

Clinical Review

Mary E. Singer, M.D., Ph.D.

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

success in the FAS because most patients with overall therapeutic success were clinically “cleared” rather than “cleared or improved” at the EOT.

Relapse of Esophageal Candidiasis at 2- and 4-weeks Post-Treatment

Relapse of EC was assessed by the Applicant in patients who achieved overall therapeutic success (clinically and endoscopically “cleared” or “improved”) at EOT. Relapse was defined as clinical and endoscopic worsening in comparison to the EOT evaluation. In the applicant’s analysis shown in Table 15 below, missing values were counted as relapses. Overall, relapse rates at 2- and 4 weeks post-treatment were similar in the micafungin and fluconazole treatment groups. In the FAS, relapse rates at 2 weeks post-treatment were 15.4% and 11.1% for micafungin and fluconazole-treated patients, respectively; and cumulative relapse rates at 4 weeks post-treatment were 26.2%, and 23.1% in the micafungin and fluconazole groups, respectively. Similar results were observed in the MFAS and PPS. The differences between the two treatment groups were not statistically significant.

Table 15: Incidence of Relapse during the Posttreatment Period (Including Missing Values) (Applicant’s Table 11, study report, 03-7-005)

Posttreatment Visit	Treatment Group		P-Value
	Micafungin	Fluconazole	
Full Analysis Set			
Relapse at 2-Week Visit	35/227 (15.4%)	25/225 (11.1%)	0.168
Relapse at 4-Week Visit	24/192 (12.5%)	27/200 (13.5%)	0.888
Relapse through Week 4 Visit	59/227 (26.0%)	52/225 (23.1%)	0.424
Modified Full Analysis Set			
Relapse at 2-Week Visit	29/190 (15.3%)	23/187 (12.3%)	0.418
Relapse at 4-Week Visit	20/161 (12.4%)	24/164 (14.6%)	0.764
Relapse through Week 4 Visit	49/190 (25.8%)	47/187 (25.1%)	0.801
Per Protocol Set			
Relapse at 2-Week Visit	27/182 (14.8%)	23/181 (12.7%)	0.559
Relapse at 4-Week Visit	19/155 (12.3%)	23/158 (14.6%)	0.686
Relapse through Week 4 Visit	46/182 (25.3%)	46/181 (25.4%)	0.975

Patient base: Incidence of relapse was assessed only for patients with an overall therapeutic response at the end of therapy.

Full Analysis Set: all randomized patients who received at least one dose of study drug.

Modified Full Analysis Set: all randomized patients who received at least one dose of study drug and had a positive histology or cytology at baseline.

Per Protocol Set: all randomized patients who received at least 10 doses of study drug, who had confirmed esophageal candidiasis at baseline, who had a baseline and end of therapy endoscopy performed, and who did not have major protocol deviations.

n=total number of patients in each treatment group in each analysis set.

P-value is based on the CMH test controlling for pooled center.

The 2-week patient evaluation was treated as no relapse if it was not done and the 4-week patient evaluation was assessed as no relapse and the patient did not receive any systemic antifungal medication during posttreatment. Patients that relapsed at the 2-week posttreatment visit are not included in the 4-week posttreatment

Clinical Review

Mary E. Singer, M.D., Ph.D.

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

Medical Officer Comments: In the analysis above, the applicant used as a patient base, those who had overall therapeutic success (clinically and endoscopically cured or improved). In this medical officer's opinion, patients who did not have complete resolution of EC at the end-of-therapy were not appropriate for relapse evaluation. These data were re-analyzed below in patients who had both clinical and endoscopic resolution at the end-of-therapy.

Relapse data was re-analyzed by the medical and statistical reviewers in patients who achieved overall therapeutic cure, defined as endoscopic cure (grade 0) plus clinical cure ("cleared") at EOT. Additionally, patients who received systemic antifungal therapy during the post-treatment period, and patients not evaluated were counted as relapses, as were missing values. The MFAS was used for this analysis because these patients had confirmed EC at baseline. Results of this analysis are shown in Table 16 below. Using these strict criteria for relapse in a population of patients who was cured both clinically and endoscopically, relapse rates were similar for both treatment groups.

**APPEARS THIS WAY
ON ORIGINAL**

Clinical Review
 Mary E. Singer, M.D., Ph.D.
 Micafungin sodium for Esophageal Candidiasis
 Mycamine (Micafungin sodium)

Table 16. Relapse at 2- and 4- weeks Post-treatment in Patients with Overall Therapeutic Cure in MFAS (Medical and Statistical Reviewer’s Analysis)

Parameter	Micafungin	Fluconazole	Treatment difference [95% confidence interval]
Two Weeks Post-treatment	N=223	N=220	
No relapse	186	193	
Relapse	13	8	
No evaluation*	24	19	
Patients not counted as relapse, but received systemic AFT post-treatment	3	3	
Total Relapse (relapse, not evaluated, or AFT use post-treatment)	40 (17.9)	30 (13.6)	4.3 [-2.5,11.1]
Four Weeks Post-treatment	N=184	N=192	
No relapse	163	169	
Relapse	16	12	
Not evaluated*	5	11	
Patients not counted as relapse, but received systemic AFT post-treatment	12	9	
Total Relapse (relapse, not evaluated, or AFT use post-treatment)	33 (17.9)	32 (16.7)	1.2 [-6.4, 8.9]
Cumulative Relapse at 4 weeks	73/223 (32.7)	62/220 (28.2)	4.5 [-4.0, 13.1]

N= number of patients with overall therapeutic success (endoscopic and clinical resolution “cleared” at EOT

* Patients not evaluated included patients who died, were lost-to-follow up, or relapse evaluation was not performed

AFT= antifungal therapy

Medical Officer Comments: Because receipt of systemic antifungal therapy could confound the analysis of relapse, patients who received systemic antifungal therapy during the post-treatment period were considered as relapses in this analysis, even if they received only prophylactic therapy. Although the relapse rates in this analysis were somewhat higher than those shown in the Applicant’s analysis (Table 15 above), the rate of relapse at 2 weeks, 4 weeks, and cumulative relapse at 4 weeks, remained similar for the micafungin and fluconazole treatment groups. These data support the conclusions drawn from the primary efficacy analysis, endoscopic cure.

Clinical Review
 Mary E. Singer, M.D., Ph.D.
 Micafungin sodium for Esophageal Candidiasis
 Mycamine (Micafungin sodium)

Mycological Response at EOT

Mycological response, determined by culture and histology or cytology at the EOT is shown in Table 17 below. In EC, a favorable mycological response would include either eradication of the organism, or persistent colonization (non-invasive). These results support those of the primary endpoint, endoscopic response.

Table 17. Mycological Response at EOT (Applicant's Table 17, 03-7-005 study report)

Mycological Response	Treatment Group	
	Micafungin	Fluconazole
Full Analysis Set		
n	260	258
Eradication	179 (68.8%)	139 (73.3%)
Persistence (Colonization)	42 (16.2%)	31 (12.0%)
Persistence (Presumed Colonization)	7 (2.7%)	3 (1.1%)
Persistence (Invasive)	3 (1.1%)	10 (3.9%)
Not Evaluable	24 (9.2%)	20 (7.5%)
Modified Full Analysis Set		
n	220	215
Eradication	148 (67.3%)	135 (72.1%)
Persistence (Colonization)	40 (18.2%)	26 (12.1%)
Persistence (Presumed Colonization)	4 (1.8%)	3 (1.4%)
Persistence (Invasive)	6 (2.7%)	10 (4.7%)
Not Evaluable	22 (10.0%)	16 (7.4%)
Per Protocol Set		
n	189	192
Eradication	141 (74.6%)	149 (77.6%)
Persistence (Colonization)	38 (20.1%)	25 (13.0%)
Persistence (Presumed Colonization)	4 (2.1%)	3 (1.6%)
Persistence (Invasive)	6 (3.2%)	10 (5.2%)

Patient base:
 Full Analysis Set: all randomized patients who received at least one dose of study drug.
 Modified Full Analysis Set: all randomized patients who received at least one dose of study drug and had a positive histology or cytology at baseline.
 Per Protocol Set: all randomized patients who received at least 10 doses of study drug, who had confirmed esophageal candidiasis at baseline, who had a baseline and end of therapy endoscopy performed, and who did not have major protocol deviations.
 n=total number of patients in each treatment group in each analysis set.

Medical Officer Comments: When the number of patients with mycological eradication and colonization (non-invasive), including presumed colonization in the FAS were combined, a favorable mycological response was observed in 228/260 (87.6%) patients who received micafungin, and in 228/258 (88.4%) patients who received fluconazole. In the MFAS, a favorable mycological response was observed in 192/220 (87.3%) in micafungin- and 189/215 (87.9%) fluconazole-treated patients, respectively. In the PPS, a favorable mycological response was observed in 183/189 (96.8%) micafungin-treated, and in 182/192 (94.8%) fluconazole-treated patients. These response rates are similar to those seen for endoscopic cure, clinical cure, and overall treatment response for both treatment groups. These data support the conclusions drawn from analysis of the primary outcome measure, endoscopic cure.

Summary of Esophageal Candidiasis Treatment in Study 03-7-005

Treatment outcomes for esophageal candidiasis in this study are summarized in the following table, as included in the proposed micafungin label.

BEST POSSIBLE COPY

Clinical Review
 Mary E. Singer, M.D., Ph.D.
 Micafungin sodium for Esophageal Candidiasis
 Mycamine (Micafungin sodium)

Table 18. Endoscopic, Clinical, and Mycological Outcomes for Esophageal Candidiasis at End-of-Treatment

Treatment Outcome*	MYCAMINE 150 mg/day	Fluconazole 200 mg/day	% 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 (85.8%)	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 outcome were measured in modified intent-to-treat population, including all randomized patients who received ≥ 1 dose of study treatment. Mycological outcome was determined in the per protocol (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

Oropharyngeal Candidiasis (OPC) Outcomes

Although treatment of OPC is not a proposed indication for micafungin in this NDA, these results are of interest because most patients with EC also have OPC, and it is generally thought that patients with OPC may progress to the more invasive mucosal disease, EC. In this study, OPC was present in 459 of 518 (88.6%) patients with EC at baseline. Among those patients with OPC at baseline, approximately 83.5% (192/230) micafungin-treated patients, and 188/229 (82.1%) fluconazole-treated patients experienced resolution of OPC signs and symptoms at the EOT. Of these, 32.3% in the micafungin 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 micafungin group and 39.4% in the fluconazole group (treatment difference 12.7%, 95% confidence interval [2.8, 22.7]).

Medical Officer Comments: Micafungin is similar to fluconazole for treatment of OPC, but relapse rates were higher for micafungin-treated patients at 2 weeks and cumulatively at 4 weeks. OPC is generally a superficial infection, treated frequently with oral or topical antifungal agents. Intravenous antifungal therapy is not generally required for treatment of OPC. Similar OPC relapse results have been reported with caspofungin. Approximately 43% patients treated with caspofungin had OPC relapse at two weeks post-treatment in comparison to 13% patients who received fluconazole; while OPC relapse rates at 4 weeks post-treatment were 59% for caspofungin-treated patients and 36% for fluconazole-treated patients (Cancidas® package insert). Echinocandins are large lipopeptide molecules and may not achieve high levels in oral mucosa or saliva, which may explain the earlier and more frequent OPC relapses with these agents in comparison to fluconazole, which is highly water-soluble and is known to achieve

Clinical Review

Mary E. Singer, M.D., Ph.D.

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

relatively high mucosal and salivary concentrations. At this time, micafungin should not be indicated for treatment of OPC.

Efficacy Evaluation by Race, Gender and Age

Logistic regression analysis by the statistical reviewer showed that age, race, and gender did not predict the primary outcome in this study, endoscopic response at end of therapy. Baseline CD₄ count, however, independently predicted treatment outcome regardless of treatment.

Medical Officer Comments: The finding that baseline CD₄ count predicted the primary treatment outcome is not unexpected. Patients with lower CD₄ counts have more compromised T-cell immunity, which is required for eradicating fungal infections.

Conclusions Regarding Efficacy of Micafungin for Treatment of EC in Study 03-7-005

1. Micafungin is non-inferior to fluconazole for treatment of esophageal candidiasis as evaluated by the primary endpoint, endoscopic response at end-of-treatment. This conclusion is supported by the secondary outcome measures, clinical response, overall therapeutic response, mycological response, and EC relapse rates post-treatment.
2. Although micafungin was also effective for treatment of OPC, and response at the end-of-therapy was similar to that obtained with fluconazole, higher relapse rates were observed with micafungin than with fluconazole at 2- and 4- weeks post-treatment.

Medical Officer Comments: Study 03-7-005, a pivotal study for evaluation of efficacy for this NDA was a well-designed study, and fulfills the regulatory requirements for an adequate and well-controlled study. No serious design flaws, or concerns about conduct of the study were raised in review of this study.

Study FG463-21-09

Patient Demographics

In this study, approximately 50% of enrolled patients were black, 40% were Caucasian or Hispanic and 10% of patients had other racial/ethnic origins. Approximately 50% of patients were male, and the mean patient age was 35.7 ± 8.2 years, overall. The treatment groups were similar with respect to age, race, and gender. Patient demographics are shown in Table 19 below.

Clinical Review

Mary E. Singer, M.D., Ph.D.

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

Table 19. Baseline Patient Demographics (FAS) (adapted from applicant's Table 6, study report FG463-21-09)

Characteristic	Micafungin 50 mg/day N=64	Micafungin 100 mg/day N=62	Micafungin 150 mg/day N=59	Fluconazole 200 mg/day N=60	Total N=245
Age (years)					
Mean \pm SD	33.9 \pm 7.5	36.8 \pm 8.1	36.7 \pm 8.8	35.5 \pm 8.2	35.7 \pm 8.2
Median	33	35	36	34	34
Range	19-54	24-68	23-68	19-56	19-68
Gender	n (%)	n (%)	n (%)	n (%)	n (%)
Male	30 (46.9)	26 (41.9)	33 (55.9)	28 (46.7)	117 (47.8)
Female	34 (53.1)	36 (58.1)	26 (44.1)	32 (53.3)	128 (52.2)
Race/Ethnic Origin	n (%)	n (%)	n (%)	n (%)	n (%)
Caucasian*	25 (39.1)	26 (41.9)	25 (42.4)	22 (36.7)	98 (40.0)
Black	31 (48.4)	33 (53.2)	30 (50.8)	32 (53.3)	126 (51.4)
Other**	8 (12.5)	3 (4.8)	4 (6.8)	6 (10.0)	21 (8.6)

*note that Hispanic patients were counted as Caucasian

** Other includes mulatto (15 patients), native Brazilian (2 patients), cape colored (2 patients), colored (1 patient), mestizo (1 patient).

SD= standard deviation

n (%) = number and percentage of patients with characteristic

Baseline Patient Characteristics

The overall mean CD₄ count for patients in the study was 68 cells/mm³ and the median CD₄ count was 29 cells/mm³, with no statistically significant differences between treatment groups. Baseline disease (EC) severity was assessed by endoscopic grade and clinical symptoms grade. These were similar across treatment groups, with the exception that the fluconazole treatment group had a higher proportion of patients with severe EC (endoscopic grade 3). The baseline clinical and endoscopic grade of EC in patients at baseline are shown in Table 20 below.

Clinical Review
 Mary E. Singer, M.D., Ph.D.
 Micafungin sodium for Esophageal Candidiasis
 Mycamine (Micafungin sodium)

Table 20. Baseline Clinical and Endoscopic Grade (FAS) (adapted from applicant's Tables 7 and 8, study report FG463-21-09)

Baseline characteristic	Micafungin 50 mg/day N=64	Micafungin 100 mg/day N=62	Micafungin 150 mg/day N=59	Fluconazole 200 mg/day N=60	Total N=245
Endoscopic grade:*	n (%)	n (%)	n (%)	n (%)	n (%)
0	0 (0)	0 (0)	0 (0)	1 (1.7)	1 (0.4)
1	11 (17.2)	13 (21.0)	11 (18.6)	10 (16.7)	45 (18.4)
2	42 (65.6)	37 (59.7)	37 (62.7)	31 (51.7)	147 (60.0)
3	11 (17.2)	12 (19.4)	11 (18.6)	18 (30.0)	52 (21.2)
Mean endoscopic grade	2.0	2.0	2.0	2.1	2.0
Clinical symptom grade:**					
Mean clinical symptom grade ± SD	3.9 ± 2.1	4.3 ± 2.2	4.2 ± 2.3	4.0 ± 2.6	4.1 ± 2.3
Median clinical symptom grade	3.0	4.0	4.0	3.5	4.0

N= total number of patients in FAS

N (%) = number and proportion of patients with specific endoscopic grade

*endoscopic grade: 0 = no plaques; 1=individual raised plaques of ≤ 2 mm in size; 2 = multiple raised plaques > 2 mm in size; and 3 = confluent plaques and ulceration

** Clinical symptom grade: odynophagia, dysphagia and retrosternal pain were each assigned a grade of 0 (no symptoms), 1, 2, or 3

Medical Officer Comments: Although somewhat more patients in the fluconazole treatment group had more severe EC at baseline, based on endoscopic grade, this difference was not statistically significant, and would not be expected to affect outcomes significantly.

