	65	16	9	11	13	114

Disseminated* proven	7	12	2	4	2	27
probable	0	3	0	1	0	4
Abscess	4	2	0	0	1	7
Peritoneal	3	1	1	0	0	5
Other*	8	3	1	1	1	14

*Other: Cholangitis, colon, emphysema, emphysema of pleural- paricardial space, endocarditis (2 patients), endocarditis (tricuspid), oropharynx, septic arthritis, sternal osteomyelitis, and wound infection – not a systemic process.

Global Assessment of Outcome at End of Therapy by Primary Site of Infection
As Per Independent Reviewers' Assessment (Per Protocol Set)

		Efficacy Failure		Breakthrough Infection		Total
	De Novo N=179	FK463 & Other N=38	FK463 Alone N=19	FK463 & Other N=17	FK463Alone N=18	N=271
Blood						
Complete Response	49	14	6	9	9	87
Partial Response	7	0	0	0	0	7
Failure	8	2	2	2	3	17
Not Evaluable	1	0	1	0	1	3
Esophageal						
Complete Response	64	0	2	0	1	67
Partial Response	21	0	2	0	0	23
Failure	6	1	2	0	0	9
Not Evaluable	1	0	0	0	0	1
Disseminated						
Complete Response	4	2	2	2	1	11
Partial Response	1	7	0	1	0	9
Failure	2	6	0	2	1	11
Not Evaluable	0	0	0	0	0	
Abscess						
Complete Response	1	2	0	0	1	4
Partial Response	1	0	0	0	0	1
Failure, n (%)	1	0	0	0	0	1
Not Evaluable	1	0	0	0	0	1
Peritoneal						
Complete Response	0	0	1	0	0	1
Partial Response	0	0	0	0	0	0
Failure, n (%)	3	1	0	0	0	4
Not Evaluable	0	0	0	0	0	0
Other						
Complete Response	4	1	1	0	1	7
Partial Response	2	1	0	0	0	3
Failure, n (%)	1	1	0	1	0	3
Not Evaluable	1	0	0	0	0	1

Overall Response (complete and partial)	**154/179 (86.0%)**	**27/38 (71.1%)**	**14/19 (73.7%)**	**12/17 (70.6%)**	**13/18 (72.2%)**	**220/271 (81.2%)**

Other: Cholangitis (2 patients), colon, emphysema, emphysema of pleural- paricardial space, endocarditis (2 patients), endocarditis (tricuspid), mediastinitis, oropharynx, pyelonephritis by culture and echo, septic arthritis, sternal osteomyelitis, wound infection – not a systemic process.

The Agency held another teleconference with the sponsor on December 19, 2002 following review of the additional data to inform the sponsor that the entire database was still less than adequate to support the proposed indications. The sponsor then informed the Agency that they recently completed a randomized blinded trial of micafungin versus fluconazole for the treatment of esophageal candidiasis and promised to submit data from that study while considering other options in the development of the product for the proposed indications.

6.4 EFFICACY CONCLUSIONS

Summary of deficiencies in the efficacy trials reviewed

1. At this moment, data provided in the NDAs do not support the proposed indications
2. There is lack of substantial evidence from adequate and well controlled trials to show that micafungin is efficacious in the treatment of documented cases o: invasive candidiasis/candidemia
3. In cases where micafungin is used alone, the numbers are too small for reliable assessments
4. It is difficult to assess the contribution of micafungin to clinical and mycologic responses in combination therapy in the setting of uncontrolled studies
5. Literature synthesis to gain perspective on response in invasive candidiasis/candidemia, while sufficient for filing, does not appear to provide an adequate control group for comparison of response. In the , trial, for examples, the sponsor provided prospectively specified patient level data for the historical control cohort
6. Although the study to support the prophylaxis indication was a large randomized blinded and actively controlled study, the lack of substantial evidence of activity precludes a conclusive determination of the efficacy of micafungin as a drug for fungal prophylaxis in the setting it was studied. Generally, it is expected that products for empiric therapy or prophylaxis indication demonstrate efficacy in the treatment of documented disease.
7. Moreover, the result of that single controlled study is marginal and fails to stand up to sensitivity analyses. During the course of development, the Agency had emphasized the need for a robust study result. Results of the prophylaxis study is driven by suspected fungal infection rather than breakthrough fungal infections, which occurred at a rate much lower than expected during the design of the study
8. Nevertheless, the results presented in the NDAs are sufficiently encouraging to warrant further investigation. The experience might facilitate the design of additional study (ies)
9. For example, in situations of uncertain activity of micafungin combined with existing therapy, it may be reasonable to consider a randomized controlled study.

7 INTEGRATED REVIEW OF SAFETY

7.1 Brief Statement of Findings

At the intended dose of micafungin and for the proposed indications, there appears to be no major safety concerns. In addition, there were no safety flags when the safety database was analyzed by race, age, gender, and indication. Further, the review did not reveal any safety issues among subjects on concomitant calcineurin inhibitors (cyclosporine and tacrolimus) or steroid. Finally, review of the safety database for evidence of hemolysis is confounded by the complexity of the patient population. Notwithstanding, a potential exists for micafungin to cause hepatotoxicity and hemolysis, given animal data and data from caspofungin post-marketing safety rview

7.2 Materials Utilized in the Review

- Medical Officer review of safety of caspofungin in the caspofungfin NDA
- Post-marketing adverse events reported for caspofungin reviewed by Sarah Singer, R.Ph. Safety Evaluator, Division of Drug Risk Evaluation, CDER.
- Safety data of micafungin in NDA 21-506
- Literature search for safety of echinocandin antifungal drug class

Medical Officer review of safety of caspofungin in the caspofungfin NDA concluded that caspofungin is "frequently associated with systemic symptoms such as fever, myalgias, flu-like symptoms, nausea, and vomiting." The review further noted that "local infusional toxicities are also frequent, including phlebitis, pain, erythema and rash" and that "transaminase elevations occurred at a frequency and magnitude similar to that seen with fluconazole." However, the review also noted that caspofungin is "rarely associated with renal toxicity and electrolyte abnormalities are less frequent than those seen with amphotericin B."

In addition, the MO review pointed out important gaps in the safety information of caspofungin available in the NDA, including information on safe use caspofungin with cyclosporine.

7.3 Description of Human Subject Exposure

The safety database for micafungin comprises a total of 1368 human subjects that received at least one dose of micafungin. Of the 1368 subjects, females comprised 523 (38.2%), children under 16 years 187 (13.7%), and the elderly 116 (8.4%). Racially, the safety database for micafungin comprises 65.1% Caucasian, 15.4% Blacks, and 19.6% other races. Table--- shows the demographics for the three pivotal studies (050, 046, and 047). These data was later updated in 120-Day Safety Update submission of August 28, 2002 (Please see Section 7.8 of this review).

Table--- shows the drug exposure by daily dose of FK463 (mg) and subject days of exposure. Of 1368 subjects, 142 were healthy volunteers and 70 were enrolled in Study —— . These 212 subjects are excluded from the safety analysis, leaving a population size of 1156 patients. The demographics of the 1156 patients is reminiscent of the population likely to use FK463.

Table---Demographics (Micafungin Recipients only) for the Three Pivotal Studies

Parameter	Class	Study Protocol Number		
		98-0-046 N=186	98-0-047 N=250	98-0-050 N=425
Gender	Male	123 (66.1%)	137 (54.8%)	253 (59.5%)
	Female	63 (33.9%	113 (45.2%)	172 (40.5%)
Race	Caucasian	156 (83.9%)	150 (60.0%)	387 (91.1%)
	Black	13 (7.0%)	38 (15.2%)	30 (7.1%)
	Oriental	2 (1.1%)	4 (1.6%)	5 (1.2%)
	Mestizo	11 (5.9%)	50 (20.0%)	-
	Other	4 (2.2%)	8 (3.2%)	3 (0.7%)
Age	Mean	35.3	38.9	43.2
	Std	20.94	18.77	17.12
	Median	37.5	39.0	47.0
	Range	0.2-84.0	0.1-79.0	0.6-73.0

Adapted from End-of-Text Table 13.2.1.1 of the respective study reports in the applicant's submission

7.4 Safety Findings from Clinical Studies

Invasive Aspergillosis Study 98-0-046

A total of 75.8% (141/186) of the patients in this study had chemotherapy or bone marrow transplant, with lymphoma or leukemia as the predominant underlying condition. Allogeneic bone marrow transplant recipient comprised over a third of the patients. At baseline, 26.9% of the patients were neutropenic while graft-versus-host disease was present in 39% (32/82) of patients who underwent bone marrow transplant.

Medical Officer's Comment: *This is a seriously ill population, with multiple concomitant medications and underlying conditions. Evaluation of safety of a new drug in such a population is challenging, particularly given the lack of a control arm in the study.*

The largest exposure to micafungin and the longest duration of therapy with micafungin in this NDA were among patients in Study 046. There was a total of 8091 patient days of dosing with 47.9% of those days at doses of $\geq$ 100 mg per day. The longest duration of micafungin therapy for a single patient was 470 days and the highest doses a treatment setting was 475 mg per day (5.9 mg/kg per day). Patients who received the higher mean daily doses also tended to be those given the longest duration of treatment. The distribution of mean daily dose of micafungin is as follows:

67.2% received ≤ 75 mg
32.8% received ≥ 100 mg
7.5% received ≥ 200 mg

Given the uncontrolled nature of Study 046 and to gain a perspective on the safety profile of micafungin in patients with invasive aspergillosis, this review summarizes safety for micafungin compared to safety from open label invasive aspergillosis study for the recently approved invasive aspergillosis indications, caspofungin, as shown in Table---

Table---: Summary of Safety in Invasive Aspergillosis-Comparaison Between Micafungin and Caspofungin

Safety Parameter	Micafungin N=186	Caspofungin N=69
Any Treatment Emergent AE, n(%)	186 (100)	64 (92.8)
Any Drug Related AE, n(%)	63 (33.9)	10 (14.5)
Any SAE, n(%)	135 (72.6)	54 (78.3)
Any Drug Related SAE, n(%)	22 (11.8)	1 (1.5)
Discontnued Due to AE, n(%)	52 (28)	27 (39.1)
Discontinued due to Drug Related AE, n(%)	6 (3.2)	1 (1.5)
Deaths, n(%)	109 (58.6)	38 (55.1)

Micafungin and Caspofungin studies were in patients refractory to or intolerant of other systemic antifungal therapies.

Summary of Safety in Study 98-0-047

Table--- Summary of Safety in Study 98-0-047

Safety Parameter	N=250
Any AE, n (%)	240 (96.0)
Any Drug Related AE, n (%)	119 (47.6)
Any SAE, n (%)	92 (36.8)
Any Drug Related SAE, n (%)	16 (6.4)
Discontinue Due to AE, n (%)	47 (18.8)
Discontinue Due to Drug Related AE, n (%)	16 (6.4)
Deaths, n (%)	72 (28.8)

For the patients treated with micafungin, there were no differences in number of patients who experienced any adverse events among those who received de novo therapy compared to those who received micafungin added to previous therapy or those in whom micafungin replaced prior therapy.

Table--- Summary of Safety in Study 047 by Different Patient Groups

Safety Parameter	De Novo N=165	FK463 & Other N=48	FK463 Alone N=37
Any AE, n (%)	158 (95.8)	46 (95.8)	36 (97.3)

Any Drug Related AE, n (%)	94 (57.0)	14 (29.2)	11 (29.7)
Any SAE, n (%)	50 (30.3)	24 (50.0)	18 (48.6)
Any Drug Related SAE, n (%)	11 (6.7)	1 (2.1)	4 (10.8)
Discontinue Due to AE, n (%)	28 (17.0)	11 (22.9)	8 (21.6)
Discontinue Due to Drug Related AE, n (%)	10 (6.1)	4 (8.3)	2 (5.4)
Deaths, n (%)	40 (24.2)	19 (39.6)	13 (35.1)

Taken from NDA 98-0-047 Study Report Tables 39, 40, 42, 43, 44

The investigators considered a larger proportion of adverse events to be drug related in non-efficacy failure (de novo) patients compared to efficacy failure patients. On the contrary, there were relatively more deaths among the de novo group compared to the other two groups. These findings are consistent with a sicker patient population among the efficacy failure groups, suggesting that in the efficacy failure groups, the investigators were more likely to attribute adverse events to the underlying condition or concomitant medications. It should be noted that 53.9% of de novo group were patients with HIV whereas among the efficacy failure groups 57.6% were being treated for malignancies or bone marrow transplant recipients.

Table—Summary of Safety in Study 050

Safety Parameter	**Micafungin N=425**	**Fluconazole N=457**
Any AE, n (%)	425 (100)	457 (100)
Any Drug Related AE, n (%)	64 (15.1)	77 (16.8)
Any SAE, n (%)	80 (18.8)	74 (16.2)
Any Drug Related SAE, n (%)	4 (0.9)	10 (2.2)
Discontinue Due to AE, n (%)	18 (4.2)	33(7.2)
Discontinue Due to Drug Related AE, n (%)	11 (2.6)	16(3.5)
Deaths, n (%)	18 (4.2)	26 (5.7)

Adapted from NDA 98-0-050 Study Report Tables 20-25

Narratives of death and discontinuations were reviewed. Patients considered by the reviewer to have been inappropriately discontinued from randomized study drug were 3 and 8 on the micafungin and the fluconazole arms, respectively. Five of the 8 patients discontinued on the fluconazole arm (PTID #162003, 202506, 352506, 572511, 57531) were discontinued for elevated liver function tests, one each for serum creatinine (PTID

#161002), prolonged neutropenia (PTID# 333002), and fluid overload (PTID# 2902501). The MO reviewer considers that the abnormal test results did not attain protocol-specified levels to warrant discontinuation of study drug and that options other discontinuation were available to manage these patients. After exclusion of such inappropriate discontinuations, a total of 15 (3.5%) discontinued on the micafungin arm and 25 (5.5%) discontinued on the fluconazole arm.

Two additional deaths were identified on the micafungin arm that was not included in the narratives of deaths and discontinuations bring the number of deaths on that arm to 20 (4.7%). It should be noted that these two additional deaths were found on review of a subset of case report forms from Study 050.

Table--- Integrated Summary of Frequent Treatment Emergent Adverse Events from Three Pivotal Studies (%)

Parameter	98-0-046		98-0-047		98-0-050	
	De Novo N=17	Efficacy Failure* N=169	De Novo N=165	Efficacy Failure* N=85	FK463 N=425	Fluconazole N=457
Body as a whole						
Fever	41.2	15.4	28.5	21.2	52.0	54.3
Abdominal Pain	29.4	37.3	21.2	10.6	40.9	37.2
Asthenia	0.0	23.7	15.2	10.6	36.0	40.5
Infection	23.5	27.2	18.8	16.5	32.9	33.9
Procedural Complication	29.4	28.4	7.9	18.8	31.5	35.0
Sepsis	5.9	30.2	14.5	21.2	24.0	27.8
Chills	11.8	18.3	5.5	10.6	24.9	26.0
Pain	23.5	16.6	10.9	15.3	20.2	18.4
Cardiovascular System						
Atrial Fibrillation	0.0	3.0	2.4	2.4	2.6	2.6
Tachycardia	5.9	17.2	NA	NA	26.6	24.5
Hypertension	5.9	17.2	6.7	9.4	21.9	25.6
Hypotension	11.8	28.4	10.9	14.1	26.6	24.5
Digestive System						
Mucositis	5.9	10.7	0.6	10.6	77.9	80.5
Diarrhea	11.8	34.3	8.5	17.6	74.1	78.6
Nausea	23.5	33.1	14.5	22.4	70.6	68.9
Vomiting	17.6	36.1	26.1	22.4	66.4	67.4
Anorexia	17.6	17.8	7.9	5.9	52.7	50.5
Constipation	23.5	24.5	8.5	16.5	30.4	31.3
Dyspepsia	0.0	6.5	4.2	3.5	28.5	31.1
Hemic and Lymphatic System						
Leukopenia	23.5	15.4	23.0	9.4	77.9	75.7
Thrombocytopenia	17.6	10.1	11.5	8.2	74.8	70.2
Anemia	11.8	7.7	12.1	7.1	40.5	42.2
Metabolic and Nutritional Disorders						
Hypomagnesemia	23.5	18.3	21.8	21.2	53.2	58.6
Hypokalemia	29.4	31.4	15.2	27.1	50.1	51.4
Hyperlaemia	5.9	16.6	9.7	3.5	3.5	7.7
SGOT Increased	29.4	7.1	19.4	3.5	5.6	6.3
SGPT Increased	11.8	7.1	15.2	3.5	7.3	7.9
Edema	0.0	17.8	3.0	8.2	27.3	24.5
Musculosketal						
Arthralgia	5.9	14.8	3.6	7.1	12.5	12.5

Nervous System						
Headache	23.5	27.2	20.0	12.9	42.8	36.5
Insomnia	23.5	11.2	7.9	11.8	35.8	32.4
Respiratory System						
Dyspnea	29.4	32.5	11.5	16.5	15.3	18.8
Cough increased	11.8	21.3	8.5	18.8	24.2	26.0
Respiratory Failure	5.9	17.8	5.5	4.7	1.4	1.3
Skin and Appendages						
Rash	5.9	18.9	9.1	17.6	42.8	40.9