Efficacy Results

Primary Endpoint: Endoscopic Response at EOT

Endoscopic cure rates (endoscopic grade 0) at the EOT are shown in Table 21 below for the Full Analysis Set (FAS), which included all patients who received at least one dose of micafungin. A clear dose-response was demonstrated with micafungin, with the highest rates of cure achieved with 150 mg/day micafungin, comparable to that seen with fluconazole. Similar results were observed in the modified full analysis set (MFAS),

Clinical Review

Mary E. Singer, M.D., Ph.D.

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

which included all patients who received at least one dose of micafungin, with histologically confirmed EC.

Table 21. Endoscopic Response at End of Therapy in Full Analysis Set (FAS) (from Applicant's Table 13.5.1.1.1, FG463-21-09 study report)

FAS	Endoscopy grade at EOT	Micafungin 50 mg/day N=64	Micafungin 100 mg/day N=62	Micafungin 150 mg/day N=59	Fluconazole 200 mg/day N=60
		n (%)	n (%)	n (%)	n (%)
Success	0	44 (66.8) [57.4, 80.1]*	48 (77.4) [67.0, 87.9]*	53 (89.9) [82.1, 97.5]*	52 (86.7) [78.1, 95.3]*
Failure	1	6 (9.4)	4 (6.5)	1 (1.7)	2 (3.3)
	2	9 (14.1)	1 (1.6)	0	0
	3	2 (3.1)	0	0	0
	Unknown	1 (1.6)	2 (3.2)	1 (1.7)	0
	Not recorded	2 (3.1)	7 (11.3)	4 (6.8)	5 (8.3)

* 95% confidence interval

N= number of patients in FAS

n (%) = number and proportion of patients with endoscopic success or failure

Medical Officer Comments: In comparison to study 03-7-005, which compared micafungin 150 mg/day to fluconazole 200 mg/day, endoscopic success in this study were similar, with 87.7% and 88.0% of patients in the micafungin (150 mg/day), and fluconazole (200 mg/day) groups, respectively, achieving an endoscopic grade =0 at the end-of-therapy in the FAS (Table 11 above)

Endoscopic cure rates in the Per Protocol Set (PPS) were higher, as expected, because patients who did not have an endoscopic evaluation at the end-of-therapy were excluded from the analysis. Although a dose-response for micafungin was still observed in the PPS, efficacy was similar for the 100 mg/day and 150 mg/day micafungin dose in this analysis, as shown in Table 22 below.

Clinical Review

Mary E. Singer, M.D., Ph.D.

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

Table 22. Primary Endpoint (Endoscopic Response) in Per Protocol Set (PPS) (from Applicant's Table 13.5.1.1.2)

PPS	Endoscopy grade at EOT	Micafungin 50 mg/day N=52	Micafungin 100 mg/day N=48	Micafungin 150 mg/day N=51	Fluconazole 200 mg/day N=48
		n (%)	n (%)	n (%)	n (%)
Success	0	37 (71.2) [58.8, 83.5]*	44 (91.7) [83.8, 99.5]*	50 (98.0) [94.2, 100]*	46 (95.8) [90.2, 100]*
Failure	1	4 (7.7)	3 (6.3)	1 (2.0)	1 (2.1)
	2	9 (17.3)	1 (2.1)	0	1 (2.1)
	3	2 (3.8)	0	0	0
	Unknown	0	0	0	0
	Not recorded	0	0	0	0

*95% confidence interval

N= number of patients in FAS

n (%) = number and proportion of patients with endoscopic success or failure

Medical Officer Comments: Endoscopic cure rates were comparable for micafungin 150 mg/day and fluconazole in the FAS and PPS. This study, however, was not designed to show non-inferiority of micafungin to fluconazole. Additionally, statistical analysis of these data revealed that the differences in endoscopic cure in the micafungin 100 mg/day and 150 mg/day dose groups were not significantly significant in the FAS or PPS.

Secondary Endpoints

Clinical Response at End of Therapy

Clinical response, defined as “cleared” or resolution of signs and symptoms (grade 0), was similar for micafungin, (100 mg/day and 150 mg/day) and fluconazole (200 mg/day); while clinical response for the lower dose of micafungin (50 mg/day) was lower in the FAS as shown in Table 23 below. When clinical response is defined as “cleared or improved”, the cure rates were similar for all treatment groups, including the 50 mg/day micafungin group.

Clinical Review

Mary E. Singer, M.D., Ph.D.

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

Table 23. Clinical Response at EOT in FAS (adapted from Applicant's Table 19, study report FG463-21-09)

Clinical Response	Micafungin 50 mg/day N=64	Micafungin 100 mg/day N=62	Micafungin 150 mg/day N=59	Fluconazole 200 mg/day N=60
	n (%)	n (%)	n (%)	n (%)
Cleared	47 (73.4)	52 (83.9)	51 (86.4)	53 (88.3)
Improved	15 (23.4)	3 (4.8)	4 (6.8)	3 (5.0)
Cleared or improved	62 (96.9)	55 (88.7)	55 (93.2)	56 (93.3)
Unchanged or worse	0	1 (1.6)	0	1 (1.7)
Missing	2	6	4	3

FAS= full analysis set; MFAS= modified full analysis set; PPS= per Protocol set

N= number of patients in analysis set

n = number of patients with clinical response (resolution of EC signs and symptoms, grade = 0) at EOT

Missing data: 50 mg/day micafungin group: 1 patient lost to follow-up on day 6; 1 missing value); 100 mg/day micafungin group: 4 patients lost to follow-up; 1 death on day 14, 1 patient withdrew consent day 16; 150 mg/day micafungin group: 2 patients lost to follow-up, 1 patient died on day 3, 1 patient withdrew consent on day 13; fluconazole group: 1 missing value; 1 death on day 11; 1 withdrew consent on day 1.

Medical Officer Comments: This endpoint may be most relevant for the clinician because endoscopy is not usually performed to assess efficacy unless the patient has not improved with treatment. These results support the conclusions drawn using the primary endpoint. These data support the primary efficacy outcome measure, endoscopic response at EOT.

These results are similar to those reported in study 03-7-005. Clinical success in that study, defined as clinically cleared or improved at EOT, was observed in 94.2% patients treated with micafungin 150 mg/day, and in 94.6% fluconazole patients treated with fluconazole, as shown in Table 12 above; while clinical success, defined as clinically cleared or improved at EOT in this study, was observed in 93.2% and 93.3% of patients who received micafungin (150 mg/day) and fluconazole, respectively.

Overall Therapeutic Response

Overall therapeutic response was defined by the applicant as complete resolution or improvement in both clinical response and endoscopic grade from baseline to end of therapy. Improvement in clinical response required improvement of at least 2 grades in at least one clinical sign/symptom of EC; while improvement in endoscopic assessment required improvement of at least 1 grade. Table 24 shows the overall therapeutic response at end of therapy using the applicant's definition.

Clinical Review

Mary E. Singer, M.D., Ph.D.

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

In this analysis, patients with missing values were counted as therapeutic failures. In the FAS, a similar response was seen with micafungin 150 mg/day and fluconazole.

Table 24. Overall Therapeutic Response at EOT (FAS) (adapted from Applicant's Table 23, study report, FG463-21-09)

Overall Therapeutic Response EOT	Micafungin 50 mg/day N=64	Micafungin 100 mg/day N=62	Micafungin 150 mg/day N=59	Fluconazole 200 mg/day N=60
	n (%)	n (%)	n (%)	n (%)
Success*	51 (79.7)	52 (83.9)	54 (91.5)	55 (91.7)

FAS= full analysis set

N= number of patients in FAS

n= number of patients with overall therapeutic success

*Success = complete resolution or improvement in clinical response and endoscopic grade from baseline

Medical Officer Comments: For this endpoint, a clear dose-response for micafungin in was observed, and response rates were similar for the 150 mg/day micafungin dose and fluconazole. A composite endpoint combining clinical cure (defined as resolution of all clinical signs/symptom) plus endoscopic cure (defined as grade= 0 at EOT) would be a stricter measure of efficacy than overall therapeutic response as defined by the applicant, and may be more appropriate to use for evaluation of relapse. These data are shown in Table 25 below.

Table 25. Overall Therapeutic Cure at EOT in FAS (Medical and Statistical Reviewer's Analysis, adapted from applicant's Tables 13.5.4.1.1, study report FG 463-21-09)

	Micafungin 50 mg/day N=64	Micafungin 100 mg/day N=62	Micafungin 150 mg/day N=59	Fluconazole 200 mg/day N=60
	n (%)	n (%)	n (%)	n (%)
Overall Therapeutic Cure EOT*	39 (60.9)	48 (77.4)	50 (84.7)	51 (85.0)

* defined as clinically "cleared" and endoscopic resolution (grade 0) at EOT

n= number of patient with overall therapeutic success

N= number of patients in FAS

n= number of patients with overall therapeutic success

*Success = complete clinical and endoscopic resolution

Medical Officer Comments: When overall therapeutic cure is measured using these stricter criteria, cure rates were somewhat lower across treatment groups. A clear dose-response is shown for micafungin, and the overall cure rate in patients treated with 100 mg/day or 150 mg/day micafungin was similar to that in patients who received fluconazole (p-values were 0.36, and 1.0, for the

Clinical Review

Mary E. Singer, M.D., Ph.D.

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

micafungin 100 and 150 mg/day dosing groups, respectively vs. fluconazole); while overall therapeutic cure in patients who received 50 mg/day micafungin was lower than each of the other treatment groups (p-value 0.004 vs. fluconazole, 0.06 vs. micafungin 100 mg/day, and 0.004 vs. micafungin 150 mg/day).

These results as similar to those obtained in study 03-7-005, where overall therapeutic cure, defined as endoscopic and clinical resolution, was 85.7% in patients treated with micafungin 150 mg/day and 85.3% in patients treated with fluconazole, as shown in Table 14 above.

Relapse of EC at Two Weeks Post- Treatment

Relapse at 2 weeks post-treatment was assessed by in those patients who had overall therapeutic cure (endoscopic and clinical cure) at the EOT. Relapse was determined by clinical assessment. Patient who had an EC clinical signs/symptoms score > 0 at the follow-up visit, or who received non-prophylactic antifungal medication during the follow-up phase were considered relapses. Table 26 shows the applicant's analysis of relapse in patients who had both clinical and endoscopic resolution at EOT. No patients in the fluconazole treatment group had a recurrence of EC; while a total of 9 micafungin-treated patients in the full analysis set had an EC recurrence. No dose-response for EC relapse was noted. When patients who were not evaluated for EC relapse were counted as relapses, higher rates of relapse were noted in all treatment groups. When analyzed this way, a dose-response relationship is seen, with highest rate of EC relapse in the lowest micafungin dose group, and lowest with the highest micafungin dose group. Relapse rates were similar for fluconazole and 150 mg/day micafungin.

Table 26. Relapse of EC at 2-week Follow-up Visit in patients who had clinical and endoscopic resolution at EOT (FAS) (adapted from Table 13.5.4.1.1.1, study report FG463-21-09)

	Micafungin 50 mg/day N=64	Micafungin 100 mg/day N=62	Micafungin 150 mg/day N=59	Fluconazole 200 mg/day N=60
	n /No.(%)	n/No. (%)	n/No. (%)	n/No. (%)
Relapse	1/39 (2.6)	5/48 (10.4)	3/50 (6.0)	0/51 (0)
Missing data**	8	3	3	6
Total Relapse	9/39 (23.1)	8/48 (16.7)	6/50 (12.0)	6/51 (11.8)

FAS= full analysis set

**Missing data refers to patients with clinical and endoscopic cure at EOT who were not evaluated for relapse but were counted as relapses in this analysis

No. = number of patients with clinical and endoscopic cure (overall therapeutic cure) at EOT

n= number of patients with relapse (clinical signs/symptoms score >0, or receipt of non-prophylactic antifungal medication during follow-up phase of study)

Medical Officer Comments: *In this analysis, EC relapse rates were similar for patients who received 150 mg/day micafungin or fluconazole. Higher rates of*

Clinical Review

Mary E. Singer, M.D., Ph.D.

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

relapse were noted when lower doses of micafungin were used. However, no statistically significant differences were seen between treatment groups. In review of the database, it was noted that some patients who received systemic antifungal therapy in the post-treatment period were not counted as relapses. Relapse data was re-analyzed by the medical and statistical reviewers, including these patients as relapses. These data are shown in Table 27 below.

Table 27. Relapse of EC at 2-week Follow-up Visit (Medical and Statistical Reviewer's Analysis, including patients who received post-treatment systemic antifungal therapy for any indication as relapses) (FAS)

	Micafungin 50 mg/day N=64	Micafungin 100 mg/day N=62	Micafungin 150 mg/day N=59	Fluconazole 200 mg/day N=60
	n /No.(%)	n/No. (%)	n/No. (%)	n/No. (%)
Relapse	1/39	5/48	3/50	0/51
Missing**	8/39	3/48	3/50	6/51
No relapse, but received systemic antifungal therapy PT***	4/39	5/48	4/50	2/51
Total Relapse	13/39 (33.3)	13/48 (27.1)	10/50 (20.0)	8/51 (15.7)

FAS= full analysis set

**Missing data refers to patients with clinical and endoscopic cure at EOT who were not evaluated for relapse.

*** Patients not counted as having relapse, but had received systemic antifungal therapy (for any indication) during the post-treatment (PT) period

No. = number of patients with clinical and endoscopic cure at EOT

n = number of patients with relapse

Medical Officer Comments: *The protocol had indicated that patients who received additional antifungal therapy (except for prophylaxis) during the post-treatment period would be counted as a relapse. A small number of patients in each treatment group were identified who were not counted as relapses, but who had received systemic antifungal therapy, including prophylactic antifungal therapy. These were counted as relapses in this analysis because the use of systemic antifungal therapy, even at prophylactic doses, could confound the evaluation of relapse. In this analysis, EC relapse rates for patients treated with micafungin were highest with the lowest dose of micafungin (50 mg/day), and lowest with 150 mg/day micafungin. Relapse rates in the latter group were comparable to those seen in the fluconazole group. None of the differences between treatment groups was statistically significant.*

In comparison to study 03-7-005, in which relapse rates at two weeks post-treatment were 17.9% among patients who received 150 mg/day micafungin, and

Clinical Review

Mary E. Singer, M.D., Ph.D.

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

13.6% for patients who received fluconazole (Table 16 above), relapse rates in this study were somewhat higher, occurring in 20% and 15.7% of patients who received micafungin (150 mg/day) and fluconazole, respectively.

Mycological Response

Mycological response was graded as fungal eradication (negative fungal culture, histology and cytology), colonization (fungal culture positive, but histology and cytology negative), or persistence (positive histology and cytology, with positive or negative fungal culture). Mycological response, defined as fungal eradication at end of therapy is shown in Table 28 below. Two analyses were performed: 1) patients with missing data are considered mycological failures; and 2) patients with missing data are excluded from the analysis. Similar results were seen with both analyses. No clear dose-response relationship for mycological eradication was noted with micafungin. Response rates in the 100 mg/day micafungin treatment group were similar to those observed with fluconazole; while response rates were lower for the highest micafungin dose (150 mg/day) than for the 100 mg/day dose group. The lowest dose of micafungin (50 mg/day) resulted in lowest mycological response.

Table 28. Mycological Eradication at end-of therapy (adapted from Tables 13.5.1.6.1 and 13.5.1.6.2, study report FG463-21-09)

Analysis Set	Micafungin 50 mg/day	Micafungin 100 mg/day	Micafungin 150 mg/day	Fluconazole 200 mg/day
	n/N (%)	n/N (%)	n/N (%)	n/N (%)
FAS*	20/64 (31.3)	36/62 (58.1)	28/59 (47.7)	35/60 (58.3)
FAS	20/57 (35.1)	36/46 (78.3)	28/49 (57.1)	35/52 (67.3)
PPS*	13/52 (25.0)	33/48 (68.8)	26/51 (51.0)	30/48 (62.5)
PPS	13/50 (26.0)	33/42 (78.6)	26/46 (56.5)	30/46 (65.2)

FAS= full analysis set; PPS= per Protocol set

For FAS* and PPS*, patients who did not undergo mycological evaluation were counted as failures, and the denominator included all patients in the analysis set.

For FAS and PPS, patients who did not have mycological evaluation were excluded.

n = number of patients with fungal eradication at EOT

Medical Officer Comment: *It is not clear why mycological response was higher in the 100 mg/day micafungin than at the higher dose (150 mg/day). Because the goal of EC treatment is not necessarily fungal eradication, but resolution of invasive fungal infection, it may be more appropriate to evaluate mycological response defined as eradication or fungal colonization, as shown below.*

When mycological response is defined to include patients with either fungal eradication or colonization, a similar pattern was observed. Colonization was defined as a positive fungal culture with negative histology or cytology. This analysis is shown in Table 29 below.

Clinical Review

Mary E. Singer, M.D., Ph.D.

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

Table 29. Favorable Mycological Response at EOT (Eradication or Colonization)

(adapted from Tables 13.5.1.6.1 and 13.5.1.6.2, study report FG463-21-09)

Analysis Set	Micafungin 50 mg/day	Micafungin 100 mg/day	Micafungin 150 mg/day	Fluconazole 200 mg/day
FAS*	35/64 (54.6)	42/62 (67.7)	35/59 (59.3)	39/60 (65.0)
FAS	35/57 (61.4)	42/46 (91.3)	35/49 (71.4)	39/52 (75.0)
PPS*	28/52 (53.8)	38/48 (79.2)	32/51 (62.7)	34/48 (70.8)
PPS	28/50 (56.0)	38/42 (90.5)	32/46 (69.6)	34/46 (73.9)

FAS= full analysis set; MFAS= modified full analysis set; PPS= per Protocol set

For FAS* and PPS*, patients who did not undergo mycological evaluation were counted as failures, and the denominator included all patients in the analysis set.

For FAS and PPS, patients who did not have mycological evaluation were excluded.

n = number of patients with fungal eradication at EOT

***Medical Officer Comments:** Mycological response as measured as Candida eradication (Table 28 above) or eradication plus colonization (Table 29 above), was lower than either clinical or endoscopic response at the EOT for all treatment groups. Inability to eradicate the organism (a surrogate endpoint) may be related less to the antifungal agent than to the inability of the immune system (particularly cell-mediated immunity) to eliminate the pathogen, or to pharmacologic properties such as mucosal tissue levels. Additionally, it is not clear why a lower mycological response was achieved with 150 mg/day than with 100 mg/day micafungin.*

In comparison to study 03-7-005, where a favorable mycological response (eradicated or non-invasive colonization) was observed in 96.8% of patients who received 150 mg/day micafungin and in 94.8% of patients who received fluconazole (Table 17, Per Protocol Set); a favorable mycological response (eradication or non-invasive colonization) in this study was somewhat lower, 62.7% in patients who received 150 mg/day micafungin, and 70.8% of patients who received fluconazole.

Oropharyngeal Candidiasis Outcomes

The majority 230/245 (93.8%) of patients had signs/symptoms of OPC at baseline. In this analysis, patients with an OPC score of 0 (no signs or symptoms of OPC) and EC endoscopic grade 0 were scored as cured at EOT. Patients with both OPC and EC cure were assessed for OPC relapse at the end-of-study, as shown in Table 30 below. Similar rates of OPC plus EC cure were observed in patients who received 100 or 150 mg/day micafungin or fluconazole. Relapse of OPC was higher in the micafungin treatment groups than in the fluconazole group, but the difference was not statistically significant.

Clinical Review

Mary E. Singer, M.D., Ph.D.

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

Table 30. Oropharyngeal Candidiasis (OPC) at End-of-Therapy (EOT) and End-of-Study (EOS) in Patients who had OPC at baseline (Medical and Statistical reviewer's analysis)

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
	n (%)	n (%)	n (%)	n (%)
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/ 61 (62.3)	45/59 (76.3%)	46/53 (86.7%)	50/57 (87.7)
OPC status EOS:				
-No relapse	23	28	32	39
-Relapse	7	14	12	5
-Missing*	8	3	2	6
-Counted as no relapse but received systemic AFT PT	3	4	3	2
-Total OPC Relapse EOS	18/38 (47.4)	21/45 (46.7)	17/46 (40.0)	13/50 (26.0)

*missing = death, lost to follow-up, or other

AFT= antifungal therapy

PT= post-treatment

***Medical Officer Comments:** Cure of OPC at EOT was similar in patients treated with micafungin 150 mg/day and fluconazole; and lower rates were observed in patients who received micafungin 50 or 100 mg/day. OPC relapse rates were similar across micafungin treatment groups, and higher than in the fluconazole group. This difference was not statistically significant. Oropharyngeal candidiasis often accompanies EC, but differs from EC pathophysiologically, in that OPC is generally not a tissue-invasive disease. Higher OPC relapse rates for micafungin could reflect low levels of micafungin in saliva in comparison to fluconazole post-treatment. Similar results have been shown previously for Cancidas®, which is not found in significant levels in saliva; whereas high concentrations of fluconazole are found in saliva.*

Efficacy as a Function of Race, Gender, Age, and CD4 count

A logistic regression analysis, performed by the statistical reviewer, demonstrated that CD₄ count was an independent predictor of EC cure by endoscopic evaluation; while race, age, and gender did not predict EC cure using the primary endpoint.

Clinical Review

Mary E. Singer, M.D., Ph.D.

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

Efficacy Conclusions for Study FG463-21-09

1. For the primary outcome measure, endoscopic response at EOT, a clear dose-response was observed with micafungin, with the highest rate of endoscopic cure seen in patients who received micafungin 150 mg/day. The endoscopic response rate for the micafungin dose of 150 mg/day (98%) was comparable to that observed with fluconazole (95.8%) in this study.
2. The secondary outcome measures, clinical response at EOT, overall therapeutic response at EOT, and mycological response generally support the conclusions drawn for the primary efficacy endpoint.
3. The rate of EC relapse at 2 weeks post-treatment was similar for patients who received micafungin 150mg/day or fluconazole. No clear dose-response was observed for micafungin in EC relapse, except when all patients who received post-treatment systemic antifungal therapy were counted as having EC relapse.
4. Although the rate of OPC cure was similar in patients who received micafungin 150 mg/day or fluconazole, relapse rates at two weeks post-treatment were somewhat higher for patients who received micafungin than those who received fluconazole. The difference however, was not statistically significant.

6.1.5 Clinical Microbiology

See Dr Shukal Bala's Microbiology Review for full details regarding clinical microbiology. Most patients in each of the pivotal studies had *Candida albicans* isolated at baseline from esophageal biopsy or brushings. In study FG463-21-09, only 10 patients had *C. glabrata*, 4 had *C. tropicalis*, and 1 had *C. krusei*. Fifteen patients (6.9%) were infected with more than one *Candida* species. The number of patients with *Candida* species other than *C. albicans* was too small to draw conclusions regarding efficacy of micafungin in other *Candida* species.

In study 03-7-005, most patients were infected with *C. albicans* at baseline. Infections with more than one *Candida* species were identified in 7 patients in the micafungin treatment arm, and in 8 patients in the fluconazole treatment arm (Per Protocol Set). Micafungin efficacy was similar to fluconazole in the treatment of patients with infections due to *C. albicans*; however, the number of infections due to *Candida* species other than *C. albicans* was too small to draw conclusions regarding relative activity against these species.

From results of several different studies, FG463-21-02, 98-0-047, 97-7-003, and 03-7-005, the Microbiology reviewer concluded that micfungin was active against *C. albicans*, *C. tropicalis*, *C. glabrata*, *C. krusei*, and *C. parapsilosis*.

Clinical Review

Mary E. Singer, M.D., Ph.D.

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

***Medical Officer Comments:** These studies were not designed to determine the efficacy of micafungin for treatment of non-albicans Candida species, many of which may be resistant or susceptible in a dose-dependent manner to fluconazole. Additionally, the number of non-albicans isolates was small in both studies, so no firm conclusions can be drawn regarding treatment of EC in patients infected with Candida species other than C. albicans.*

6.1.6 Efficacy Conclusions

Micafungin was non-inferior to fluconazole for treatment of EC in the pivotal study 03-7-005, a phase 3, randomized, double-blind study. Non-inferiority of micafungin for this indication was demonstrated for the primary endpoint, endoscopic response at the end-of-therapy, as well as for the secondary endpoints, clinical response, overall therapeutic response, mycological response, and relapse at 2- and 4-weeks post-treatment.

These conclusions are supported by the second pivotal study for this review; study FG463-21-09, in which a clear dose-response for micafungin was demonstrated for the primary endpoint, endoscopic response. Although not designed as a non-inferiority study, micafungin at doses of either 100 or 150 mg/day was similar to fluconazole for endoscopic response, clinical response, and overall therapeutic response. Relapse at two weeks post-treatment was highest in patients who received 50 mg/day and 100 mg/day micafungin, and lowest in those received 150 mg/day micafungin or fluconazole.

***Medical Officer Comments:** The proposed dose of micafungin for treatment of EC, 150 mg/day, was based on these studies. An argument could be made that 100 mg/day micafungin was similar in efficacy to 150 mg/day in study FG463-21-09; however, although not statistically significant, EC relapse rates were higher in patients who received micafungin 100 mg/day than in those who received 150 mg/day in that study.*

Treatment of OPC was a secondary outcome measure in these studies. The rate of OPC cure was similar at the EOT in patients who received either fluconazole or micafungin in study 03-7-005; but relapse rates were higher in patients treated with micafungin. In study FG463-21-09, OPC cure rates at EOT were similar for the 150 mg/day dose of micafungin and fluconazole; however, although not statistically significant, a higher rate of relapse was observed in patients who received micafungin.

***Medical Officer Comments:** Although OPC is not proposed as an indication in this NDA, these studies do not support OPC as a treatment indication for micafungin labeling because of the higher relapse rates seen with micafungin than with fluconazole. We have proposed a section on treatment OPC, including relapse rates in the Clinical Studies section of the micafungin label.*

Clinical Review

Mary E. Singer, M.D., Ph.D.

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

Comparison of Micafungin to other Available Agents for Esophageal Candidiasis

Caspofungin, which is the only echinocandin antifungal agent currently licensed for marketing in the U.S., was compared to fluconazole for treatment of EC in a randomized double-blind study (Villanueva A, et al, Am J. Med. 2002; 113:294-9). In that study, treatment success for the primary endpoint, clinical and endoscopic cure or improvement, was 82 % of 83 patients treated with caspofungin and 85% of 94 patients treated with fluconazole, measured at 5-7 days post-treatment in the modified intent-to-treat (MITT) population. Endoscopic cure was reported in 73% of patients who received caspofungin, and in 81% of patients who received fluconazole. Relapse rates were 11% and 8% at 2 weeks post-treatment for caspofungin and fluconazole, respectively, and were 28% and 17% at 4 weeks post-therapy.

Medical Officer Comments: In study 03-7-005, the overall therapeutic response (clinical cure or improvement plus endoscopic cure or improvement) was 86% for micafungin and 87% for fluconazole in the MFAS (MITT) population (Table 13 above). Endoscopic cure was reported in 87% of patients who received micafungin, and in 87% of patients who received fluconazole (Table 11 above); and relapse rates were 17.9% and 13.6% at 2 weeks post-treatment for micafunin and fluconazole, respectively, and were 33% and 28% at 4 weeks in the MFAS population (Table 16 above). Overall, micafungin appears to have similar efficacy to caspofungin for treatment of EC, despite the differences in study design.

The efficacy of anidulafungin, an echinocandin not currently licensed in the U.S., was compared to fluconazole in a randomized, double-blind study for the treatment of EC (Krause DS, et al., Clin. Infect. Dis. 2004; 39:770-5). In this study, for the primary endpoint, endoscopic response, defined as cure or improvement from baseline, treatment success was reported in 97% of 249 patients treated with anidulafungin and 99% of 255 patients treated with fluconazole at the end of therapy in the Per Protocol Population.

Medical Officer Comments: In study 03-7-005, endoscopic cure at the EOT was reported in 97% of patients treated with micafungin, and in 95% of patients who received fluconazole in the Per Protocol Set. These response rates are similar to those reported with anidulafungin and fluconazole reported above.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

Background

The Sponsor submitted original micafungin NDAs (N21-506, _____) on April 29, 2002. N21-506 was deemed approvable for the prophylaxis _____ in patients undergoing hematopoietic stem cell transplantation pending the fulfillment of certain deficiencies. These included demonstration of efficacy and safety in the treatment of esophageal candidiasis, _____

Clinical Review

Mary E. Singer, M.D., Ph.D.

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

further evaluating interactions with relevant drugs, characterizing steady state kinetics of micafungin and its major metabolites, and evaluating the extent of protein binding of the parent drug. The safety review provides an overall assessment of the safety of micafungin from the resubmitted database and focuses on the safety of micafungin in the clinical areas of deficiency noted in the initial submission. In particular, the safety of the 150 mg dose is assessed in the pivotal esophageal candidiasis study. The [redacted] had evaluated the safety of the 50 mg (N21-506 -prophylaxis) and the 100 mg [redacted] (invasive candidiasis and aspergillosis) doses. The clinical and clinical pharmacology and biopharmaceutics reviews address the micafungin dose-response relationship from an efficacy and safety perspective. Finally, the interaction profile of micafungin from the original and resubmitted studies is evaluated. The following table shows the duration of micafungin exposure in patients evaluated for safety in NDA 21-506 and NDA 21-754 submissions.

Table 31. 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 NDA 21-506 submission (29 April, 2002) (from Dr. Ibia's review)						
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
Original NDA 21-754 submission (23 April, 2004)						
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 to NDA 21-754 (24 August, 2004)						
N	1049	270	357	529	197	2402
Total	19926	6846	774	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

The echinocandin class of antifungal drugs, of which micafungin is a member, inhibit fungal cell wall glucan synthesis. The applicant proposes that micafungin is unlikely to cause significant adverse events in humans due to the absence of a mammalian structural analogue for the fungal cell wall. However, *ex vivo* studies conducted by the applicant on red blood cells and hepatocytes indicate that a direct action on the cell membrane may also occur with micafungin, as is known to occur with the polyene amphotericin B and other members of the echinocandin drug class. Furthermore, a review of the drug's safety profile in the applicant's resubmission, as well as the postmarketing safety from Japan,

Clinical Review

Mary E. Singer, M.D., Ph.D.

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

reveals potential safety concerns for micafungin similar to other members of the echinocandin drug class. These include hepatic dysfunction, hemolysis, events associated with histamine release, and injection site reactions. These events were noted in the Medical Officer review of the original NDA [please see Dr. Ekopimo Ibia's Integrated Summary of Safety (ISS) review of NDAs 21-506,

Preclinical studies indicate that the primary target of micafungin toxicity is the liver. In all species tested, transaminase elevations and histologic changes ranging from discoloration, centrilobular hypertrophy, vacuolation, increased mitosis and single cell necrosis, were noted in the liver in these animals at doses 3-5 times the human equivalent dose (HED). Some of these changes were irreversible with increasing dose /duration of exposure (the reader is referred to Dr. Mc Master's review for details).

In addition, limited information in normal volunteers suggest that concomitant micafungin and immunosuppressant exposure was associated with transaminase elevations when micafungin was coadministered with tacrolimus (up to 3 times ULN) and mycophenolate (up to 8 times the ULN), respectively. These findings occurred in the absence of a significant pharmacokinetic interaction. Enhanced hepatic toxicity has previously been noted with concurrent echinocandin (caspofungin) and the immunosuppressant (cyclosporine) exposures. The increased caspofungin plasma levels that are caused by the interaction is theorized to be the basis for the enhanced toxicity. Paradoxically, radiolabel studies in rats indicate that cyclosporine inhibits hepatocyte uptake of caspofungin. On the other hand, *in vitro* studies indicate a possible homology between the echinocandin and immunosuppressant target, as concurrent cyclosporine and caspofungin exposure enhances activity against the echinocandin-resistant fungus *C neoformans*.

A preclinical signal for histamine mediated events was also noted with micafungin, as with the other approved member of the class of drugs, caspofungin. Increases in plasma histamine and heart rate were noted in rats that received micafungin at doses 3-5 times the HED. Other effects observed in the preclinical studies include hemolysis, and injection site reactions. An *in vitro* hemolysis assay indicates that micafungin induced red blood cell lysis at concentrations that are clinically relevant (see review by Dr. McMaster). This is consistent with preclinical findings of reduced erythrocytes, hemoglobin and hematocrit, temporally associated with hyperbilirubinemia. More chronic dosing is associated with increased nucleated red blood cells, elevated MCV, MCHC, passive splenic congestion, extramedullary hematopoiesis, and hypercellularity of the bone marrow.

A series of separate preclinical experiments indicates that the drug is well tolerated following a single injection of increasing concentrations of micafungin solution into a perivenular or intraarterial site in the rabbit. These recently completed studies were performed following the Agency's approvable action on the original NDA submission. However, repeat dose injection in the animals was associated with intravascular and

Clinical Review

Mary E. Singer, M.D., Ph.D.

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

pervascular irritation, ranging from cellular infiltration with inflammatory cells, perivascular hemorrhage, necrosis and fibrosis.

Several chronic dosing studies also indicate gender-related toxicity, with reduced sperm counts, reduced testicular volume and vaculation of the ductal epithelium in the epididymis. These findings were corroborated in several experiments and animal species. The reproductive toxicity NOAEL was 10 fold lower in males (3.2 mg/kg) compared to females (32mg/kg). On the other hand, the NOAEL for maternal effects in rabbits was 10mg/kg for abortions and 32 mg/kg for visceral abnormalities.