Adapted from End-of-Text Tables 13.5.1.1 of Applicant's Reports of Study 98-0-046, 98-0-047, and 98-0-050
Frequent event defined by applicant as adverse event experienced by ≥ 20% in any of the patient groups for Study 046 and 047 and ≥ 25% of patients in any of the treatment groups for Study 050. To populate all cells in this Table across the three Studies, these definitions of more frequent events do not always hold.
Within a body system patients may experience more than one adverse event
*Includes efficacy failure and toxicity failure FK alone or FK and other systemic antifungal agent

Table--- Integrated Summary of Frequent Treatment Emergent Adverse Events Considered Drug Related from Three Pivotal Studies (%)

Parameter	**98-0-046**		**98-0-047**		**98-0-050**	
	De Novo N=17	**Efficacy Failure* N=169**	**De Novo N=165**	**Efficacy Failure* N=85**	**FK463 N=425**	**Fluconazole N=457**
Body as a whole						
Fever	5.9	1.2	5.5	3.5	1.4	1.5
Abdominal Pain	5.9	1.2	3.6	0.0	1.4	0.4
Asthenia	0.0	2.4	3.0	1.2	0.0	1.1
Infection	0.0	0.0	0.0	0.0	0.5	1.5
Chills	0.0	1.2	1.2	0.0	0.2	1.3
Cardiovascular System						
Vasodilatation	5.9	2.4	1.2	1.2	0.5	1.3
Tachycardia	5.9	1.2	0.0	0.0	0.7	0.4
Hypertension	0.0	3.0	0.6	0.0	0.2	0.2
Digestive System						
Diarrhea	0.0	5.3	1.2	1.2	2.1	3.3
Nausea	0.0	3.6	1.2	4.7	2.4	2.6
Vomiting	0.0	3.6	6.1	2.3	1.6	1.1
LFTs Abnormal	0.0	1.8	1.8	2.4	0.9	2.2
Hemic and Lymphatic System						
Leukopenia	0.0	1.8	12.7	0.0	1.2	0.9
Thrombocytopenia	0.0	2.4	4.8	0.0	0.9	1.1
Metabolic and Nutritional Disorders						
Bilirubinemia	5.9	6.5	0.6	2.4	3.3	3.1
Alkaline Phosphatase Increased	0.0	2.4	12.1	1.2	0.0	0.4
Creatinine Increased	5.9	1.8	3.0	0.0	0.2	0.9
Hypocalcemia	0.0	0.6	10.9	1.2	0.9	0.9
Hypomagnesemia	0.0	0.6	12.7	2.3	1.2	1.3
Hypokalemia	0.0	2.4	3.0	1.2	1.9	1.8
Hyperchloremia	0.0	0.0	6.1	0.0	0.0	0.0
Hypophasphatemia	0.0	0.6	0.0	0.0	1.6	0.9
SGOT Increased	0.0	1.8	15.2	1.2	0.9	2.0
SGPT Increased	0.0	1.8	12.7	2.3	0.7	2.0
Nervous System						
Dizziness	0.0	0.0	0.0	0.0	0.0	1.1
Respiratory System						
Dyspnea	0.0	2.4	0.0	0.0	0.0	0.4
Skin and Appendages						
Rash	0.0	1.8	4.2	4.7	1.9	1.3

Adapted from End-of-Text Tables 13.5.3.1 of Applicant's Reports of Study 98-0-046, 98-0-047, and 98-0-050
More frequent events defined by applicant as follows: ≥ 2% patients overall in Study 98-0-046; ≥ 5% patients in any treatment group in 98-0-047, and ≥ 1% patients in any treatment group in 98-0-050. To populate all cells in this Table across the three Studies, these definitions of more frequent events do not always hold.
Within a body system patients may experience more than one adverse event
*Includes efficacy failure and toxicity failure FK alone or FK and other systemic antifungal agent

Table--- Integrated Summary of More Frequent Treatment Emergent Serious Adverse Events Other Than Death from Three Pivotal Studies (%)

Parameter	98-0-046		98-0-047		98-0-050	
	De Novo N=17	Efficacy Failure* N=169	De Novo N=165	Efficacy Failure* N=85	FK463 425	Fluconazole N=457
Any SAE	58.8	74.0	30.3	49.4	18.8	16.2
Body as a Whole						
Sepsis	0.0	13.0	6.1	7.1	3.3	2.8
Fever	0.0	7.1	1.2	2.4	3.1	1.3
Infection	0.0	4.7	0.6	2.4	1.9	0.0
Cardiovascular System						
Shock	0.0	4.7	4.8	5.9	0.2	0.4
Hypotension	5.9	7.7	1.2	5.9	2.1	0.7
Heart Arrest	0.0	0.6	1.8	1.2	0.0	0.7
Hemorrhage	0.0	0.0	1.2	1.2	0.2	0.0
Heart Failure	0.0	0.6	1.2	0.0	1.9	0.4
Atrial Fibrillation	0.0	0.6	0.6	1.2	1.9	0.4
Digestive System						
Diarrhea	0.0	1.2	0.6	1.2	0.7	1.3
Nausea	0.0	1.2	0.0	0.0	0.2	1.3
Vomiting	0.0	1.2	0.6	0.0	0.2	1.1
Hemic & Lymphatic System						
Leukopenia	0.0	3.0	0.0	1.2	0.0	0.2
Thrombocytopenia	0.0	0.6	1.8	1.2	0.2	0.0
Metabolic & Nutritional System						
Bilirubinemia	0.0	3.0	0.0	0.0	0.9	0.9
Hpokalemia	0.0	0.0	1.8	2.4	0.0	0.0
Acidosis	0.0	0.6	0.0	3.5	0.0	0.2
Alkaline Phosphatase Increased	0.0	0.6	1.2	0.0	0.0	0.0
Nervous System						
Convulsion	0.0	1.8	0.6	2.4	0.9	0.9
Respiratory System						
Respiratory Failure	5.9	16.6	4.8	4.7	1.4	1.1
Pneumonia	5.9	4.1	3.6	3.5	1.6	1.3
Dyspnea	11.8	10.1	0.6	4.7	0.7	1.8
Lung Edema	0.0	1.8	1.2	1.2	0.0	0.7
Lung/Respiratory Disorder	0.0	4.1	1.2	1.2	0.2	0.9
Lung/Respiratory Hemorrhage	5.9	1.8	0.0	2.4	0.2	1.3
Hypoxia	0.0	3.0	0.0	2.4	0.2	0.4
Urogenital System						
Kidney Failure	5.9	5.3	2.4	2.4	0.5	1.3
Acute Renal Failure	0.0	1.2	1.2	0.0	0.5	0.9

Adapted from End-of-Text Tables 13.5.5.1 of Applicant's Reports of Study 98-0-046, 98-0-047, and 98-0-050
More frequent events defined by applicant as follows: ≥ 5 patients in any treatment group in Study 98-0-046; ≥ 2 patients in any treatment group in 98-0-047, and ≥ 1% patients in any treatment group in 98-0-050. To populate all cells in this Table across the three Studies, these definitions of more frequent events do not always hold.
Within a body system patients may experience more than one adverse event
*Includes efficacy failure and toxicity failure FK alone or FK and other systemic antifungal agent

Table--- Integrated Summary of Incidence of Treatment Emergent Serious Adverse Events Other Than Death Considered Drug Related from Three Pivotal Studies (Actual Counts)

Parameter	98-0-046		98-0-047		98-0-050	
	De Novo N=17	Efficacy Failure N=169	De Novo N=165	Efficacy Failure N=85	FK463 N=425	Fluconazole N=457
Any SAE	1	21	11	5	4	10
Body as a Whole						
Abdominal Pain	0	0	0	0	0	1
Asthenia	0	0	0	0	0	1
Neck Pain	0	0	0	0	0	1
Pain	0	0	0	0	0	1
Allergic Reaction	0	0	1	0	0	0
Fever	0	1	0	0	0	0
Cardiovascular System						
Subdural Hematoma	0	0	0	0	0	1
Tachycardia	0	0	0	0	0	1
Vasodilation	0	1	0	0	0	1
Shock	0	0	0	1	0	0
Thrombophlebitis	0	0	1	0	0	0
Hypotension	0	1	0	0	0	0
Hypertension	0	1	0	0	0	0
Atrial Fibrillation	0	1	0	1	0	0
Digestive System						
LFTs Abnormal	0	0	0	0	0	2
Diarrhea	0	0	0	0	0	1
Hepatic Failure	0	0	0	0	0	1
Hepatitis, Nonspecific	0	0	0	0	0	1
Nausea	0	1	0	0	0	1
Hemic & Lymphatic System						
Leukopenia	0	2	0	0	0	0
Thrombocytopenia	0	1	3	0	0	0
Coagulation Disorder	0	0	1	1	0	0
Anemia	0	0	0	1	0	0
Pancytopenia	0	1	0	1	0	0
Hemolysis	0	1	0	0	0	0
Metabolic & Nutritional System						
Bilirubinemia	0	4	0	0	1	2
SGOT Increased	0	1	0	0	0	1
SGPT Increased	0	1	0	0	0	1
Hypokalemia	0	0	3	1	0	0
Alkaline Phosphatase Increased	0	1	2	0	0	0
BUN Increased	0	0	1	0	0	0
Hyponatremia	0	0	1	0	0	0
Creatinine Increased	1	1	1	0	0	0
Nervous System						
Anxiety	0	1	0	0	0	0
Confusion	0	1	0	0	0	0
Neuropathy	0	1	0	0	0	0
Dizziness	0	0	0	0	0	1
Meningitis	0	0	1	0	0	0
Respiratory System						
Dyspnea	0	3	0	0	0	2
Lung/Respiratory Disorder	0	0	0	0	0	1
Hypoxia	0	1	0	0	1	0
Skin and Appendages						
Rash	0	0	0	0	2	0