In vitro studies in guinea pig papillary muscle and hERG-transfected cells indicate that significant QT interval prolongation is not likely to occur with micafungin administration at clinically relevant doses. Preclinical studies in dogs and normal volunteer EKG studies performed at trough and C_{max} confirm the preclinical findings.

Conclusion and recommendations:

In the initial review of micafungin, the Agency concluded that “at the intended dose of micafungin and for the proposed indications, there appears to be no major safety concerns” that would preclude its availability would it prove efficacious in esophageal candidiasis. The review did “not reveal any safety issues among subjects on concomitant calcineurin inhibitors (cyclosporine and tacrolimus) or corticosteroids. 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 review.”

Upon review of the resubmission of NDA 21-506 (micafungin 50 mg in the prophylaxis of *Candida* infections in the hematopoietic stem cell transplant) and the new NDA 21-754 (micafungin 150 mg for the treatment of esophageal candidiasis) the Agency

- confirms the signal for hepatic and hematologic toxicity
- finds rare but serious events of anaphylaxis and renal insufficiency
- is unable to conclude that a safe dose has been characterized in pediatric patients.

However, in this resubmission, the applicant has successfully demonstrated efficacy of micafungin in the treatment of established *Candida* infection, whereas this was in doubt in the initial evaluation of the drug. The Agency therefore finds support for the availability of micafungin predicated on adequate communication risk through the negotiated label.

Materials Utilized in the Review

In addition to a review of the archival copy of NDA 21-754 the review team evaluated the following:

- the 120 day safety update submitted to NDA 21-754
- medical officer’s reviews of micafungin IND 55,322

Clinical Review

Mary E. Singer, M.D., Ph.D.

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

- medical officer's reviews of micafungin NDA 21-506,
- NDA 21-506 action package, including the approvable letter and subsequent correspondence between the applicant and FDA
- medical officer's review of Cancidas® (caspofungin), V-fend® (voriconazole), Ambisome® (liposomal amphotericin B), Sporonox® (itraconazole), and Abelcet® (amphotericin B colloidal dispersion), Neoral® (cyclosporine), CellCept® (mycophenolate mofetil) and Prograf® (tacrolimus).
- consult report from the ODS on the post-marketing safety of Cancidas®
- consult report from the ODS on the post-marketing safety of Micafungin
- consult report from Dr. John Senior on the post-marketing safety of Cancidas®
- Final Product Labels for Micafungin (translated from Japanese by the applicant), Cancidas® (caspofungin), V-fend® (voriconazole), Ambisome® (liposomal amphotericin B), Sporonox® (itraconazole), and Abelcet® (amphotericin B colloidal dispersion), Neoral® (cyclosporine), CellCept® (mycophenolate mofetil) and Prograf® (tacrolimus).

Method of Review:

The safety of micafungin in the applicant's original NDA 21-506 was previously reviewed by Drs. Ekopimo Ibia and Sary Beidas. The safety database in the original submission consisted of a total of 1582 patients and normal volunteers. The resubmitted NDA consisted of 2082, and the 120-day safety update consisted of 2402 patients and normal volunteers.

The following review methodology was pursued. The study reports of the studies listed for safety were reviewed, as were individual patient reports on deaths and serious adverse events. These were correlated with the findings from preclinical study reports. The safety findings were evaluated across all studies, and across various study populations and dosages, with an emphasis in patients that received the highest dose of micafungin for >10 days, as well as in studies where comparative safety data was available. A correlation of safety and drug exposure conducted by the applicant in subsets of patients was also evaluated. Evaluation of safety in the normal volunteer studies was similarly undertaken. Finally, a review of the 120 days safety update and Japanese post-marketing adverse event reports for micafungin was undertaken, the latter in consultation with the Office of Drug Safety (ODS).

The review of the aggregate deaths, severe adverse events, events leading to discontinuation, and common adverse events reflects the applicant's adverse event rates reported in the NDA submission. The 120 days safety report was separately reviewed in detail, and the findings do not materially alter the general conclusions on the safety of micafungin. However, as the pivotal study for esophageal candidiasis utilizing the highest label dose of micafungin (150 mg QD), was submitted with 120 day safety report, the sections on individual organ system includes this updated safety information to more accurately reflect the safety of micafungin. Likewise the data from the 120 days safety was the basis for the negotiated final label for the drug.

Clinical Review

Mary E. Singer, M.D., Ph.D.

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

This review evaluates the safety data for the individual studies submitted in support of the esophageal candidiasis, including that of the pivotal studies 03-7-005 and FG463-21-09, and the supporting study 97-7-003, in addition to the aggregate safety database, including organ-specific toxicities, _____ and adverse events reported in the Japanese postmarketing database. Dr. Joette Meyer reviewed the safety of micafungin in the pivotal study for prophylaxis of *Candida* infections (98-0-050).

In the course of review of the original NDA application for micafungin, the Office of Drug Safety (ODS) was requested to review the postmarketing spontaneous adverse event reports for an approved echinocandin, caspofungin, to evaluate whether any serious hepatic events had emerged post-approval. In their evaluation the ODS concluded that hyperbilirubinemia and possibly clinical liver disorders (including liver failure) could possibly be related to caspofungin, although this conclusions were limited by the small size of the utilization database. In this review cycle, the Division similarly consulted with the Office of Drug Safety and Dr. John Senior in its evaluation of the postmarketing and serious hepatic adverse events. These consults are appended to this review, following the medical officer reviews of the individual clinical trials in the NDA.

Brief Overview of Findings

The typical patient enrolled in the studies presented with complex comorbid conditions and/or received multiple concomitant medications. A total of 1581 human subjects (patients and normal volunteers) were evaluated for safety in the original NDA 21-506. In this submission, the number of subjects who received at least one dose of micafungin totalled 2402 subjects from 32 clinical studies or 821 more subjects than initially evaluated.

To separately evaluate the safety of micafungin in conditions of clinical use, an evaluation of safety for subjects that received at least 150 mg of micafungin for duration of 10 days is presented. In aggregate, 493 patients and 113 normal volunteers or 606 subjects have been exposed to a micafungin dose relevant to that proposed for esophageal candidiasis (150 mg/day). Additionally, the micafungin safety database contains 807 patients who received at least 100 mg/day micafungin for a minimum of 10 days. These also represent a population that has received exposures that are a multiple of the proposed prophylaxis dose (50 mg/day). The safety of higher dose exposures remains relevant for the prophylaxis indication given the current medical practice of dose escalation for patients who have not responded to initial doses of antifungals.

The adverse events observed in the 32 clinical studies completed in the micafungin drug development program indicate that hepatic toxicity, hemolysis, histamine mediated reactions, dermatologic, injections site reactions and phlebitis occur in normal volunteers and patients who receive micafungin. Several of these adverse events were noted in preclinical studies or are predicted from the experience with other drugs from the echinocandin class of antifungals. In addition, a review of the Japanese postmarketing experience uncovers several reports of the same adverse events, some of which have led to precautionary labeling in the Japanese package insert.

Clinical Review

Mary E. Singer, M.D., Ph.D.

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

The overall safety of micafungin was assessed in 2402 subjects (including 422 volunteers and 1980 patients) in 32 clinical studies. These studies were listed in Table 1, section 4.2 above. The applicant provided a summary of clinical safety with the initial NDA submission, received April 23, 2004, and with the 120 day safety update, received August 24, 2004. The former safety summary included safety data from 2083 subjects in 28 clinical studies, including the two studies originally designated as "pivotal" studies to assess efficacy of micafungin in esophageal candidiasis, studies FG463-21-09 and 97-7-003, and the supportive study for this indication, study 98-0-047. Safety data submitted previously with NDA 21-506 (29 April, 2002) is included with these clinical safety summaries. The 120-day safety update also included safety data from 5 additional non-clinical studies and from 4 additional clinical studies not included in the original submission. The following new clinical studies were included in the safety update:

1. Study 03-7-005, a phase 3, randomized, comparative trial (micafungin vs. fluconazole) in patients with esophageal candidiasis (subsequently designated as a pivotal study for this NDA);
2. Study 01-0-124, a phase 3 placebo-controlled study of micafungin for _____ . This study was stopped prematurely by the sponsor because of _____ after enrollment of 103 patients. Summaries of the data, and narrative for patients who died in this study were provided with the safety update, but a full study report and the study database were not included, but the applicant plans to submit them _____ in the future.
3. Study 01-0-125, a phase 2, open-label trial of micafungin in combination with liposomal amphotericin B (Ambisome®) as first-line treatment for invasive aspergillosis. This study was stopped prematurely by the applicant after enrollment of 2 patients because of study design issues. Neither of the patients completed the study, but both were included in the safety database, where relevant. Narrative summaries for these patients were also provided. The applicant plans to submit a final study report _____.
4. Study FG-463-21-14, a phase 1, pharmacokinetic study in healthy volunteers, using radiolabeled micafungin for collection of urine and feces for 28 days. The final report for this study was submitted with this NDA.

Safety data from study 04-0-193, a phase 1 study of safety and pharmacokinetics of steady-state micafungin and steady-state voriconazole in healthy volunteers, was not included in the integrated safety database, but was appended to the safety update.

Overall Safety Profile

The overall safety of micafungin was assessed in 1980 patients and 422 volunteers who received single or multiple doses of micafungin, ranging from 12.5 mg to ≥ 150 mg/day in 32 clinical studies. Of these, 606/2402 (25%) received at least 150 mg/day for a minimum of 10 days. The majority of these patients had esophageal candidiasis, however, patients with invasive aspergillosis also received the significant exposures with micafungin, including a patient who was treated with 150 mg for over 600 days, and

Clinical Review

Mary E. Singer, M.D., Ph.D.

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

another who received 200 mg of micafungin for over 300 days. Patients treated successfully for esophageal candidiasis received micafungin for a mean duration of 15 days (range 10-30 days), whereas hematopoietic stem cell transplant recipients where *Candida* infections were successfully prevented received a mean of 19 days (range 6-51 days) micafungin treatment.

Safety data was presented in the applicant's reports by summary of adverse events and changes in laboratory tests, and summary of significant and serious adverse events, including deaths. Adverse events were analyzed for relationship to drug exposure, intrinsic factors such as age, gender, race, underlying disease, renal and hepatic impairment, and extrinsic factors such as drug-drug interactions.

Adverse events in the micafungin safety database are summarized in the table below for all subjects (patients and volunteers) and all patients. None of the volunteer subjects had a serious adverse event or died during the clinical studies. 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.

Table 32. Summary of Adverse Events in Micafungin Safety database (from Applicant's Appendices 2.7.4.3.1, 2.7.4.3.2, Tables 6.1.1, 6.1.2, 7.1.1, 7.1.2, 8.1.1, and 8.1.2, 9.2.1, 9.2.2, 120-Day Safety Update)

Safety Parameter	Micafungin-Treated Subjects (Patients and Volunteers) N=2402	Micafungin-Treated Patients N=1980
Any Adverse Event	2028 (84.4%)	1824 (92.1%)
Drug-Related Adverse Events	717 (29.9%)	591 (29.8%)
Serious Adverse Events	554 (23.1%)	554 (28.0%)
Drug-Related Serious Adverse Events	72 (3.0%)	72 (3.6%)
Discontinuation due to Adverse Events	251 (10.4%)	245 (12.4%)
Discontinuation due to Drug-Related Adverse Event	73 (3.0%)	68 (3.4%)
Deaths	383 (15.9%)	383 (19.3%)
Drug-Related Deaths	2 (0.1%)	2 (0.1%)

As shown in the following table, comparison of the adverse event profile for MYCAMINE™ across studies reveals that adverse event rates in each category varied widely across the different patient populations, indicating the confounding influence of underlying disease and concomitant medication in adverse event evaluation. This factor should be taken into consideration in evaluating the integrated summary of safety for MYCAMINE™.

Clinical Review

Mary E. Singer, M.D., Ph.D.

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

Table 33. Comparative profile of adverse events in the various populations that received MYCAMINE

MICAFUNGIN					FLUCONAZOLE	
AE classification	Prophylaxis In HSCTR 98-0-050 (N=425) (%)	Esophageal candidiasis 03-7-005 (N=260) (%)	Invasive candidiasis 98-0-047 (N=353) (%)	Invasive Aspergillosis 98-0-046 (N=326)	Prophylaxis 98-0-050 400 mg (N=457) (%)	EC 03-7-005 200 mg (N=258) (%)
AEs	100	77.7	96.9	99.7	100.0	72.1
Serious AE	18.8	13.5	39.9	75.5	16.2	19.3
DRAE:	15.1	27.7	42.5	31.9	16.8	21.3
Serious DRAE:	0.9	1.2	6.2	11.8	2.2	0.3
Discontinuation:	4.2	6.2	20.1	28.1	7.2	3.9
DRAE w/ D/C:	2.6	2.3	6.8	2.8	3.5	0.8
Deaths:	4.2	11.5	29.7	56.1	5.7	10.9
Hepatic DRAE:	5.2	3.8	16.1	9.5	6.8	3.1
Renal DRAE:	0.7	1/260	1.7	3.7	1.3	0
Allergic/histamine DRAE:	3.5	9.2	7.1	4.3	3.9	3.1
Phlebitis/injection site reaction DRAE :	2.1	3.8	2.4	0.6	2.2	2.3

AEs= adverse events; DRAE= drug-related adverse events

Of 2402 patients evaluated for safety, close to a third, 28.3% (679/2402) received MYCAMINE for systemic fungal infections. These patients were generally sicker than patients with AIDS or who had HSCT and are briefly summarized below to enable an appreciation of the influence they would have made on the overall AE profile for MYCAMINE. The safety in patients with invasive aspergillosis from the original submission and in the safety update is shown in the following table.

Treatment regimen: 1-hr infusion QD (or min 3 d/wk if QD not feasible) MYCAMINE 75mg initial with 75 mg increments after 7 days. Treatment for 90 days or more (6wk follow-up). Efficacy failure could receive MYCAMINE + current antifungal or MYCAMINE alone.	AE classification	Original NDA 21-506 (N=128)	Resubmission 21-506 (N=326)
	AEs on study	100	99.7
	Severe AE	72.6	75.5
	DRAE:	33.9	31.9
	Deaths:	58.6	56.1
	Discontinuation:	28	28.1
	DRAE w/ D/C:	3.2	2.8
	Hepatic DRAE:	19.6	9.5
	Renal DRAE:	NA	3.7
	Allergic/histamine-release DRAE:	8.0	4.3
	Phlebitis/injection site reaction:	2.4	0.6

AEs= adverse events; DRAE= drug-related adverse events; NA=not available

Clinical Review

Mary E. Singer, M.D., Ph.D.

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

The safety experience in patients enrolled in the invasive aspergillosis study reflects some of the most extensive exposures with micafungin in the clinical drug development program. Several patients received doses of micafungin ≥ 150 mg for several days, including one patient that received 681 days and another who was treated with 200 mg of micafungin for 340 days. Eighty percent of the patients were receiving chemotherapy or had undergone a bone marrow transplant, 28% were neutropenic at baseline, half of the transplant recipients experienced graft-versus-host disease and were receiving immunosuppression. In this seriously ill population the evaluation of safety of a new drug is challenging and attribution of drug relationship is limited. Furthermore, only 69/325 (21%) of these patients received micafungin as the sole antifungal therapy, and the adverse event profile reflects the safety experience of patients on multiple concomitant therapies. Notable however is the fact that treatment discontinuation occurred only in 28% of patients. Overall safety in the invasive candidiasis/candidemia study is shown in the following table.

1-hr infusion QD (or min 3 d/wk if QD not feasible) MYCAMINE 75mg <i>initial with</i> 75 mg increments after 7 days. Treatment for 90 days or more (6wk follow-up). Efficacy failure could receive MYCAMINE + current antifungal or MYCAMINE alone.	AE classification	Original NDA 21-506 (N=250)	Resubmission 21-506 (N=353)
	AEs on study	96	96.9
	Severe AE	36.8	39.9
	DRAE:	47.6	42.5
	Deaths:	28.8	29.7
	Discontinuation:	18.8	20.1
	DRAE w/ D/C:	6.4	6.8
	Hepatic DRAE:	10.8	16.1
	Renal DRAE:	2.7	1.7
	Allergic/histamine-release DRAE:	5.9	7.1

AEs= adverse events; DRAE= drug-related adverse events

The resubmitted NDA presents safety data from over 300 patients who received therapy for candidemia and invasive candidiasis. The micafungin doses employed in this study are similar to those employed in the invasive aspergillosis therapy, including the option to use micafungin with other antifungal therapies. However, the adverse event profile in invasive candidiasis differed from the adverse event profile seen in invasive aspergillosis. Although similar proportions of patients experienced adverse events in both studies, the serious adverse event rate, death rate and rate of drug related adverse events in the invasive candidiasis study were less that reported with invasive aspergillosis. Of interest, however, the incidence of drug related hepatic adverse events in invasive candidiasis was close to twice that reported in invasive aspergillosis, whereas the converse was noted for renal adverse events.