Sweating	0	0	0	0	0	1
Urticaria	0	0	0	1	0	0
Urogenital System						
Acute Renal Failure	0	0	1	0	0	0

Adapted from End-of-Text Tables 13.5.6.1 of Applicant's Reports of Study 98-0-046, 98-0-047, and 98-0-050
Within a body system patients may experience more than one adverse event
*Includes efficacy failure and toxicity failure FK alone or FK and other systemic antifungal agent

Adverse Events in Relationship to Study Drug Exposure and Duration of Treatment
Overall, patients receiving the two highest doses (150 mg/day and 200 mg/day or 3.0-3.9 mg/kg/day and $\geq$ 4.0 mg/kg/day) of micafungin tended to have the highest frequencies of adverse events. This might reflect a more severe illness in these groups. However, it is interesting that patients in the lowest dose cohort (50 mg/day or < 1 mg/kg/day) tended to have higher frequencies of adverse events compared to those in the middle dose cohorts (75 mg/day and 100 mg/day or 1.0-2.9 mg/kg/day and 3.0-3.9 mg/kg/day). This is likely a result of the fact that low dose cohort probably represents patients who underwent hematopoietic stem cell transplantation in the prophylaxis trials, a population with the highestproportion of any treatment emergent AE.

A trend towards increasing frequency of adverse events with increasing dose was found for the following adverse events:

- Ecchymosis, prothrombin decreased, hemorrhage, phlebitis, peripheral vascular disorder, deafness

When the lowest dose (12.5 mg) group is excluded a trend towards increasing frequencies of adverse events with increasing dose was found for the following additional adverse events:

- Body as a whole: abdominal pain, infection, chills, accidental injury
- Digestive System: diarrhea, nausea, constipation, dyspepsia, stomatitis, hematemesis, esophagitis
- Metabolic and Nutritional Disorders: hypokalemia, hyperglycemia, hypervolemia, bilirubinemia
- Nervous System: Insomnia
- Respiratory System: Pharyngitis
- Cardiovascular System: Tachycardia
- Skin and Appendages: Rash, maculopapular rash
- Special senses: Eye hemorrhage, eye pain

There are caveats to interpretation of these findings. In some instances the number of events is very small. In addition, there is significant confounding, given the differences in patient population. However, the findings may provide events to watch for, should micafungin receive marketing approval. This caution is particularly necessary as the more common adverse events in the three maximum tolerated dose studies included mucositis, fever, infection, thrombocyopenia, rash, diarrhea, abdominal pain, headache, chills, and

hypokalemia. Further, in one of the MTD studies (Study 97-0-041) asthenia occurred in 21% of subjects that received micafungin but in none on the control arm. Similarly in another MTD study (Study FG463-21-03), there was some evidence of dose-related hepatotoxicity, nephrotoxicity, and allergic/histamine-like reactions. It should however, be added that there was no dose-limiting toxicity in any of the MTD studies.

When frequencies of treatment emergent adverse events were reviewed by duration of micafungin therapy, there were no discernable trends, apparently because of the small number of event counts in those who received micafungin for 29 days or longer.

Deaths

The NDA documents death in a total of 217/1156 (18.8%) patients across all studies. The highest mortality rate occurred in the invasive aspergillosis and candiasis studies (Studies 98-0-046 and 98-0-047, respectively) with overall mortality of 58.6% in Study 046 and 28.8% in Study 047. Not surprisingly, patients with these infections are seriously sick and mortality rate in this patient population is generally high. Of note, mortality among the De Novo group of patients in the invasive candidiasis study, mortality rate was 24.2%. This was surprisingly high, as the overwhelming majority of these were HIV-infected patients with esophageal candidiasis. Indeed, of the 102 HIV-infected patients enrolled in the study, 99 (97.1%) were enrolled in the De Novo group, making up 60% of this group. However, these HIV-infected patients were enrolled mainly from South America and South Africa. Only about a third of the HIV-infected patients were on any form of antiretroviral treatment prior to enrollment, and very few of them were receiving highly active antiretroviral therapy (HAART) at the time of enrollment. CD4 cell count was available for only 11 (10.8%) of the 102 HIV-infected patients. Median CD4 count within 6 weeks prior to enrollment and up to 2 weeks after enrollment was 7 (range 1-43). While these 11 patients with CD4 cell count results may represent a highly selected group with more severe underlying disease, it does suggest the HIV population is a sick population and thus helps to explain the relatively high mortality rate.

Adverse Events Leading to Study Drug Discontinuation

This section is excerpted from the sponsor's integrated summary of safety. A total of 137/1156 (11.9%) patients had adverse event that led to discontinuation of study drug therapy. The more common adverse events leading to study drug discontinuation were respiratory failure (1.0%), shock (1.0%), sepsis (0.9%), pneumonia (0.8%), and bilirubinemia (0.5%). The highest rates of discontinuation due to an adverse event occurred in Study 98-0-046 (invasive aspergillosis) and 98-0-047 (candidemia/invasive candidiasis) with rates of 28.0% and 18.8%, respectively. In Study 98-0-050 (the randomized, comparative trial of micafugin versus fluconazole as prophylaxis against fungal infections in hematopoietic stem cell transplant recipients), fewer patients in the micafungin arm discontinued study medication due to adverse event compared to the fluconazole arm (4.2% versus 7.2%).

Medical Officer's Comment: *In Study 98-0-050, review of the narratives of patients who discontinued study medication due to adverse events corroborates sponsor' findings. However as noted earlier, more patients on the fluconazole arm appear to have been inappropriately discontinued from study medication.*

Adverse events considered at least possibly related to study medication that led to discontinuation occurred in 37/1156 (3.2%) patients. The more frequently reported (occurring in more than 2 patients) related adverse events that led to discontinuation were bilirubinemia (6 patients), rash (5 patients, alkaline phosphatase increased (4 patients), creatinine increased, thrombocytopenia, liver function tests abnormal, and allergic reaction (3 patients each).

Additional Relevant Safety Information from Non-Pivotal Studies

In the maximum tolerated dose study 97-0-041 (a randomized, controlled, blinded trial comparing micafungin plus fluconazole with fluconazole plus saline as prophylaxis in patients undergoing hematopoietic stem cell transplant), mild to moderate asthenia occurred in 21.0% of patients on the micafungin arm compared to none on the control arm.

Medical Officer's Comment: *Although these events were considered not related to micafungin by the investigator, this reviewer considers the events likely related to micafungin, given the strength of the study design and the applicant's failure to provide alternative explanation.*

7.5 Miscellaneous Studies

In studies of micafungin in rats and dogs, the primary target of toxicity is the liver. Both biochemical and histologic changes are noted in the liver in these animals (at doses $\geq$ 32 mg/kg). In addition, in rats micafungin increases plasma histamine and heart rate (at doses $\geq$ 32 mg/kg) and decreases blood pressure (at a dose of 100 mg/kg). Although toxicities occur at doses relatively higher than used in the clinical development program, animal findings are still relevant as some of the patients who may use micafungin may have underlying liver impairment. Moreover, in some of the animals studied the liver changes do not reverse at the end of the recovery period. Other effects observed in rats include effects related to histamine release, hemolysis, and injections site reactions. In addition, in vitro, micafungin induces platelet aggregation and hemolysis.

7.6 Literature Review for Safety

No additional safety concerns emerged on a literature review conducted on January 03, 2003.

7.7 Postmarketing Surveillance of Echinocandins

In general, there appears to be no mechanism-related toxicity for the echinocandins. Utilization of the only marketed echinocandin, caspofungin, is limited making

determination of the safety profile difficult. However, in a review of postmarketing adverse reports for caspofungin, the Office of Drug Safety noted as follows

"It would appear from the sheer number of cases and the temporal relationship with caspofungin, however, that the drug may play a role in the development of hyperbilirubinemia and possibly clinical liver disorders (including liver failure) as well."

"Cases are also presented of bronchospastic reactions which are different from the anaphylaxis case mentioned in the Cancidas® labeling in that they occurred after later infusions."
"Caspofungin has been reported as a suspect drug in other concerning events (coronary vasospasm, hypercalcemia, myocardial infarction, multi-organ failure, pancreatitis, pancytopenia, renal failure / insufficiency, respiratory alkalosis, stroke, sudden death), but its role is not clear from the cases received to date."

Based on literature and the caspofungin label, potential safety concerns for the echinocandin class of drugs includes hepatic dysfunction, hemolysis, events associated with histamine release, injection site reactions, drug interactions, and embryopathy. Review of safety of micafungin lays emphasis on these potential safety concerns.

7.8 Review of 120-Day Safety Update
The 120-Day safety Update was submitted on August 28, 2002. The Update includes safety data from additional 179 patients (97 from Study 98-0-046 and 82 from Study 98-0-047) as well as safety and PK data on 34 subjects from the renal and hepatic impairment studies. These studies were ongoing at the time of NDA submission. Finally, the Update contains data from 3 additional PK drug-drug interaction studies conducted in Europe in 24 healthy male volunteers. These additional data brings to a total of 1581 subjects exposed to micafungin during the development program. Of these, 1335 are patients in the combined safety database, 70 are patients in the — Study —, and 176 are healthy volunteers.

Among all micafungin-exposed subjects, age ranged from 2 weeks to 92 years with children < 16 years comprising 12.6%. In the micafungin-exposed patient population, children < 16 years were 16.0%, elderly ≥ 65years 7.6%, males 59.5%, and Caucasians 74.9%.

Eight three additional deaths are included in this Update (56 deaths in Study 046 and 27 in Study 047). From the Update, the proportions of patients who died in the two studies are 165/283 (58.3%) and 99/332 (29.8%) for Studies 046 and 047, respectively. These are not significantly different from mortality rates noted in the data submitted in the original NDA.

This Update also includes data from three PK studies conducted in Europe in which single 200 mg intravenous doses of micafungin are given concomitantly with repeated doses of tacrolimus, cyclosporine, or prednisolone (Studies FG-463-21-04, FG-463-21-05, FG-463-21-06, respectively). No PK interactions were found. However, in the

prednisolone interaction study, one patient developed intravacular hemolysis considered to be drug related. This was not severe and resolved spontaneously (please see Section---).

Further, the NOAEL for developmental toxicity in offspring of rats has been reduced from 32 mg/kg to 10 mg/kg (equivalent to 1.6-0.8 times the proposed human clinical dose range based on body surface area correction) in response to an inquiry by the Japanese regulatory authority.

The 120-Day Safety Update presents no major new safety concerns different from the review of the safety database in the NDA.

7.9 Drug Withdrawal, Abuse and Overdose Experience

There has been no known or documented evidence of either withdrawal or rebound effects with micafungin. Similarly, there has been no evidence of psychological or physical dependence with micafungin and the drug is not known to impair metal ability. In clinical trials repeated daily doses of micafungin up to a maximum of 5.9 mg/kg in children and up to 8 mg/kg in adults were administered with no dose-limiting toxicity. No overdose with micafungin has been reported.

7.10 Adequacy of Safety Testing

The safety database provided in the micafungin NDA and the 120-Day Safety Update provide adequate data to assess safety of micafungin in the targeted population. Of the 1581 human subjects exposed to micafungin, 1421 subjects have been treated with 50-100 mg of micafungin for a mean duration of about 20 days. Additional 160 subjects have been treated with 150-200 mg of micafungin for a mean duration of 46 days. The duration of exposure is typical of the duration of treatment for the proposed indications. In all studies, monitoring and follow up were adequate.

Medical Officer's Comment: *A sufficient number of patients have been exposed at the proposed clinical dose of 50-100 mg/day for a typical duration of therapy (14-28 days). Occasionally though, patients with invasive fungal infections could be treated for a much longer duration and at higher doses. The safety database is rather lean to fully address safety of micafungin in such clinical scenarios.*

The applicant has made appropriate and diligent attempt to identify all safety issues and highlight those peculiar to this class of drugs. The dose and duration of micafungin exposure in the 1156 patients in the NDA as originally submitted is summarized by Study on Table---

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Table--- Subject Drug Exposure by Daily FK463 Daily (Mg) and Subject Days
All FK463 Treated Subjects
(Taken from Safety Appendix 6 of Applicant's Integrated Summary of Safety)

	Daily Dose (mg)*					
	50 (N=974)	**75 (N=319)**	**100 (N=217)**	**150 (N=111)**	**200 (N=85)**	**Overall (N=1368)**
Subject Days	n (%)					
1-14	517 (53.1)	219 (68.7)	176 (81.1)	72 (64.9)	31(36.5)	638 (46.6)
15-28	391 (40.1)	57 (17.9)	26 (12.0)	18 (16.2)	35 (41.2)	529 (38.7)
29-60	61 (6.3)	30 (9.4)	11 (5.1)	14 (12.6)	13 (15.3)	151 (11.0)
>60	5 (0.5)	13 (4.1)	4 (1.8)	7 (6.3)	6 (7.1)	50 (3.7)
Total Subject Days	14732	5083	2912	2163	2362	27252
Range of Subject Days	1-135	1-126	1-253	1-127	1-267	1-346
Mean of Subject Days	15.1	15.9	13.4	19.5	27.8	19.9

COMBINATION INCLUDES: 97- 0- 040, 01- 0- 104, 01- 0- 105, 97- 7- 003, 97- 0- 041, 98- 0- 043, 98- 0- 046/ FG463- 21- 01, 98- 0- 047/ FG463- 21- 02, 98- 0- 050, FG463- 21- 03, FJ- 463- 0001, FG- 463- 0002. — FJ- 463- 0004, AND FJ- 463- 0005.
*Dose Rounded as follows 50= [<= 62.5] 75= [> 62.5 - <= 87.5] 100= [> 87.5 - <= 125] 150= [> 125 - <= 175] 200= [> 175].
Study 97-0-041 Patients treated with FK463+Fluconazole are considered FK463

Table--- Patient drug Exposure by Study and Patient Days
All Treated Patients
(Taken from Safety Appendix 6 of Applicant's Integrated Summary of Safety)

	97-7-003 (N=120)	**97-0-041 (N=62)**	**FG463-21-03 (N=36)**	**98-0-043 (N=77)**	**98-0-046/FG463-21-01 (N=186)**	**98-0-047/FG463-21-02 (N=250)**	**98-0-050 (N=425)**	**Total (N=1156)**
Patient Days	n (%)							
1-14	98 (81.7)	56 (90.3)	9 (25.0)	73 (94.8)	50 (26.9)	100 (40.0)	90 (21.2)	476 (41.2)
15-28	22 (18.3)	6 (9.7)	27 (75.0)	4 (5.2)	43 (23.1)	97 (38.8)	303 (71.3)	502 (43.4)
29-60	-	-	-	-	47 (25.3)	49 (19.6)	32 (7.5)	128 (11.1)
>60	-	-	-	-	46 (24.7)	4 (1.6)		50 (4.3)
Total Patient Days	1541	664	700	511	8091	5140	8093	24740
Range of Patient Days	1-21	1-27	8-28	1-27	1-346	1-95	1-51	1-346
Mean of Patient Days	12.8	10.7	19.4	6.6	43.5	20.6	19.0	21.4

Study 97-0-041 Patients treated with FK463+Fluconazole are considered FK463

7.11 Labeling Safety Issues and Postmarketing Commitments
Labeling review, discussions, and negotiations have been deferred.

8 Dosing, Regimen, and Administration Issues
For prophylaxis [redacted] would be administered 50 mg once daily [redacted] once daily. Micafungin will be marketed in [redacted] d 50 mg vials, to be given as intravenous infusion. Lyophilized micafungin powder is to be reconstituted with [redacted] or 5% dextrose and further diluted with any of the two solutions.

The micafungin vial is [redacted] to ensure the withdrawal of the labeled amount from the vial.

9 Safety Considerations and Use in Special Population

Pediatrics
A total of 187/1156 patients in the safety database were children (< 16 years of age). Overall, rates of adverse events in children were similar to those of adults. Adverse events that were reported more frequently in pediatric than adult patients were hepatomegaly (9.1% versus 0.7%), hypoproteinemia (12.8% versus 6.9%), hypertension (19.8% versus 13.3%), pruritus (16.6%versus 10.3%), and urticaria (6.4% versus 2.2%).