The pivotal *Candida* prophylaxis study, 98-0-050 employed 50 mg of micafungin and 400 mg of fluconazole. The overall safety in this study is shown in the following table.

Clinical Review
 Mary E. Singer, M.D., Ph.D.
 Micafungin sodium for Esophageal Candidiasis
 Mycamine (Micafungin sodium)

Study 98-0-050 1-hr infusion QD <u>MYCAMINE</u> 50mg <u>FLUCONAZOLE</u> 400mg Maximum of 42 days (4-wk follow-up).	AE classification	MYCAMINE 50 mg (N=425, 402 in original NDA) (%)	Fluconazole 400 mg (N=457, 428 in original NDA) (%)
	AEs	100	100
	DRAE:	15.1	16.8
	Serious AEs	0.9	2.2
	Deaths:	4.2	5.7
	Discontinuation:	4.2	7.2
	Hepatic DRAE:	5.2	6.8
	Renal DRAE	0.7	1.3
	Injection site DRAE	2.1	2.2
	Histamine DRAE	3.5	3.9

AEs= adverse events; DRAE= drug-related adverse events

Despite the low dose of micafungin employed in the prophylaxis study, adverse events were universally reported in these patients. By contrast, however, a smaller proportion of events were considered drug related in these patients compared to the invasive aspergillosis, which had twice the rates of drug related events, and in invasive candidiasis, where the drug related adverse event rates were close to 3 times the rates reported in the prophylaxis studies. The overall rates of events in the categories of serious AEs, death, discontinuations, related hepatic and renal adverse events were numerically more frequent with fluconazole compared to micafungin. Note that the dose of fluconazole employed in this study is 8 times that used for micafungin

By contrast, the dose of micafungin (150 mg) used in the treatment of esophageal candidiasis more closely matched that of the comparator, fluconazole (200 gm). At these dose levels, all adverse events, drug related adverse events, deaths, discontinuations, related hepatic, renal, injection site and histamine mediated reactions were more numerous with micafungin than fluconazole.

Clinical Review
 Mary E. Singer, M.D., Ph.D.
 Micafungin sodium for Esophageal Candidiasis
 Mycamine (Micafungin sodium)

Table 37. Esophageal candidiasis: Safety in the pivotal Study 03-7-005			
Study 1-hr infusion QD	AE classification	MYCAMINE 150 mg (N=260) (%)	Fluconazole 200 mg (N=258) (%)
<u>MYCAMINE</u> 150 mg/day	AEs on study	77.7	72.1
<u>FLUCONAZOLE</u> 200mg/day Maximum of 42 days (4-wk follow-up).	DRAE:	27.7	21.3
	Serious AEs	13.5	9.3
	Deaths:	11.5	10.9
	Discontinuation:	6.2	3.9
	Hepatic DRAE:	3.8	3.1
	Renal DRAE	1/260	0
	Injection site	3.8	2.3
	Histamine DRAE	9.2	3.1

AEs= adverse events; DRAE= drug-related adverse events

Drug Related Adverse Events

Attribution of a relationship of adverse events to drug therapy is often limited due to the nature of fungal infections and the complicated clinical course of high risk patients. In the fluconazole comparative studies that consisted of less severely ill patients based on mortality rates of ~5% for HSCT recipients and 10% in untreated HIV with EC. Nonetheless, the adverse event rates were similar between the two treatment arms in either study population, as were the mortality rates. However, in the uncontrolled studies in patients with either invasive candidiasis or aspergillosis, there was a greater tendency to attribute adverse events to the study drug in the less severely ill invasive candidiasis population whereas fewer adverse events were attributed to drug in the sicker population of patients with invasive aspergillosis.

Clinical Review

Mary E. Singer, M.D., Ph.D.

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

Table 38. Incidence of Drug-Related Adverse Events in Studies 98-0-050, 98-0-047, 98-0-046, and 03-7-005

AE classification	Prophylaxis in HSCT 98-0-050		Proven systemic infection In ICU In HSCT		AIDS 03-7-005	
	MICA	FLU	MICA in Invasive Candida 98-0-047	MICA in Invasive Aspergillosis 98-0-046	MICA	FLU
Drug related adverse events	15.1	16.8	42.5	31.9	27.7	21.3
Deaths	4.2	5.7	28.7	56.1	11.5	10.9

Mica= Micafungin; AE= adverse event

Drug-related adverse experiences occurring in $\geq 0.5\%$ of the patients with esophageal candidiasis and in those who received antifungal prophylaxis are shown in the following table.

**APPEARS THIS WAY
ON ORIGINAL**

Clinical Review
Mary E. Singer, M.D., Ph.D.
Mycamine (Mycamfungin sodium)
Mycamine (Mycamfungin sodium)

Table 39. Common ($\geq 0.5\%$) Drug Related * Adverse Events Among Patients with Esophageal Candidiasis and in HSCT Recipients receiving Antifungal Prophylaxis

	Esophageal Candidiasis 03-7-005		Candida Prophylaxis 98-0-050	
	Mycamfungin 150 mg n (%)	Fluconazole 200 mg n (%)	Mycamfungin 50 mg n (%)	Fluconazole 400 mg n (%)
Number of Patients	260	258	425	457
All Systems	58 (22.3%)	50 (19.4%)	54 (12.7%)	72 (15.8%)
Blood and Lymphatic System				
Anemia	3 (1.2%)	4 (1.6%)	4 (0.9%)	3 (0.7%)
Eosinophilia	0	2 (0.8%)		
Leukopenia	7 (2.7%)	2 (0.8%)	4 (0.9%)	2 (0.4%)
Lymphopenia	2 (0.8%)	1 (0.4%)		
Neutropenia	3 (1.2%)	1 (0.4%)	5 (1.2%)	4 (0.9%)
Thrombocytopenia	3 (1.2%)	4 (1.6%)	4 (0.9%)	5 (1.1%)
Gastrointestinal Disorders				
Abdominal Pain	5 (1.9%)	4 (1.6%)	4 (0.9%)	3 (0.7%)
Nausea	6 (2.3%)	7 (2.7%)	10 (2.4%)	12 (2.6)
Vomiting	3 (1.2%)	4 (1.6%)	7 (1.6%)	5 (1.1%)
General Disorders and Administration Site Conditions				
Infusion Site Inflammation	4 (1.5%)	3 (1.2%)		
Pyrexia	5 (1.9%)	1 (0.4%)		
Rigors	6 (2.3%)	0		
Laboratory Tests Increased				
Alanine Aminotransferase	1 (0.4%)	5 (1.9%)	4 (0.9%)	9 (2.0%)
Aspartate Aminotransferase	2 (0.8%)	4 (1.6%)	3 (0.7%)	9 (2.0%)
Blood Alkaline Phosphatase	4 (1.5%)	4 (1.6%)		
Blood Lactate Dehydrogenase	2 (0.8%)	3 (1.2%)		
Transaminases	2 (0.8%)	1 (0.4%)	1 (0.2%)	4 (0.9%)
Metabolism and Nutrition Disorders				
Hypomagnesemia	0	3 (1.2%)	5 (1.2%)	6 (1.3%)
Hypokalemia			8 (1.9%)	8 (1.8%)
Nervous System Disorders				
Dizziness	1 (0.4%)	2 (0.8%)	0	5 (1.1%)
Headache	7 (2.7%)	3 (1.2%)	4 (0.9%)	4 (0.9%)
Somnolence	1 (0.4%)	7 (2.7%)		
Psychiatric Disorders				
Delirium	2 (0.8%)	2 (0.8%)		
Skin and Subcutaneous Tissue Disorders				
Pruritus	3 (1.2%)	3 (1.2%)	4 (0.9%)	3 (0.7%)
Rash	8 (3.1%)	5 (1.9%)	6 (1.4%)	4 (0.9%)
Vascular Disorders				
Phlebitis	11 (4.2%)	6 (2.3%)	Via central line	Via central line

Patient base: all randomized patients who received at least 1 dose of trial drug

*Relationship to drug was determined by the investigator to be possibly, probably, or definitely drug-related.

Despite the limitations in attribution, certain adverse events (bolded in the above table, excluding those due to a difference in a reported event) were more frequently reported

Clinical Review

Mary E. Singer, M.D., Ph.D.

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

with the 150 mg of micafungin than with the 50 mg dose. These include the events rash, headache and leukopenia.

The applicant summarized the key safety results by study in the 120-day safety update, as shown in the following table.

Table 40. Applicant's Summary of Micafungin Safety in Clinical Studies

Appendix Table 2.7.4.8: Key Safety Results By Study in Patient Studies

Study n { }	Regimen	M/F Age Range Race	Key Safety Results
03-7-0057 (NEH) 776 (523)	Once daily infusion of 150 mg FK463 or 200 mg fluconazole for a minimum of 14 days, or for 7 days after resolution of all clinical symptoms of esophageal candidiasis. The maximum allowable length of study drug administration was 42 days.	Micafungin: M 131 (50.4%), F 129 (49.6%); Age Range: 17.0 to 80.0 yrs; W 38 (14.6%), B 176 (67.7%), Mestizo: 33 (12.3%), Other: 14 (5.4%). Fluconazole: M 116 (45.0%), F 142 (55.0%); Age Range: 17 to 87.0 yrs; W 35 (13.6%), B 178 (69.0%), Mestizo 29 (11.2%); Other 16 (6.2%)	Overall AEs during the study: 77.7% (202/260) FK463 and 73.1% (186/258) FLU. DRAE: 27.7% (72/260) FK463 (more common: rash, phlebitis, headache, nausea, abdominal pain, chills) and 21.3% (55/258) FLU (more common: somnolence, nausea, phlebitis). Adverse events resulting in discontinuation: 6.2% (16/260) FK463, and 3.9% (10/258) FLU. DRAE leading to discontinuation: 2.3% (6/260) FK463, and 0.8% (2/258) FLU. Death rates were comparable and occurred in 30/260 (11.5%) FK463, and 38/258 (10.9%) FLU. Two patients in each group died during therapy, and the remainder died during posttreatment. Patient Number 10655006 (micafungin) died from progression of HIV; however, the investigator could not rule out the possibility that the death was related to study drug. Other serious adverse events occurred at an incidence of 13.5% (35/260) FK463 and 9.3% (24/258) FLU. Serious treatment related adverse events occurred in 1.2% (3/260) FK463, and 0.4% (1/258) FLU. Hepatic-related adverse events: 3.8% (10/260) FK463 and 3.1% (8/258) FLU. More than 80% of patients in both treatment groups had normal SGOT and SGPT values at baseline and end of treatment, and the incidence of elevated transaminase >3 X ULN at the end of treatment was 0.9% (1/114 FK463; 1/108 FLU) for both treatment groups. Renal-related adverse events: 1 (0.4%) FK463 and 0 FLU. There were minimal to no changes from baseline to the end of treatment for blood urea nitrogen and creatinine concentrations in either group. Injection-related adverse events: phlebitis 10/260 (3.8%) FK463 and 6/258 (2.3%) FLU, thrombophlebitis 1/260 (0.4%) and 0 FLU. Most treatment related injection site reactions were mild or moderate in intensity. Histamine-related adverse events: 17/260 (6.5%) FK463 and 11/258 (4.3%) FLU; rash was the most commonly reported allergic/histamine-release related adverse event (11/260, 4.2% FK463; 5/258, 1.9% FLU).

Table continued on next page

(Appendix Table 2.7.4.8 continued)

Study n { }	Regimen	M/F Age Range Race	Key Safety Results
97-7-0031 120 (89)	1-hour infusion once daily of 100.0, 75.0, 50.0, 25.0, or 12.5 mg of FK463 for 14 days to a maximum of 21 days (3-week follow-up).	M 43 (51.2%) F 41 (48.8%) Age Range: 19-59 yrs W 12 (14.3%) B 68 (81.0%) O 4 (4.8%)	Overall AEs during study: 75%; incidence tended to increase with dose level; lowest (57.7%) in 12.5 mg/day dose group and highest (87.5%) in 100 mg/day group. DRAE: 19.2% (more common: vomiting, LFT abnormal, nausea, rash); majority were mild or moderate intensity. Deaths: 3 while on therapy and 10 posttreatment; all due to progression of patient's underlying disease; none considered related to study drug. Serious DRAE: 1 patient (potentially life-threatening moderate diarrhea). DRAE resulting in discontinuation of study drug: 2 patients (1 increased LFTs, 1 moderate allergic reaction). LFTs/renal lab parameters: no consistent changes or dose-related trends from baseline to end of treatment. Infusion-related DRAE: 2 patients experienced chills; 1 patient experienced fever.
FC-463-21-09 245 (208)	1-hour infusion once daily of 50, 100, or 150 mg FK463 or 200 mg fluconazole for 14 days to a maximum of 28 days (2-week follow-up)	FK463 (EAS, n=185) M 89 (48.1%) F 96 (51.9%) Age Range: 19-68 yrs W 76 (41.1%) B 94 (50.8%) O 15 (8.1%) Fluconazole (FLU, EAS, n=60) M 28 (46.7%) F 32 (53.3%) Age Range: 19-56 yrs W 22 (36.7%) B 33 (53.3%) O 6 (10.0%)	Overall incidence of AEs during the study: 89.2% (FK463) and 93.3% (FLU), indicative of the overall morbidity of patients in this study. There was no apparent dose-related toxicity. DRAE incidence, for FK463, 49.7% (more common AEs were injection site inflammation, leukopenia, nausea, SGOT increased, and alkaline phosphatase increased); for FLU, 43.3% (more common AEs were injection site inflammation, leukopenia, nausea, and dizziness); most DRAEs were mild or moderate in severity. Deaths: 2 occurred prior to receiving any treatment; no deaths occurred during the treatment period; 10 deaths occurred during the 2-week follow-up period (9 FK463; 1 FLU). No death was considered related to study drug. Serious DRAEs: 1 FK463 50 mg/day (chills, hypotension, and vomiting); 4 FK463 100 mg/day (HIV dementia complex; allergic reaction in 2 patients; anaphylactoid reaction); 1 FK463 150 mg/day (leukopenia; rash); and 2 FLU (leukopenia; GI anomaly with flu syndrome, vaginal hemorrhage, and vaginitis). DRAEs that resulted in discontinuation of study drug occurred in 5.9% (11) of patients who received FK463 and 1.7% (1) of patients who received FLU. Injection site events were experienced by 11.4% of FK463-treated patients and 20.0% of FLU-treated patients. Phlebitis (4.3%) and thrombophlebitis (2.7%) were reported in FK463 treatments only.

Table continued on next page

Clinical Review

Mary E. Singer, M.D., Ph.D.

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

Table 40. (continued) Applicant's Summary of Micafungin Safety in Clinical Studies

(Appendix Table 2.7.4.8 continued)

Study n { }	Regimen	M/F Age Range Race	Key Safety Results
98-0-047s 353 (221)	1-hour infusion once daily (or minimum of 3 days/week if daily therapy was no longer feasible) Beginning dose of 50 mg/day FK463 (1 mg/kg/day weight ≤40 kg) that could be increased in 50 mg increments (1 mg/kg increments weight ≤40 kg) after 5 days. (Patients with <i>Candida non-albicans</i> infections could receive initial dose of 100 mg/day). Minimum of 6 weeks (6-week follow-up) Efficacy failure patients could receive micafungin and current systemic agent or micafungin alone.	M 201 (56.9%) F 152 (43.1%) Age range: 0-92 yrs W 130 (65.2%) B 51 (14.4%) O 72 (20.5%)	Overall AEs: 96.9% of all patients; 96.7% of de novo patients; 96.4% refractory/intolerant FK463 & other patients and 98.2% of refractory/intolerant FK463 alone patients. DRAE: 42.5% of all patients; more common events: SGOT increased (7.9%), hyponatremia (6.8%), SGPT increased (6.5%), leukopenia (6.2%), alkaline phosphatase increase (6.2%) and hypocalcemia (5.7%). Serious DRAE: 6.2% of all patients; more common events: hypokalemia (1.1%), thrombocytopenia (0.8%) and alkaline phosphatase increased (0.6%). Deaths: 29.7% of all patients; 26.0% of de novo, 36.1% of refractory/intolerant FK463 & other and 34.5% of refractory/intolerant FK463 alone. Fourteen patient deaths during study treatment; 91 patient deaths during posttreatment period. A total of 24 (6.8%) patients discontinued study drug due to a DRAE; 7.1% of patients had potential allergic/histamine-type DRAE; 16.1% of patients had hepatic DRAEs; minimal evidence of nephrotoxicity, but 1 patient discontinued due to acute renal failure and increased creatinine DRAEs.