Medical Officer's Comment: *As noted by the sponsor, the significance of hepatomegaly and hypoproteinemia is uncertain but may be related to the fact that majority of the pediatric patients were recipients of hematopoietic stem cell transplant (primarily an allogeneic transplant) or were undergoing chemotherapy for a hematologic malignancy.*

Geriatrics
Patients 65 years of age or older comprised 75 of the total of 1156 patients in the safety database. Adverse events were generally similar in the elderly patients compared to those 16 to 64 years old. Adverse events reported more frequently among the elderly patients were asthenia (33.3% versus 23.3%), peripheral edema (24.0% versus 15.1%), hypophosphatemia (24.0% versus 10.3%), ecchymosis (12.0% versus 4.4%), skin disorder (12.0% versus 6.2%), oliguria (14.7% versus 4.5%), urinary tract infection (12.0% versus 4.4%), and accidental injury (9.3% versus 1.7%)

Gender
Of the total patient population of 1156 in the safety database, males comprise 57.3% and females 42.7%. No gender differences in the incidence or type of adverse events are apparent.

Race
Overall, adverse events were less frequent among black patients. As noted by the sponsor, the difference in rate of adverse events likely reflects the differences in the patient populations and the underlying conditions. White patients were predominantly enrolled from North America and Europe and were recipients of hematopoietic stem cell transplant or were undergoing chemotherapy for a malignancy. On the contrary, most of the black patients were HIV-infected patients with esophageal candidiasis enrolled from South Africa.

Medical Officer's Comments: *When the differences in patient populations and underlying conditions are taken into consideration, there is no apparent racial differences in frequency or type of adverse events.*

Pregnancy and Lactation
Micafungin has not been adequately studied in pregnant human subjects. Not unexpectedly, there is no information in this patient database on use of micafungin in pregnant women. In animal (rats and rabbits) reproductive studies given 2.6 times the expected upper human dose (100 mg) of micafungin, there was no evidence of impaired fertility or harm to the fetus due to micafungin. The Segment I study showed that the nontoxic dose for fertility was 32 mg/kg per day. In males vacuolation of epithelial cells of the epididymis was seen at doses of 10 mg/kg or higher and at 32 mg/kg, there was a 14% decrease in the number of sperm in the cauda epididymis compared to the control group. From the Segment II studies, micafungin has no teratogenic potential in the species studied. In rats and rabbits, the respective maternal non-toxic dose is estimated to be equivalent to 1.6 to 0.8 and 5.2 to 2.6 times the recommended human clinical dose range of 1 to 2 mg/kg based on surface area correction. In both rats and rabbits, the NOEL for embryo-fetal developmental toxicity is 32 mg/kg. Animal studies also show that labeled micafungin and/or its metabolites are excreted into the breast milk.

The sponsor seeks a designation of [redacted] for micafungin. It should be mentioned here that caspofungin, the first marketed echinocandin, is labeled pregnancy category C due to embryonic toxicity observed in rats and rabbits at exposures similar to those in clinical trials of caspofungin.

Organ-Specific Adverse Events
Liver Toxicity
The overall incidence of any hepatic event in the clinical studies was 26.9% (311/1156). The incidence of hepatic event considered at least possibly related to study drug was 9.1% (105/1156). The more common events considered related to study drug therapy were SGOT increased (3.0%), bilirubinemia (2.8%), SGPT increased (2.7%), alkaline phosphatse increased (2.4%) and liver function tests abnormal (1.6%). There were a few patients with outliers in liver function test values. When these are excluded, the results of the various liver function parameters remain same at end of therapy compared to baseline. Of note, however, approximately 6-8% of patients with normal bilirubin, SGOT or SGPT at baseline had elevation (to $\geq$ 2.5 times the upper limit of normal) in these

parameters at the end of therapy. In addition, patients enrolled with elevated bilirubin at baseline were more likely to have increased bilirubin at end of therapy. Such finding was not apparent for patients with increased SGOT or SGPT at baseline. There were no apparent associations between hepatic events and age or gender but was somewhat associated with underlying condition and race as summarized below from the sponsor's submission:

- Bilirubinemia occurred more frequently in patients with a hematologic maligancy/bone marrow transplant (16.0%) compared to patients with HIV and other underlying conditions.
- Increased SGOT (15.0%), increased SGPT (10.7%), and increased alkaline phosphatase (13.3%) occurred more frequently in patients with HIV.
- White patients had the highest rate of bilirubinemia (13.9%).
- Patients of other race had the highest rate of increased SGOT (26.7), increased SGPT (22.8), and increased alkaline phosphatase (18.8%).
- Regardless of race, patients with hamatologic malignancy/bone marrow transplant had the highest rates of bilirubinemia.

The abnormalities of liver function were rarely treatment limiting. There were no unique patterns regarding timing of resolution and dose-relationship.

Renal Function

A total of 153/1156 (13.2%) patients experienced an adverse event associated with renal function; 13 of these patients had events considered at least possibly related to the study medication. Increases in serum creatinine were reported in 63/1156 (5.4%) patients and in 10 of these patients, the event was considered at least possibly related to study medication. Two patients had acute kidney failure; both were considered related to study drug. Of 1105 patients with baseline serum creatinine less than twice the upper limit of normal, 24 (2.2%) had increases at end of therapy to greater than twice the upper limit of normal. These findings were corroborated on reanalysis during the review.

Cardiac Events

In rats administered 10 mg/kg bolus intravenous injection, micafungin did not affect blood pressure, heart rate, and plasma histamine concentration, but in those given 32 mg/kg of micafungin heart rate increased by a maximum of 28% up to 10 minutes after administration while plasma histamine level increased about 2.5 folds. At 100 mg/kg, micafungin decreased rat bllod pressure by a maximum of 26%, increased heart rate by a maximum of 29% and increased plasma histamine level 70 folds. When the infusion was administered over 30 minutes no effect was found on the heart rate, blood pressure, and plasma histamine release at doses of 10 and 32 mg/kg but a decrease in blood pressure, increase in heart rate and plasma histamine level still occurred as noted with the bolus injection. Increasing infusion rate to 60 minutes eliminated effect on heart rate and blood pressure at 100 mg/kg but histamine level was still increased by many folds. When the infusion volume was increased to 30 mL over 30 minutes heart rate was not affected but blood pressure was decreased by a maximum of 22% and histamine level increased over 100 folds. (Source: Final Report of Sponsor's General Animal Pharmacology Study CRR980005 of January 1997.)

No studies were performed to specifically address the potential for micafungin to prolong the QT interval of the electrocardiogram.

In the three MTD studies, cardiac AEs were few, similar to control and demonstrated no dose-response relationship. In the entire safety database, a total of 709/1335 (53.1%) patients had at least one cardiovascular event with 66 patients experiencing events considered at least possibly related to micafungin. The more common related events included hypertension (1.1%), vasodilatation (1.0%), hypotension (0.6%), and tachycardia (0.5%). In the pivotal prophylaxis study, incidence of events considered at least possibly related was similar on both arms. In addition, there were a total of 54 deaths with cardiovascular events as the primary cause of death in the refractory and intolerance studies (shock 40, endocarditis 4, heart failure 4, heart arrest 2, and 1 each of hemorrhage, hypotension, myocardial infarct, and peripheral vascular disorder). In the prophylaxis studies, deaths with cardiovascular events as primary cause occurred in 6 and 7 patients on the micafungin and fluconazole arms, respectively.

Hemic and Lymphatic System including Hemolysis
Of the 1156 patients in the safety database, 684 (59.2%) patients had an adverse event within the hemic and lymphatic system. Of these, 65 patients experienced an adverse event considered at least possibly related to study drug. The more common related events were leukopenia (2.5%), thrombocytopenia (1.5%), anemia (1.3%), and WBC abnormal (0.7%). Although hemolysis was observed at high doses in the nonclinical toxicology studies, only five patients had hemolytic anemia or hemolysis with an additional patient developing abnormal erythrocytes. One of the hemolysis cases was considered related to study drug.

Medical Officer's Comment: *There remains a non-quantified potential for intravascular hemolysis with micafungin. The NDA includes a narrative of a healthy volunteer who developed intravascular hemolysis while on a micafungin study ir* —
Extensive work up failed to identify any other cause of the hemolysis.

Allergic or Histamine Release-Related Events and Infusion-Related Reactions
The overall incidence of any histamine-like or allergic-type reactions (including rash, pruritus, maculopapular rash, urticaria, vesiculobullous rash, vasodilatation, allergic reaction or eosinophilia) was 42.0% (486/1156). Those considered at least possibly related to study drug occurred in 61/1156 (5.3%) patients. A total of 2 infusion-related adverse events were considered at least possibly related to micafungin in Study 98-0-050. Corresponding number of events on the fluconazole arm was 4.