Table continued on next page

(Appendix Table 2.7.4.8 continued)

Study n { }	Regimen	M/F Age Range Race	Key Safety Results
01-0-124f (NE/N) FK463: 51 (43) PBO: 51 (43)	30-minute infusion once daily. A dose of 100 mg/day FK463. Maximum of 42 days (3-week follow-up).	Micafungin: M 29 (57%) F 22 (43%) Age range: 19-84 yrs W 46 (90%) B 2 (4%) A 1 (2%) Am. Indian 1 (2%) Other 1 (2%) PBO: M 33 (63%) F 19 (37%) Age range: 17-88 yrs W 47 (92%) B 2 (4%) Am. Indian 1 (2%) Other 1 (2%)	Overall AEs: 92.2% (47/51) FK463 and 100% (51/51) PBO. DRAE: 11.8% (6/51) FK463, 9.8% (5/51) PBO (each AE occurred in one patient (FK463): cachexia, congestive heart failure, liver function tests abnormal, enzymatic abnormality, dizziness, hypoxia, rash); (each AE occurred in one patient (PBO): fever, blood bilirubin increased, atrial fibrillation, liver function tests abnormal, insomnia, sinusitis, herpes simplex). Adverse events resulting in discontinuation: 13.7% (7/51) FK463, 7.8% (4/51) PBO. DRAE leading to discontinuation: 5.9% (3/51) FK463, 0 PBO. DREA leading to discontinuation in the FK463 group: liver function tests abnormal, enzymatic abnormality, and hypoxia. Deaths: 9.8% (5/51) FK463, 15.7% (8/51) PBO. Primary cause of death: (FK463) pneumonia, respiratory failure, sepsis, and shock. Primary cause of death (PBO): hemorrhage, hepatic failure, infection, pneumonia, shock. No deaths were related to study drug. Two patients in each treatment group died during treatment; the remaining deaths occurred posttreatment. Serious AEs: other than death: 21.6% (11/51) FK463, 23.5% (12/51) PBO. More common SAEs (reported in more than 1 patient): (FK463) sepsis, respiratory failure, shock.; (PBO): shock, sepsis, pneumonia, hemorrhage, acidosis. Hepatic AEs: 9.8% (5/51) FK463, 19.6% (10/51) PBO. Related hepatic AEs: liver function tests abnormal (FK463) and liver function tests abnormal and blood bilirubin increased (PBO). Histamine release/allergic reaction AEs: 11.8% (6/51) FK463, 19.6% (10/51) PBO; related: (FK463) rash, (PBO) 0. Renal AEs: 11.8% (6/51) FK463, 9.8% (5/51) PBO; no related renal events. Injection site reactions: 2.0% (1/51) FK463, 9.8% (5/51) PBO; no related injection site reactions. Demographic, baseline characteristics, and safety data for patients in Study 01-0-124 are included in the tables for the 120-day Safety Update to NDA 21-754. Subject narratives for patients in the study who died or discontinued due to an adverse event are located in Attachment 8, and case report forms for such patients are located in Attachment 9. A final study report will be submitted to the IND when available.

Table continued on next page

Clinical Review

Mary E. Singer, M.D., Ph.D.

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

Table 40. (continued) Applicant's Summary of Micafungin Safety in Clinical Studies

(Appendix Table 2.7.4.8 continued)

Study n ({})	Regimen	MF Age Range Race	Key Safety Results
97-0-041# FK463 + fluconazole 62 (44) Control: Fluconazole + saline 12 (7)	FK463/saline: 1-hour infusion once daily; fluconazole: PO once daily (1-hour infusion if PO not possible) Maximum of 4 weeks (4-week follow-up). FK463 + fluconazole FK463: 12.5, 25, 50, 75, 100, 150, or 200 mg/day Fluconazole: 400 mg/day Fluconazole + saline 400 mg fluconazole; 100 mL normal saline infusion.	All randomized patients W 83.8%/B 16.2% FK463 + fluconazole M 20 (32%) F 42 (68%) Age range 19-65 yrs W 80.6%/B 19.4% Fluconazole + saline M 5 (42%) F 7 (58%) Age range: 20-56 yrs W 100%	Overall incidence of AE: 100% in both treatment arms, with no clinically significant differences between FK463 treated group and control and no evidence of dose dependent relationship. Deaths: 5, all during posttreatment; none related to study drug. Serious DRAE: FK463 2 patients (pancreatitis, atrial fibrillation) vs control 0. Discontinuation of study drug due to an AE: FK463 2 patients (1 [acute renal failure] unrelated to study drug; 1 [atrial fibrillation] possibly related to study drug) vs control 0. No changes in mean serum creatinine, AST, ALT, total bilirubin, and alkaline phosphatase levels from baseline to end of therapy for any FK463 dose level; no apparent dose relationship for these parameters within the FK463 dose levels, and no differences in these parameters between the FK463-treated group and control. No infusion-related or histamine-like reactions reported.
98-0-043# 77 (76)	1-hour infusion once daily. 0.5 mg/kg/day FK463. Escalation to 1.0, 1.5, 2.0, 3.0, and 4.0 mg/kg/day (up to 200 mg/day) for ages 2-12 until 2 patients in same age group experience the same dose limiting toxicity; because of slow enrollment highest dose studied for 13-17 year olds was 1.5 mg/kg/day. Maximum of 4 weeks (1-week follow-up).	M 44 (57.1%) F 33 (42.9%) Age range 2-17 yrs W 58 (75.3%) B 14 (18.2%) A 5 (6.5%)	No dose-related treatment-emergent AE noted. DRAE: 11.7% (each occurring in 1 or 2 patients [most common: diarrhea, headache and vomiting]; 3 severe events [vomiting, headache, bilirubinemia]). Deaths: 1 (due to septic shock) during study (not related to study drug); 1 after posttreatment period (due to pulmonary aspergillosis). Serious treatment emergent DRAE: None. Discontinuation of study drug due to AE: 2 patients (1 not related [subcutaneous hematoma] and 1 possibly related [severe headache] to study drug). Liver/kidney function: no clinically meaningful increases in mean serum creatinine, AST, ALT, total bilirubin, and alkaline phosphatase levels from baseline to end of therapy. Hepatic DRAE: 2 patients (moderate ALT elevated to day 3 only; severe bilirubinemia). Infusion-related AE: 1 patient developed chills; considered probably related to study drug. Allergic DRAE: none.

Table continued on next page

(Appendix Table 2.7.4.8 continued)

Study n ({})	Regimen	MF Age Range Race	Key Safety Results
EG-463-21-03 38 (24)	1-hour infusion once daily. 3.0, 4.0, 6.0, or 8.0 mg/kg/day FK463. Maximum of 28 days.	M 21 (64%) F 13 (56%) Age range: 19-63 yrs W 32 (88.9%) O 4 (11.1%)	No evidence of dose-limiting toxicity was noted. DRAE (all were mild or moderate) in at least 1 patient: injection-site reaction, fever, abdominal pain, asthenia, phlebitis, hypertension, diarrhea, dyspepsia, nausea, vomiting, bilirubinemia, hypervolemia, hypocalcemia, maculopapular rash, pruritus, rash, and albuminuria. Serious DRAE: none. Deaths: none. AE leading to treatment discontinuation: none. Hepatic lab values: generally, changes between baseline and end of treatment tended to be small; no differences among dosage groups noted in most instances. Renal lab values: generally, changes between baseline and end of treatment were small and showed no differences among dosage groups. No infusion related reactions reported. Injection-site reactions (including phlebitis): 6 incidents.
98-0-050 FK463 425 (402) Fluconazole 457 (428)	1-hour infusion once daily FK463 50 mg/day (1 mg/kg/day < 50 kg weight) Fluconazole 400 mg/day (8 mg/kg/day < 50 kg weight) Maximum of 42 days (4-week follow-up).	FK463 M 253 (59.5%) F 172 (40.5%) Age range 0.6-73.0 yrs W 387 (91.1%) B 30 (7.1%) O 8 (1.9%) Fluconazole M 274 (60.0%) F 183 (40.0%) Age range: 0.6-71.0 yrs W 411 (89.9%) B 37 (8.1%) O 9 (2.0%)	Overall incidence of AE while on study drug therapy: 100% in both treatment arms; with no apparent clinically significant differences between adult and pediatric patients. DRAE: FK463 15.1% (more common AE: bilirubinemia, nausea, diarrhea, hypokalemia, rash) vs fluconazole 16.8% (more common AE: diarrhea, bilirubinemia, nausea, LFT abnormal, AST and ALT increased). Serious DRAE: FK463 0.9% (bilirubinemia, hypoxia, rash) vs fluconazole 2.2% (more common AE: LFT abnormal, bilirubinemia, dyspnea). Discontinuation of study drug due to AE: FK463 4.2% vs fluconazole 7.2% (p=0.058). Deaths during study: FK463 4.2% vs fluconazole 5.7% (p=0.322); none were related to study drug. Hepatic DRAE: FK463 5.2% vs fluconazole 6.8%. Renal DRAE: FK463 0.7% vs fluconazole 1.3%. Infusion related reactions: FK463 0.5% vs fluconazole 0.9%. Injection-site AE: FK463 2.1% vs fluconazole 2.2%. Histamine-related events related to study drug: FK463 3.5% vs fluconazole 3.9%. There was no evidence of interaction between cyclosporine and FK463.

Table continued on next page

Clinical Review

Mary E. Singer, M.D., Ph.D.

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

Table 40. (continued) Applicant's Summary of Micafungin Safety in Clinical Studies

(Appendix Table 2.7.4.3 continued)

Study n { }	Regimen	MF Age Range Race	Key Safety Results
<p>FL463-0903⁴</p> <p>All patients 70 (49)</p> <p>(67 patients were safety evaluable; 3 patients met an exclusion criterion)</p>	<p>30-min infusion once daily for 25-, 50-, or 75 mg dose; 1-hour infusion once daily for ≥100 mg dose. Initial dose of 12.5, 25, 50 or 75 mg/day FK463 (or higher for immunocompromised patients with invasive aspergillosis or disseminated mycosis). After 7 days with no safety problems (4 days for esophageal candidiasis), dose increased to a maximum of 150 mg/day (7 to 28 days of treatment with a max. of 56 days).</p>	<p>All patients M 53 (79.1%) F 14 (20.9%) Age range: 26-77 yrs Asian (oriental) 67 (100%)</p>	<p>Safety results described herein are based on the 67 safety evaluable patients in the study report. The overall incidence of AEs while on study drug therapy: 76.1%; DRAE: 31.3%; DRAEs that occurred in 2 or more patients: increased alkaline phosphatase, BUN increased, creatinine increased, GTP increased, gamma-GTP increased, and phlebitis). Serious AEs: 13.4%; all unrelated except for one (decreased neutrophils). There were 9 deaths that occurred within 2 weeks after the final micafungin dose; all deaths were unrelated to micafungin with primary cause of aggravated mycosis and/or underlying disease/complication. A total of 9 patients discontinued the study due to an adverse event or abnormal laboratory value change; these events were not considered by the investigator to be related to study drug except for decreased neutrophils in 1 patient (serious AE); this patient recovered with appropriate treatment.</p> <p><i>NOTE: All 70 patients who received study drug are included in the integrated safety database.</i></p>

Table continued on next page

(Appendix Table 2.7.4.3 continued)

Study n { }	Regimen	MF Age Range Race	Key Safety Results
<p>01-0-125⁷</p> <p>(NEH)</p> <p>2 (0)</p>	<p>Combination therapy with FK463 + AmBisome®, once daily, with dosing as follows:</p> <p>FK463: 1-hour infusion once daily at a dose of 100 mg/day (or 2 mg/kg per day for patients weighing <40 kg).</p> <p>AmBisome®: 1 to 2-hour infusion once daily at a dose of 3 to 5 mg/kg.</p> <p>Combination therapy was to continue until one of the following occurred: patient had sufficient therapeutic response; patient received maximum of 24 days of treatment; patient requires therapy with other systemic antifungals; patient develops toxicity; patient declines further participation; Investigator decides it is best for patient to discontinue participation in study.</p>	<p>All patients 1 M (50%) 1 F (50%) 26 - 55 yrs 2 White</p>	<p>Two patients enrolled in this trial and did not complete the study.</p> <p>Demographic, baseline characteristics, and safety data for patients in Study 01-0-125 are included in the tables for the 120-day Safety Update to NDA 21-754. Subject narratives for patients in the study who died or discontinued due to an adverse event are located in Attachment 8, and case report forms for such patients are located in Attachment 9. A final study report will be submitted to the IND when available.</p>

Table continued on next page

Clinical Review

Mary E. Singer, M.D., Ph.D.

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

Table 40. (continued) Applicant's Summary of Micafungin Safety in Clinical Studies

(Appendix Table 2.7.4.8 continued)

Study n (%)	Regimen	MF Age Range Race	Key Safety Results
98-0-046§ 326(128)	1-hour infusion once daily (or minimum of 3 days/week if daily therapy was no longer feasible). Beginning dose of 75 mg/day FK463 (1.5 mg/kg/day weight ≤40 kg) that could be increased in 75 mg increments (1.5 mg/kg increments weight ≤40 kg) after 7 days to 225 mg/day (4.5 mg/kg per day weight ≤40 kg), or higher with PHL medical monitor's approval. 90 days or more with approval (6-week follow-up). Efficacy failure patients could receive micafungin plus current systemic antifungal agent or micafungin alone.	M 210 (64.4%) F 116 (35.6%) Age range: 0.2-84.0 yrs W 288 (88.3%) B 18 (5.5%) O 20 (6.1%)	Overall incidence of AEs while on study drug therapy: 99.7%; there were no clinically apparent differences in AEs reported in adult vs pediatric patients. DRAE: 31.9% (more common AE: bilirubinemia, nausea, vomiting, diarrhea, increased serum glutamic pyruvic transaminase [SGPT], increased alkaline phosphatase, hypertension). Deaths: 56.1% (183/326); 1 death considered related to study drug (pancytopenia). Serious DRAE (excluding non-fungal infections) other than death: 9.5% (more common AE: bilirubinemia, dyspnea, hypertension, leukopenia, and increased creatinine). DRAE (excluding non-fungal infections) resulting in discontinuation of study drug: 2.8%. Drug related phlebitis/injection site reaction: 2 patients (0.6%). Hepatic DRAE: 9.5% (majority mild or moderate in intensity). Kidney function DRAE: minimal evidence 3.7%. Allergic-type/histamine-release DRAE: 4.3%.

n = number in safety analysis; all patients who received at least 1 dose of study drug; {completed}; M: male; F: female; W: white; B: black; Am Indian: American Indian; A: Asian; O: other; (included Indian and colored in Study 97-7-003; mulatto, native Brazilian, cape coloured, coloured, and mestizo in Study FG-463-21-03; mestizo, oriental, American Indian, colored, cape colored, Hindu, Aboriginal, Polynesian and metis in Study 98-0-047; Arabic, Pakistani, Indian, and Asian in Study FG-463-21-03; Indian and Indian-Asian in Study 98-0-050; and oriental, Asian, mestizo, Asian Indian, Eastern Indian, Southeast Asian, coloured, and Egyptian in Study 98-0-046); Cape coloured, Cape coloured, coloured, mixed, mixed race, mulatto, mulatto, and multiracial in Study 03-7-005. AE: adverse event(s); DRAE: drug related adverse event(s); LFT: liver function tests; AST: aspartate aminotransferase; ALT: alanine aminotransferase; FHF: Fujisawa Healthcare, Inc.; BUN: blood urea nitrogen; SGPT: serum glutamate pyruvate transaminase; SGOT: serum glutamic oxaloacetic transaminase; GTP: glutamyl transpeptidase; N/A: not applicable; PBO: placebo

† This study is a new study submitted in the 120-Day Safety Update to NDA 21-754; a final report for Studies 03-7-005 and FG-463-21-14 are provided in Attachments 6 and 7, respectively. Final reports for Studies 01-0-124 and 01-0-125 will be submitted to IND 55,323 when available.

‡ This report was resubmitted in NDA 21-754 because it is one of the primary efficacy studies in esophageal candidiasis patients.

§ This study report was submitted as an interim report in NDA 21-506; a final report was included in NDA 21-754.

Pharmacokinetic data from this study was re-analyzed at the request of the Division of Special Pathogen and Immunologic Drug Products during review of NDA 21-506.

¶ An English Extended Synopsis was provided in NDA 21-506; a final, complete safety report was provided in NDA 21-754.

Safety in Relationship to Study Drug Exposure and Duration of Treatment

The experience with the 50 mg dose of micafungin, administered for a mean of 19 days, constituted almost half of the patient exposures in the safety database (19926/48379 patient-days) or 41.2%, whereas the exposures at the 150 mg dose for the treatment of esophageal candidiasis, represented 23.3% (11295/48379 patient-days) of the aggregate patient exposure experience.

Micafungin dose tolerance was evaluated in three maximum tolerated dose (MTD) studies, 97-0-041 and FG-463-21-03 (peripheral stem cell or bone marrow transplant recipients at from 12.5 to 200 mg per day or 3.0 to 8.0 mg/kg per day) and Study 98-0-043 (febrile neutropenic pediatric patients at doses of 0.5 to 4.0 mg/kg per day. The applicant concludes that the maximum tolerated dose was not reached [NDA 21-506, eNDA clinstat folder, Integrated Summary of Safety, Section 1.2.2], as the maximum dose received (8.0 mg/kg per day or 896 mg per day in an adult patient) was well tolerated.

Although the number of patient exposures above the usual dosing schedule for the approved indication is rather limited, it constitutes a source of information regarding the tolerance of these higher dose ranges or longer treatment durations. Exposures to doses above the therapeutic approved dose include 13 patients who received 200 mg of micafungin for over 60 days. Durations beyond the usual 14 day treatment course for esophageal candidiasis at the 150 mg/day dose consisted of one patient who received over 681 days of micafungin at that dose; whereas another received 200 mg of

Clinical Review

Mary E. Singer, M.D., Ph.D.

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

micafungin for 340 days. Micafungin exposure by mean daily dose and treatment duration is summarized in the following table.

Best Possible Copy

Table 41. Patient Drug Exposure by Mean Daily Dose and Treatment Duration
All Treated Patients (Appendix 2.7.4.1.1.1 of Applicant's 120-day Safety Update)

TREATMENT DURATION (DAYS)	MEAN DAILY DOSE (mg) (1)					TOTAL (N=2402)
	50 (N=1049)	75 (N=270)	100 (N=357)	150 (N=529)	200 (N=197)	
1 - 9	164 (25.2%)	70 (25.9%)	138 (38.7%)	38 (7.2%)	129 (65.5%)	639 (26.6%)
10 - 20	461 (43.9%)	88 (32.6%)	146 (40.9%)	405 (76.7%)	23 (11.7%)	1124 (46.8%)
21 - 60	297 (28.3%)	88 (32.6%)	57 (14.8%)	61 (11.5%)	32 (16.2%)	531 (22.1%)
> 60	27 (2.6%)	24 (8.9%)	20 (5.6%)	24 (4.5%)	13 (6.6%)	108 (4.5%)
TOTAL TREATMENT DURATION	19926	6846	7074	11295	3238	48379
RANGE OF TREATMENT DURATION	1 - 495	1 - 173	1 - 490	1 - 681	2 - 340	1 - 681
MEAN OF TREATMENT DURATION	19.0	25.4	19.8	21.4	16.4	20.1

The mean duration of treatment for all subjects was 20.1 days (range 1-681 days), with 73.4% of subjects treated for at least 10 days, compared to a mean treatment duration of 23.1 days (range 1-681 days) for patients, with a 82.0% of patients treated for at least 10 days, and a mean of 6.4 days for normal volunteers (range of 1-15 days) with 32.9% of volunteers receiving at least 10 days of exposure. The duration of micafungin therapy in patients treated for esophageal candidiasis is shown in the following table.

Table 42. Duration (days) of Micafungin Treatment in Patients with Esophageal Candidiasis
(Applicant's Table 4, 120-day Safety Update)

Study	n	Mean ±SD	Range	Median
03-7-005	n=260	14.3 ±3.68	1 - 33	14
FG-463-21-09	n=185	14.6 ±4.27	1 - 22	14
97-7-003	n=120	13.2 ±5.05	1 - 23	14
98-0-047	n=109	21.5 ±12.34	1 - 77	17

Subject base: Full analysis set for each study.

SD: Standard Deviation

The extent of micafungin exposure is further discussed in section 7.2 of this review. Long-term clinical safety studies in humans (or animals) have not been conducted because micafungin is not intended for long-term use.

Demographics of the Safety Database

Of the 2402 subjects, males comprised 62.0% of the population, likely reflecting the predominance of males in the normal volunteer studies, whereas females were better represented in the database of micafungin-treated patients. Several of the normal volunteer studies were performed in Japan, whereas the majority of the patients treated in the clinical studies were recruited from North American study sites.

The majority of patients were adults, with a mean age of 38.8 ± 18.2 years (range 1 week to 92 years) whereas 244 (12.3%) subjects were pediatric patients (<16 years of age) and 186 (7.7%) were elderly (≥65 years of age). Approximately half of the patients had underlying hematologic malignancies, one-third had HIV and the rest had other concurrent diseases of interest such as solid tumors, aplastic anemia, and other

Clinical Review

Mary E. Singer, M.D., Ph.D.

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

neoplasms; 29 were _____ and 30 subjects were solid organ transplant recipients. Patients were at high risk for fungal infection overall, with 946 of 1980 (47.8%) patients having a hematologic malignancy for which they were receiving chemotherapy, or were bone marrow or hematopoietic stem cell transplant (HSCT) recipients. Of the hematopoietic stem cell transplant recipients, 443/725 (61.1%) were recipients of an allogeneic transplant, and 282/725 (38.9%) were autologous transplant recipients. In addition, 254 of the 1980 patients (12.8%) were neutropenic on study entry. The patient population therefore constituted a segment of patients that were ill with multiple comorbidities, and on concurrent therapies, making attribution of adverse events extremely challenging. Nonetheless, the demographics of the micafungin- treated patients is likely representative of the population in whom micafungin will find clinical use.

**APPEARS THIS WAY
ON ORIGINAL**

Clinical Review

Mary E. Singer, M.D., Ph.D.

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

Table 43. Demographics (Micafungin Recipients) (Modified from Safety Appendix 2.7.4.2.1.1, 2.7.4.2.1.2 of Applicant's 120-day Safety Update)

Parameter	Class	Micafungin-Treated Subjects	Micafungin-Treated Patients
		(N=2402)	(N=1980)
Gender	Male	1489 (62.0%)	1127 (56.9%)
	Female	913 (38.0%)	853 (43.1%)
Study Site	North America	1273 (53.0%)	1061 (53.6%)
	South America	304 (12.7%)	304 (15.4%)
	Europe	240 (10.0%)	113 (5.7%)
	Asia	153 (6.4%)	70 (3.5%)
	Africa	432 (18.0%)	432 (21.8%)
Race	Caucasian	1519 (63.2%)	1228 (62.0%)
	Black	531 (22.1%)	504 (25.5%)
	Oriental	177 (7.4%)	93 (4.7%)
	Other	175(7.3%)	155 (7.8%)
Age Group	<16	244 (10.2%)	244 (12.3%)
	16 - <65	1972 (82.1%)	1573 (79.4%)
	>=65	186 (7.7%)	163 (8.2%)
Underlying disease	Hematologic malignancy	946 (39.4%)	946 (47.8%)
	HIV	670(27.9%)	670 (33.8%)
	Other	786 (32.7%)	364 (18.4%)
Transplant type	Autologous	282 (11.7%)	282 (14.2%)
	Allogeneic	443 (18.4%)	443 (22.4%)
	None	1677 (69.8%)	1255(63.4%)
Neutropenia	No	1015 (42.3%)	1015 (51.3%)
	Yes	254 (10.6%)	254 (12.8%)
	No information	1133 (47.2%)	711 (35.9%)

For comparative purposes, safety in clinical studies where fluconazole was used as a comparator was analyzed as a subset of the entire micafungin safety database. This included 932 patients (47% of the micafungin safety database) who were treated with micafungin and 787 patients who were treated with fluconazole in 4 clinical studies (03-7-005, FG463-21-09, 98-0-050, and 97-0-041). Patient demographics in this subgroup are shown in the table below.

Clinical Review

Mary E. Singer, M.D., Ph.D.

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

Table 44. Patient Demographics in Fluconazole-Controlled Studies*(Modified from Safety Appendix 2.7.4.2.1.3 of Applicant's 120-day Safety Update)

Parameter	Class	Micafungin-Treated Patients (N=932)	Fluconazole-Treated Patients (N=787)
Gender	Male	493 (52.9%)	423 (53.7%)
	Female	439 (47.1%)	364 (46.3%)
Study Site	North America	487 (52.3%)	469 (59.6%)
	South America	169 (18.1%)	108 (13.7%)
	Europe	-	-
	Asia	-	-
	Africa	276 (29.6%)	210 (26.7%)
Race	Caucasian	551 (59.1%)	480 (61.0%)
	Black	312 (33.5%)	247(31.4%)
	Oriental	5 (0.5%)	8 (1.0%)
	Other	64 (6.9%)	52 (6.6%)
Age Group	<16	39 (4.2%)	45 (5.7%)
	16 - <65	852(91.4%)	714 (90.7%)
	>=65	41 (4.4%)	28 (3.6%)
Underlying disease	Hematologic malignancy	487 (52.3%)	469 (59.6%)
	HIV	430 (46.1%)	301(38.2%)
	Other	15 (1.6%)	17 (2.2%)
Transplant type	Autologous	239 (25.6%)	207 (26.3%)
	Allogeneic	246 (36.4%)	262 (33.3%)
	None	447 (48.0%)	318 (40.4%)
Neutropenia	No	447 (48.0%)	437 (55.5%)
	Yes	39 (4.2%)	32 (4.1%)
	No information	446 (47.9%)	318 (40.4%)

* Fluconazole-controlled studies included 97-0-041, 98-0-050, FG463-21-09, and 03-7-005

7.1.1 Deaths

A total of 383 deaths occurred in 1980 patients (19.3%) in the clinical studies. A summary of study deaths by population and time of occurrence is shown in the table below. No deaths occurred in volunteers. Most deaths occurred in studies of patients with invasive candidiasis or candidemia, with 105 deaths of the 383 total deaths (27.4%) occurring in study 98-0-047, and with invasive aspergillosis, with 183 deaths of the 383 total deaths (47.7%) occurring in study 98-0-046. These studies were reviewed previously by Dr. Ekopimo Ibia for NDA 21-506. Narrative summaries for micafungin-treated patients that died in studies FG463-21-09, 97-7-003, and 03-7-005 are provided in individual study reports in Appendix 10, this review. Two deaths

Clinical Review

Mary E. Singer, M.D., Ph.D.

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

were considered possibly related to micafungin in the overall safety database. Narrative for patients whose death was considered related to micafungin are provided below.

Table 45. Overall mortality in Micafungin-treated patients (adapted from appendix 7.1.2, summary of clinical safety, 120-day update)

Deaths	All Micafungin-Treated Patients N=1980	Micafungin-Treated Patients in Fluconazole-Controlled Studies N=932	Fluconazole-Treated Patients in Fluconazole-Controlled Studies N=787
	n (%)	n (%)	n (%)
Total	383 (19.3)	65 (7.0)	56 (7.1)
Deaths related to study drug ¹	2 (0.1)	1 (0.1)	0
Deaths related to fungal infection ²	145 (7.3)	3 (0.3)	2 (0.3)
Deaths while on study	55 (2.8)	2 (0.2)	4 (0.5)
Deaths during post-treatment period	328 (16.6)	63 (6.8)	52 (6.6)

N=all patients in clinical safety database

n (%) = number and percentage of patients who died

¹ Relationship to study drug was assessed by investigator as definite, probable, or possibly related

² Fungal infection was listed as cause of death, or considered a contributing cause of death

***Medical Officer Comments:** The overall incidence of mortality was lower in fluconazole-controlled studies than in all clinical studies, probably due to differences in underlying disease, co-morbidities and severity of illness.*

However, a closer evaluation of the reported mortality in the invasive candidiasis study (98-0-047) indicates that the death rate among patients with esophageal candidiasis enrolled into this study was higher than anticipated. Following is an excerpt of the review of Dr. Ibia, who noted this in the original supplement: "mortality among the De Novo group of patients in the invasive candidiasis study...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

Clinical Review

Mary E. Singer, M.D., Ph.D.

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

relatively high mortality rate.” This unexpected finding illustrates the influence of comorbid factors, rather than the infection outcomes, on death.

In the combined fluconazole-controlled studies, 7.0% (65/932) micafungin-treated and 7.1% (56/787) fluconazole-treated patients died during the studies. In the phase 3 study for esophageal candidiasis, 03-7-005, the incidence of mortality was 11.5% (30/260) micafungin-treated, and 10.9% (28/258) fluconazole-treated patients; while in the phase 2 EC study, FG463-21-09, mortality was higher in the combined micafungin treatment groups, 7.0% (13/185) in comparison to the fluconazole group, 1.7% (1/60); but was similar to that observed in study 03-7-005. In both studies the median CD4 count was < 50 cells/mm³ for enrolled HIV patients, so there was no significant difference in the degree of immunosuppression at baseline, between these pivotal studies and study 98-0-047.

Narrative Summaries for Patients with Death Related to Micafungin

Patient 466171 (study 98-0-046), was a 44 year-old male with a history of chronic obstructive pulmonary disease on chronic corticosteroid therapy was initially treated for pulmonary aspergillosis with amphotericin B, 24 mg/day and 5-flucytosine 6400 mg per day, and micafungin 75 mg/day was added due to progressive disease. Micafungin dose was increased to 150 mg/day on study day 7. Flucytosine was stopped on study day 6, and amphotericin B was discontinued on day 10. Micafungin was stopped on day 10 due to pancytopenia, considered possibly related to study drug by the investigator. *Staphylococcus epidermidis* bacteremia and sepsis was reported on study day 10. The patient died on day 14 due to pancytopenia and pulmonary hemorrhage. An autopsy was not performed.

Medical Officer Comment: This case was confounded by the patient's receipt of at least one concomitant medication known to cause pancytopenia, flucytosine. In addition, pulmonary aspergillosis is not infrequently associated with pulmonary hemorrhage, particularly in the case of progressive disease. In the medical officer's opinion, this death was most likely unrelated to micafungin.

Patient 10655006 (study 03-7-005) was a 33 year-old black male from South Africa with HIV/AIDS, a CD4 count of 0 and esophageal candidiasis, treated with micafungin 150 mg/day for 12 days. Significant baseline conditions included pneumonia (possible tuberculosis), hypokalemia, oral hairy leukoplakia, syndrome of inappropriate antidiuretic hormone, chest wall pain, and insomnia. Prior to enrollment in the study, the patient was receiving metoclopramide, cotrimoxazole, and augmentin. He was not on antiretroviral therapy. The patient weighed 44.3 kg at baseline. Concomitant medications included those listed above, plus amitriptyline, rifampin (isoniazid, rifampin, ethambutol, and pyrazinamide) for suspected tuberculosis, amikacin, paracetamol, and diclofenac. Micafungin was stopped on day 12 due to HIV progression. The patient died on day 13 due to progressive HIV, and the investigator assessed the death as possible related to study drug.

Medical Officer Comments: Despite the fact that this patient was cachectic (44.3 kg) and would be considered as having "end-stage" AIDS, death due to HIV infection itself is

Clinical Review

Mary E. Singer, M.D., Ph.D.

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

uncommon, and is usually secondary to an opportunistic infection or malignancy, or to an HIV-related complication such as HIV nephropathy, dementia, or cardiomyopathy. Not enough information is provided in the narrative summary provided by the applicant or in the case report form to determine the actual cause of death in this patient, and an autopsy was not performed. Certainly, this patient could have died of an opportunistic infection, and in fact, was being treated empirically for pneumonia and tuberculosis. In the medical officer's opinion, this death was probably not related to micafungin.

The incidence of mortality was similar in patients who received ≥ 150 mg/day for at least 10 days, 14.2% (86 deaths in 606 patients) to those who received lower doses or durations of therapy, 16.5% (297 deaths in 1796 patients). Similarly, the incidence of mortality was similar in patients who received < 100 mg/day, 14.9% (120/807 patients), compared to those who received a minimum of 100 mg/day for 10 days or more, 16.5% (263/1595 patients).

Deaths were seen more frequently in Caucasian patients, 21.7% (267/1228) compared to black patients, 13.9% (70/504), although this likely reflects the severity of the underlying condition. Most black patients had underlying HIV/AIDS, 75.8% (382/504); while most of the Caucasian patients had underlying hematological malignancy, or had received a HSCT. Overall, patients with HIV/AIDS had a lower mortality, 12.7% (85/670) compared to patients with hematologic malignancies/HSCT, 22.5% (213/946) or other underlying diseases, 23.4% (85/364).

The age-related primary cause of death in micafungin-treated patients in the safety database is shown in Table __ below. The overall incidence of mortality was highest in patients > 65 years old (26.4%), but was similar in children < 16 years old (20.1%), and in patients between the ages of 16 and 65 (18.5%). As anticipated, deaths from a respiratory process were most frequently identified as a cause of death, and encompassed infections, which were also a major contributor to death. Of note, however, one death in a pediatric patient is listed as being due to "cerebral infarction". A review of the details from this case indicates that this 15 year old patient (ID# 404773 from Study 98-0-046) presented with convulsions on the 129th day of micafungin therapy and expired 4 days later from multiorgan failure and intracranial hemorrhage. This death was attributed to his underlying disease and did not appear to represent a vasculitic process related to micafungin therapy.