Medical Officer's Comments: *Study 98-0-050 was further reviewed to more clearly define the potential for micafungin to cause these adverse events. By the sponsor's analysis, the incidence of possibly related histamine-like or allergic-type reactions was comparable between the two treatment arms (micafungin arm 3.5% and fluconazole arm 3.7%).*

Analysis from Study 98-0-050 for symptoms suggestive of histamine release/infusion-related reaction is summarized on Table---

Table---Symptoms suggestive of Histamine Release/infusion-related Reaction*

Parameter	***FK463 N=425***	***Fluconazole N=457***
Chills	*106 (24.9%)*	*119 (26.0%)*
Tightness of chest (including neck or throat)	*17 (4.0%)*	*18 (3.9%)*
Vasodilatation (facial, skin, neck, or generalized flushing)	*58 (13.6%)*	*73 (16.0%)*
Rash	*182 (42.8%)*	*187 (40.9%)*
Maculopapular Rash	*20 (4.7%)*	*14 (3.1%)*
Vesiculobullous Rash	*8 (1.9%)*	*10 (2.2%)*
Urticaria	*20 (4.7%)*	*12 (2.6%)*
Pruritus	*82 (19.3%)*	*93 (20.4%)*

**From Sponsor's Study 98-0-050 End-of-Text-Table 13.5.1.1. Fever, shortness of breath/dyspnea, lightheadedness, and diaphoresis are excluded. There were very few cases of wheeze, or angioedema*

Overall, incidence of events suggestive of histamine release or infusion-related reaction were very similar between the two treatment arms in Study 98-0-050.

Injection Site Reaction Adverse Events

These were generally few and mild in the micafungin patient database. Of note, in the maximum tolerated dose Study FG463-21-03, 2 patients reported injection site reactions and 4 patients reported phlebitis at doses less than 8 mg/kg per day. In patients dosed 8 mg/kg per day, a doubling of the volume of sterile normal saline used to dilute micafungin (from 100 mL to 200 mL) resulted in no cases of phlebitis or infusion site reactions.

Drug-drug Interactions

In studies in healthy volunteers (Studies 01-0-104 and 01-0-105), single doses of either cyclosporine or tacrolimus had no pharmacokinetic interaction with single and repeated doses of micafungin. However, it is uncertain whether potential toxicities could occur with concomitant use of repeated doses of these immunosuppressants in a sick population. With the help of the statistical reviewer, rates of adverse events in patients on concomitant systemic cyclosporine, tacrolimus, or corticosteroids were compared to rates of adverse events in patients without concomitant use of these medications in studies 98-0-046, 98-0-047, and 98-0-050. No clinically relevant differences were found in subjects who received micafungin concomitantly with these medications compared to those who did not. These findings are consistent with results of studies in healthy volunteers that showed no evidence of interactions between micafungin and either cyclosporine or tacrolimus. However, the overall incidence of bilirubinemia regardless of causality was 28.4% in patients on cyclosporine, 14.6% in those on tacrolimus, and 10.8% in patients on neither cyclosporine nor tacrolimus. In addition, the incidence of increased SGOT and SGPT among those on concomitant cyclosporine was higher than among those on concomitant tacrolimus or on neither cyclosporine nor tacrolimus. The incidence of bilirubinemia considered at least possibly related to study drug was 5.8%, 3.4%, and 2.6%, respectively. These findings suggest a potential for liver dysfunction when

micafungin is used concomitantly with cyclosporine or tacrolimus. However, the findings are confounded by the fact that the proportions of patients with GVHD were larger among those on such concomitant treatment compared to those who did not receive such treatment. Furthermore, the incidence of increased SGOT and SGPT considered at least possibly related to study drug was lower among those receiving these immunosuppressants concomitantly.

Similarly, there is no evidence that micafungin, at clinically relevant levels, would either induce or inhibit cytochrome P450 isozyme-mediated metabolism of concomitantly administered medications (including CYP isozyme inducers and inhibitors). In vitro studies of micafungin reveal that the oxidative metabolism of micafungin appears to be mediated by multiple CYP isozymes. CYP1A2, 2B6, 2C, and 3A4 have been identified as enzymes involved in M5 formation in human liver microsomes; However, the exact contribution of these isozymes to in vivo metabolism of micafungin remains unknown.

10 CONCLUSIONS, RECOMMENDATIONS, AND LABELING

10.1 Efficacy Conclusions

Although the pivotal study (Study 98-0-050) to support the prophylaxis indication was a large randomized blinded and actively controlled study, the lack of substantial evidence of activity of micafungin in the treatment of invasive infections due to — *Candida* species precludes a conclusive determination of the efficacy of micafungin as a drug for — in the setting it was studied. Moreover, the result of that study is marginal and fails to show substantial evidence of statistical superiority to fluconazole when subjected to sensitivity analyses. Nevertheless, the findings of the pivotal prophylaxis study are sufficiently encouraging to support the medical officer's conclusion that micafungin is —

Data in NDA 21-534 fails to provide substantial evidence from adequate and well-controlled trials to show that

While the results presented in the NDA — , are not sufficient to support the proposed indications, they provide basis for the applicant to consider further investigations. The experience might facilitate the design of additional study (ies). For example, in situations of uncertain activity of micafungin combined with existing therapy, it may be reasonable to consider a randomized controlled study.

10.2 Safety Conclusions

Assessment of safety of micafungin is in the context of a complex patient population and therefore should be viewed with caution. In the studies reviewed, very few treatment emergent AEs were considered to be related to study drug, most been attributed to the underlying conditions. Nevertheless, there is a potential for hepatotoxicity and hemolysis,

given the animal data. Moreover, there appears to be a trend towards increased liver dysfunction in patients receiving concomitant calcineurin inhibitors or corticosteroid. In addition, patients might be expected to develop asthenia when infused with micafungin. Allergic-type/histamine-like reactions and injection site reactions were similar between micafungin and fluconazole. The review uncovers no significant AEs related to the major organs other than the possibility of the liver and the blood as noted above. Micafungin also seems to present no major drug-drug interaction either by way of its mechanism of action or through drug metabolic pathways. Finally, the postmarketing safety database for caspofungin is somewhat reassuring, although utilization data for caspofungin is still relatively limited.

10.3 Recommendations on Approvability

The one study submitted in support of prophylaxis of — in patients undergoing hematopoietic stem cell transplantation, Study 98-0-050, alone did not provide sufficiently robust statistical evidence of superiority of micafungin over fluconazole, a comparator not approved for this indication. Specifically, the results of this analysis were largely determined by patients with "possible" as opposed to probable or proven fungal infection. In addition, prior to approval for prophylaxis of — in patients undergoing hematopoietic stem cell transplantation, it is expected that micafungin sodium should demonstrate activity in the treatment of documented invasive *Candida* — infections. Data submitted in the NDA and in other supplementary submissions are insufficient to assess the efficacy of micafungin in the treatment of patients with invasive infections caused by — *Candida* species.

Findings of Study 98-0-050 are sufficiently encouraging to support the medical officer's conclusion that micafungin is not inferior to fluconazole as prophylaxis against — — s in patients undergoing HSCT. The medical officer, therefore, recommends micafungin approvable for the indication of prophylaxis of — in patients undergoing HSCT. Approval for this indication will require data from adequate and well-controlled studies demonstrating the efficacy of micafungin in the treatment of patients with invasive infections due to — *Candida* species.

From a clinical perspective, the medical officer recommends that micafungin is not approvable for the indication of —

For recommendations regarding the indication of —

, the reader should refer to the review by Sary Beidas, M.D.

10.4 Labeling
Review, discussions, and negotiation of labeling are deferred.

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cc:
HFD-590/Divisional File, IND 34,068
HFD-590/Ag.Div.Dir./Albrecht
HFD-590/MedTL/CavailleColl
HFD-590/MO/Ibia
HFD-590/Chem/Seggel
HFD-590/Micro/Bala
HFD-590/Biopharm/Lee
HFD-590/Pharmtox/McMaster
HFD-590/Stats/Li
HFD-590/RPM/Peacock

Appendix 1

Table--- Summary of clinical Trials in Support of the NDA

Type of Study	Report No.	Objective	Design/Control	Product/Dose/Route	No. of Subjects†	Subjects/Diagnosis	Treatment Duration (FK463)	Status/Type
PK	FJ-463-0001‡	PK analysis, safety	Open-label	2-hr IV infusion at 2.5, 5, 12.5, 25, or 50 mg	27	Healthy subjects	Single dose	Complete
PK	97-0-040‡	PK analysis, including elimination routes & presence of metabolites	Open-label	1-hr infusion of 28.3 mg ^{14}C-FK463 (radioactive dose: 82.4 mcCi)	6	Healthy subjects	Single dose ^{14}C-FK463	Complete
PK	FJ-463-0002‡	PK analysis	Single- blind/saline control	1-hr IV infusion 1 x daily at 25 mg	9	Healthy subjects	7 consecutive days	Complete
PK	FJ-463-0005‡	PK analysis	Open-label, parallel groups	Single 0.5-hr infusion at 25, 50 or 75 mg; single 1-hr infusion at 150 mg; 1-hr infusion 1x daily at 75 mg	30	Healthy subjects	Single dose or repeat dose for 7 consecutive days	Complete
PK§	97-0-041	PK analysis of FK463 with fluconazole; steady state PK of fluconazole with FK463	Double- blind, randomized, sequential dose escalation/ active control	1-hr IV infusion 1 x daily at 12.5, 25, 50, 75, 100, 150, or 200 mg	FK463 + fluconazole 62 Fluconazole+ saline 12	Adult patients undergoing bone marrow or peripheral stem cell transplant	At least 7 days	Complete
PK§	98-0-043	PK in age groups 2-12 and 13-17	Open-label, sequential dose escalation	1-hr IV infusion 1x daily at 0.5, 1.0, 1.5, 2.0, 3.0, or 4.0 mg/kg/day	72	Febrile, neutropenic pediatric patients with 1 of the following: leukemia or lymphoma (except patients on maintenance therapy); bone marrow or peripheral stem cell transplant; chemotherapy inducing >10 days of neutropenia; aplastic anemia; or myelodysplastic syndrome	At least 4 days	Complete

PK§	FG463-21-03	PK analysis	Open-label, sequential Dose Escalation	1-hr IV infusion, 1x daily, at 3.0, 4.0, 6.0, or 8.0 mg/kg/day	34	Adult patients scheduled to undergo bone marrow or peripheral stem cell transplant	At least 7 days	Complete
PK§		PK analysis	Open-label	Infusion (0.5-2.08 hrs) 1x daily at 12.5, 25, 50, 75, 100 or 150 mg	66		7-28 days with possible extension of another 28 days	Complete
PK	FJ-463-0004‡	Comparison of PK in elderly and young	Open-label, parallel group	1-hr infusion of 50 mg	20	Healthy subjects	Single dose	Complete
PK	01-0-110	PK in those with normal renal function and those with severe renal dysfunction; determine if renal failure alters plasma protein binding	Open-label, parallel group	1-hr infusion of 100 mg	18	Subjects with normal renal function and severe renal dysfunction	Single-dose	Complete, Executive summary with final QA'd data and analyses¶
PK	01-0-111	PK analysis; determine if hepatic dysfunction alters plasma protein binding	Open-label, parallel group	1-hr infusion of 100 mg	16	Healthy subjects and subjects with moderate hepatic dysfunction	Single dose	Complete, Executive summary with final QA'd data and analyses¶
PK	01-0-104	Effects of single-dose and steady state FK463 on single-dose PK of cyclosporine; effects of single-dose cyclosporine on single-dose PK of FK463	Open-label	1-hr IV infusion of FK463 on days 7, 9, and 11-15; 5 mg/kg PO cyclosporine on days 1, 9, and 15	27	Healthy subjects	7 days	Complete
PK	01-0-105	Effects of single-dose and steady-state FK463 on single-dose PK of tacrolimus; effects of single-dose tacrolimus on single- dose PK of FK463	Open-label	1-hr IV infusion of FK463 on days 7, 9, and 12-16; 5 mg PO of tacrolimus on days 1, 9, and 16	26	Healthy subjects	7 days	Complete

Efficacy/ safety§	97-0-041	MTD of FK463 in combination with fluconazole	Double-blind, randomized, sequential dose escalation/active control	FK463/saline: 1-hr infusion 1x daily; fluconazole: PO 1x daily (1-hr infusion if PO not possible); FK463 at 12.5, 25, 50, 75, 100, 150, or 200 mg/day; fluconazole at 400 mg/day; saline at 100 mL	FK463 + fluconazole 65 Fluconazole + saline 14	Adult patients undergoing bone marrow or peripheral stem cell transplant	Treatment from 48 hrs prior to transplant to 24 hrs after transplant initiation; dosing continued until neutrophil recovery, up to 5 days post recovery or max of 4 weeks	Complete

Efficacy/ safety	97-7-003	MED, safety, efficacy	Open-label, dose de-escalation	1-hr infusion 1x daily: 100.0, 75.0, 50.0, 25.0, or 12.5 mg	120	HIV-positive patients with esophageal candidiasis	10 days min to 21 days max	Complete
Efficacy/ safety§	98-0-043	MTD, safety in age groups 2-12 and 13-17	Open-label, sequential dose escalation	1-hr infusion 1x daily, 0.5 mg/kg/day; escalation to 1.0, 1.5 2.0, 3.0, and 4.0 mg/kg/day; because of slow enrollment highest dose for 13-17 year olds was 1.5 mg/kg/day	78	Febrile, neutropenic pediatric patients with 1 of the following: leukemia or lymphoma (except patients on maintenance therapy); bone marrow or peripheral stem cell transplant; chemotherapy inducing >10 days of neutropenia; aplastic anemia; or myelodysplastic syndrome	Treatment at onset of fever while neutropenic for min of 3 days to max of 4 weeks or until neutrophil recovery	Complete
Efficacy/ safety§	FG463-21-03	MTD, safety	Open-label, sequential dose escalation	1-hr infusion, 1x daily, at 3.0, 4.0, 6.0, or 8.0 mg/kg/day	36	Adult patients scheduled to undergo bone marrow or peripheral stem cell transplant	Treatment from 2 or 3 days before transplantation for min of 7 days to max of 28 days or until recovery of neutropenia	Complete

Efficacy/ safety	98-0-050	Efficacy, safety of FK463 vs fluconazole	Double-blind randomized/ active control	1-hr infusion 1x daily FK463: 50 mg/day (1 mg/kg/day <50 kg); fluconazole: 400 mg/day (8 mg/kg/day <50 kg)	FK463 426 Fluconazole 463	Adult & pediatric patients undergoing hematopoietic stem cell transplant	Treatment started at time transplant-conditioning regimen was initiated or within 48 hours post-initiation; treated until neutrophil recovery + 0 to 5 days to max of 42 days posttransplantion	Complete
Efficacy/ safety	98-0-046	Efficacy, safety	Open-label/ historical control	1-hr infusion 1x daily (min of 3 days/week); beginning dose of 75 mg/day (1.5 mg/kg/day ≤40 kg), increases in 75 mg increments (1.5 mg/kg/day increments ≤40 kg) after 7 days to 225 mg/day (4.5 mg/kg/day ≤40 kg) or higher with approval	188	Adult & pediatric patients with invasive disseminated aspergillosis (pulmonary only)	7-90 days, or more with approval	Interim report

Efficacy/ safety	98-0-047	Efficacy, safety	Open label/historical control	1-hr infusion 1x daily (or min 3 days/week); beginning dose 50 mg/day (1 mg/kg/day ≤40 kg) or 100 mg/day (2 mg/kg/day ≤40 kg) if germ tube negative Candida infection or non-C. albicans infection; increases in 50 mg increments (1 mg/kg increments ≤40 kg) after 5 days	254	Adult & pediatric patients with candidemia or invasive candidiasis	Min of 5 days to max of 6 weeks	Interim report

Efficacy/ safety§		Efficacy, safety	Open label, noncomparative	1x daily 25, 50, or 75 mg initial dose (0.5-2.08-hr infusion); increases after 4-7 days to max dose of 150 mg/day	70		7-28 days with possible extension of another 28 days	Complete

PK: pharmacokinetic; hr(s): hour(s); IV: intravenous; mg: milligram; mcCi: microcuries; kg: kilogram; PO: per oral; MTD: maximum tolerated doses; max: maximum; MED: minimum effective dose; HIV: human immunodeficiency virus; min: minimum; vs: versus.

† PK studies = number included in pharmacokinetic analyses; Efficacy/ safety studies = number enrolled [Note: the same patient population was used for PK and efficacy/ safety studies]

‡ Study FJ- 463- 0001 includes supplemental reports CRR970499 and CLR970047; Study 97- 0- 040 includes a metabolite report CRD000043; Study FJ- 463- 0002 includes supplemental report CLR980025; Study FJ- 463- 0005 includes supplemental report CLR000024; Study FJ- 463- 0004 includes supplemental report CLR000023.

§ This study has both a pharmacokinetic study report and an efficacy/ safety study report.

¶ Complete reports will be provided in 120- day safety update.

†† Includes supplemental report CRE010154

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/s/

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