No cases of hepatic failure are reported to have occurred in pediatric patients. Nonetheless, a review of the deaths in the pediatric patients reveals one death due to autopsy proven adenoviral hepatitis.

Patient 262779 was a 2 year-old Caucasian female enrolled in study 98-0-046 who received chemotherapy for alveolar rhabdomyosarcoma, and developed a fungal sinusitis (*Aspergillus*) treated with micafungin. Total micafungin dose was 736 mg over 33 days. Bilirubinemia was first reported as an adverse event on day 9, and as a serious adverse event three weeks later. Interval events include the development of a respiratory adenovirus infection followed seizures on day 25. Micafungin was discontinued on day 33 due to lack of efficacy and the patient expired 4 days later. The patient died on day 37 and confirmed on postmortem examination to have adenovirus pneumonia, "massive adenoviral hepatitis" and aspergillosis. Although this

Clinical Review

Mary E. Singer, M.D., Ph.D.

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

death is likely unrelated to micafungin therapy, it is neither identified as a death due to adenoviral infection nor of fatal hepatitis in the listing of cause of death presented by the applicant, illustrating the limitations of attributability of adverse events. Furthermore, this patient did develop a hyperbilirubinemia on day 9, antedating the adenoviral pneumonia that became manifest only later in his course (see hepatic safety section for further details).

The primary cause of death by age group for patients enrolled in the clinical studies is shown in the following table. The most common cause of death for all age groups was attributable to the respiratory tract.

**APPEARS THIS WAY
ON ORIGINAL**

Clinical Review
 Mary E. Singer, M.D., Ph.D.
 Micafungin sodium for Esophageal Candidiasis
 Mycamine (Micafungin sodium)

Table 46. Primary Cause of Death in Micafungin-Treated Patients (from applicant's Appendix 7.6.2, Clinical Summary of Safety, Update, August, 2004)

BODY SYSTEM COSTART TERM	AGE GROUP (YEARS)			TOTAL (N=1980)
	< 16 (N=244)	16 TO <65 (N=1573)	>=65 (N=163)	
ALL SYSTEMS	49 (20.1%)	291 (18.5%)	43 (26.4%)	383 (19.3%)
RESPIRATORY SYSTEM				
ANY AE	19 (7.8%)	100 (6.4%)	10 (6.1%)	129 (6.5%)
RESPIRATORY FAILURE	6 (2.5%)	23 (1.5%)	3 (1.8%)	32 (1.6%)
PNEUMONIA	1 (0.4%)	24 (1.5%)	4 (2.5%)	29 (1.5%)
PULMONARY MYCOSIS	2 (0.8%)	17 (1.1%)	1 (0.6%)	20 (1.0%)
LUNG HEMORRHAGE	3 (1.2%)	5 (0.3%)	1 (0.6%)	9 (0.5%)
RESPIRATORY DISTRESS SYNDROME	2 (0.8%)	5 (0.3%)	0	7 (0.4%)
DYSPNEA	2 (0.8%)	3 (0.2%)	1 (0.6%)	6 (0.3%)
PULMONARY TUBERCULOSIS REACTIVATED	0	6 (0.4%)	0	6 (0.3%)
PULMONARY EMBOLUS	0	4 (0.3%)	0	4 (0.2%)
LUNG DISORDER	1 (0.4%)	2 (0.1%)	0	3 (0.2%)
LUNG FIBROSIS	0	3 (0.2%)	0	3 (0.2%)
INTERSTITIAL PNEUMONIA	1 (0.4%)	1 (0.1%)	0	2 (0.1%)
APNEA	0	1 (0.1%)	0	1 (0.1%)
EMPHYSEMA	0	1 (0.1%)	0	1 (0.1%)
HEMOPTYSIS	0	1 (0.1%)	0	1 (0.1%)
HYPOXIA	0	1 (0.1%)	0	1 (0.1%)
LUNG EDEMA	1 (0.4%)	0	0	1 (0.1%)
PLEURAL DISORDER	0	1 (0.1%)	0	1 (0.1%)
RESPIRATORY DISORDER	0	1 (0.1%)	0	1 (0.1%)
SINUSITIS	0	1 (0.1%)	0	1 (0.1%)
BODY AS A WHOLE				
ANY AE	10 (4.1%)	87 (5.5%)	10 (6.1%)	107 (5.4%)
SEPSIS	5 (2.0%)	32 (2.0%)	8 (4.9%)	45 (2.3%)
INFECTION	4 (1.6%)	11 (0.7%)	1 (0.6%)	16 (0.8%)
AIDS	0	10 (0.6%)	0	10 (0.5%)
GRAFT VERSUS HOST DISEASE	0	7 (0.4%)	0	7 (0.4%)
TUBERCULOSIS REACTIVATED	0	6 (0.4%)	0	6 (0.3%)
CACHEXIA	0	4 (0.3%)	0	4 (0.2%)
CARCINOMA	1 (0.4%)	3 (0.2%)	0	4 (0.2%)
RELAPSE OF PRIMARY MALIGNANCY	0	4 (0.3%)	0	4 (0.2%)
TUBERCULOSIS AGGRAVATED	0	4 (0.3%)	0	4 (0.2%)
GRAFT REJECTION	0	2 (0.1%)	0	2 (0.1%)
DEATH	0	1 (0.1%)	0	1 (0.1%)
MONILIASIS	0	1 (0.1%)	0	1 (0.1%)
NECROSIS	0	0	1 (0.6%)	1 (0.1%)
NEOPLASM BENIGN	0	1 (0.1%)	0	1 (0.1%)
PERITONITIS	0	1 (0.1%)	0	1 (0.1%)
CARDIOVASCULAR SYSTEM				
ANY AE	7 (2.9%)	57 (3.6%)	15 (9.2%)	79 (4.0%)

Table 46. (continued). Primary Cause of Death in Micafungin-Treated Patients (from applicant's Appendix 7.6.2, Clinical Summary of Safety, Update, August, 2004)

BODY SYSTEM COSTART TERM	AGE GROUP (YEARS)			TOTAL (N=1980)
	< 16 (N=244)	16 TO <65 (N=1573)	>=65 (N=163)	

Clinical Review
 Mary E. Singer, M.D., Ph.D.
 Micafungin sodium for Esophageal Candidiasis
 Mycamine (Micafungin sodium)

SHOCK	4 (1.6%)	37 (2.4%)	10 (6.1%)	51 (2.6%)
HEART ARREST	1 (0.4%)	5 (0.3%)	1 (0.6%)	7 (0.4%)
HEART FAILURE	1 (0.4%)	6 (0.4%)	0	7 (0.4%)
CONGESTIVE HEART FAILURE	0	2 (0.1%)	2 (1.2%)	4 (0.2%)
ENDOCARDITIS	1 (0.4%)	1 (0.1%)	2 (1.2%)	4 (0.2%)
ARRHYTHMIA	0	1 (0.1%)	0	1 (0.1%)
HEMORRHAGE	0	1 (0.1%)	0	1 (0.1%)
HYPOTENSION	0	1 (0.1%)	0	1 (0.1%)
INCREASED CAPILLARY FRAGILITY	0	1 (0.1%)	0	1 (0.1%)
MYOCARDIAL INFARCT	0	1 (0.1%)	0	1 (0.1%)
PERIPHERAL VASCULAR DISORDER	0	1 (0.1%)	0	1 (0.1%)
HEMIC AND LYMPHATIC SYSTEM				
ANY AE	4 (1.6%)	16 (1.0%)	5 (3.1%)	25 (1.3%)
ACUTE MYELOBLASTIC LEUKEMIA	2 (0.8%)	8 (0.5%)	1 (0.6%)	11 (0.6%)
LEUKEMIA	2 (0.8%)	1 (0.1%)	1 (0.6%)	4 (0.2%)
CHRONIC LYMPHOCYTIC LEUKEMIA	0	1 (0.1%)	2 (1.2%)	3 (0.2%)
LYMPHOMA	0	3 (0.2%)	0	3 (0.2%)
ACUTE LEUKEMIA	0	0	1 (0.6%)	1 (0.1%)
CHRONIC MYELOCYTIC LEUKEMIA	0	1 (0.1%)	0	1 (0.1%)
COAGULATION DISORDER	0	1 (0.1%)	0	1 (0.1%)
THROMBOCYTOPENIA	0	1 (0.1%)	0	1 (0.1%)
NERVOUS SYSTEM				
ANY AE	8 (3.3%)	16 (1.0%)	0	24 (1.2%)
INTRACRANIAL HEMORRHAGE	4 (1.6%)	4 (0.3%)	0	8 (0.4%)
CEREBROVASCULAR ACCIDENT	0	3 (0.2%)	0	3 (0.2%)
BRAIN EDEMA	1 (0.4%)	1 (0.1%)	0	2 (0.1%)
CEREBRAL HEMORRHAGE	0	2 (0.1%)	0	2 (0.1%)
ENCEPHALOPATHY	0	2 (0.1%)	0	2 (0.1%)
MENINGITIS	2 (0.8%)	0	0	2 (0.1%)
ACUTE BRAIN SYNDROME	0	1 (0.1%)	0	1 (0.1%)
CEREBRAL INFARCT	1 (0.4%)	0	0	1 (0.1%)
CONVULSION	0	1 (0.1%)	0	1 (0.1%)
ENCEPHALITIS	0	1 (0.1%)	0	1 (0.1%)
INTRACRANIAL HYPERTENSION	0	1 (0.1%)	0	1 (0.1%)

Clinical Review

Mary E. Singer, M.D., Ph.D.

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

Table 46. (continued) Primary Cause of Death in Micafungin-Treated Patients (from applicant's Appendix 7.6.2, Clinical Summary of Safety, Update, August, 2004)

DIGESTIVE SYSTEM				
ANY AE	0	9 (0.6%)	1 (0.6%)	10 (0.5%)
GASTROINTESTINAL HEMORRHAGE	0	4 (0.3%)	0	4 (0.2%)
VENOOCCLUSIVE LIVER DISEASE	0	3 (0.2%)	0	3 (0.2%)
HEPATIC FAILURE	0	2 (0.1%)	0	2 (0.1%)
GASTROINTESTINAL CARCINOMA	0	0	1 (0.6%)	1 (0.1%)
UROGENITAL SYSTEM				
ANY AE	1 (0.4%)	5 (0.3%)	1 (0.6%)	7 (0.4%)
KIDNEY FAILURE	1 (0.4%)	3 (0.2%)	0	4 (0.2%)
ACUTE KIDNEY FAILURE	0	2 (0.1%)	1 (0.6%)	3 (0.2%)
METABOLIC AND NUTRITIONAL DISORDERS				
ANY AE	0	1 (0.1%)	1 (0.6%)	2 (0.1%)
ACIDOSIS	0	1 (0.1%)	1 (0.6%)	2 (0.1%)

AE= adverse event

7.1.2 Other Serious Adverse Events

A serious adverse event was defined as any adverse event that resulted in death, was life-threatening, required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability/incapacity or congenital anomaly/birth defect, or was considered an important medical event.

Serious adverse events (SAEs) that occurred in micafungin-treated patients in the overall safety database are listed in the table below. No serious adverse events occurred in subjects in the volunteer studies. A total of 554 of 1980 micafungin-treated patients (28.0%) experienced an SAE. The most common SAEs were sepsis (4.2%), respiratory failure (3.8%), shock (2.4%), pneumonia (2.2%), fever (2.0%), hypotension (2.0%), dyspnea (1.9%), infection (1.5%), and kidney failure (1.4%).

Clinical Review
 Mary E. Singer, M.D., Ph.D.
 Micafungin sodium for Esophageal Candidiasis
 Mycamine (Micafungin sodium)

Table 47. Incidence of Serious Adverse Events in Micafungin-treated Patients (from applicant's Appendix 8.1.2, Clinical Safety Summary, Update, July, 2004)

BODY SYSTEM (1) COSTART TERM	Micafungin (N=1980)
	n (%)
ALL SYSTEMS	554 (28.0%)
RESPIRATORY SYSTEM	
ANY AE	217 (11.0%)
RESPIRATORY FAILURE	76 (3.8%)
PNEUMONIA	44 (2.2%)
DYSPNEA	38 (1.9%)
HYPOXIA	13 (0.7%)
RESPIRATORY DISTRESS SYNDROME	13 (0.7%)
LUNG EDEMA	11 (0.6%)
LUNG HEMORRHAGE	11 (0.6%)
RESPIRATORY DISORDER	11 (0.6%)
PULMONARY EMBOLUS	8 (0.4%)
HEMOPTYSIS	7 (0.4%)
LUNG DISORDER	7 (0.4%)
HYPERVENTILATION	4 (0.2%)
PNEUMOTHORAX	4 (0.2%)
PULMONARY TUBERCULOSIS REACTIVATED	4 (0.2%)
SINUSITIS	3 (0.2%)
COUGH INCREASED	2 (0.1%)
INTERSTITIAL PNEUMONIA	2 (0.1%)
LUNG FIBROSIS	2 (0.1%)
PLEURAL EFFUSION	2 (0.1%)
APNEA	1 (0.1%)
EMPHYSEMA	1 (0.1%)
EPISTAXIS	1 (0.1%)
PLEURAL DISORDER	1 (0.1%)
PULMONARY MYCOSIS	1 (0.1%)
BODY AS A WHOLE	
ANY AE	192 (9.7%)
SEPSIS	83 (4.2%)
FEVER	39 (2.0%)
INFECTION	29 (1.5%)
GRAFT VERSUS HOST DISEASE	12 (0.6%)
PROCEDURAL COMPLICATION	11 (0.6%)
AIDS	8 (0.4%)
ABSCESS	6 (0.3%)
ASTHENIA	6 (0.3%)
ABDOMINAL PAIN	5 (0.3%)
ALLERGIC REACTION	5 (0.3%)
CACHEXIA	5 (0.3%)

N= number of patients in integrated safety database

n(%)- number and percentage of patients with SAE (serious adverse event)

(1) Patients could have more than one SAE reported

Clinical Review

Mary E. Singer, M.D., Ph.D.

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

Table 47.(continued) Incidence of Serious Adverse Events in Patients (from applicant's Appendix 8.1.2, Clinical Safety Summary, Update, July, 2004

BODY SYSTEM (1) FK463
 COSTART TERM (N=1980)

TUBERCULOSIS REACTIVATED	5 (0.3%)
PAIN	4 (0.2%)
TUBERCULOSIS AGGRAVATED	4 (0.2%)
ASCITES	3 (0.2%)
CHILLS	3 (0.2%)
GRAFT REJECTION	3 (0.2%)
RELAPSE OF PRIMARY MALIGNANCY	3 (0.2%)
ANAPHYLACTOID REACTION	2 (0.1%)
CELLULITIS	2 (0.1%)
SARCOMA	2 (0.1%)
ABDOMEN ENLARGED	1 (0.1%)
ACCIDENTAL INJURY	1 (0.1%)
CARCINOMA	1 (0.1%)
HERNIA	1 (0.1%)
NECROSIS	1 (0.1%)
OVERDOSE	1 (0.1%)
PERITONITIS	1 (0.1%)
PRIMARY GRAFT DYSFUNCTION	1 (0.1%)
TRANSFUSION REACTION	1 (0.1%)
CARDIOVASCULAR SYSTEM	
ANY AE	154 (7.8%)
SHOCK	48 (2.4%)
HYPOTENSION	39 (2.0%)
ATRIAL FIBRILLATION	14 (0.7%)
HEART ARREST	13 (0.7%)
DEEP THROMBOPHLEBITIS	7 (0.4%)
HYPERTENSION	7 (0.4%)
PERICARDIAL EFFUSION	7 (0.4%)
CONGESTIVE HEART FAILURE	6 (0.3%)
TACHYCARDIA	6 (0.3%)
CHEST PAIN	5 (0.3%)
HEART FAILURE	5 (0.3%)
HEMORRHAGE	5 (0.3%)
ARRHYTHMIA	4 (0.2%)
BRADYCARDIA	4 (0.2%)
PERIPHERAL VASCULAR DISORDER	3 (0.2%)
SUBDURAL HEMATOMA	3 (0.2%)
ATRIAL FLUTTER	2 (0.1%)
CARDIOMYOPATHY	2 (0.1%)
ELECTROCARDIOGRAM ABNORMAL	2 (0.1%)
PERICARDITIS	2 (0.1%)

N= number of patients in integrated safety database

n(%)- number and percentage of patients with SAE (serious adverse event)

(1) Patients could have more than one SAE reported

Clinical Review
 Mary E. Singer, M.D., Ph.D.
 Micafungin sodium for Esophageal Candidiasis
 Mycamine (Micafungin sodium)

Table 47.(continued) Incidence of Serious Adverse Events in Patients (from applicant's Appendix 8.1.2, Clinical Safety Summary, Update, July, 2004

BODY SYSTEM (1) COSTART TERM	Micafungin (N=1980) n (%)
VENTRICULAR TACHYCARDIA	2 (0.1%)
ARTERIAL ANOMALY	1 (0.1%)
ENDOCARDITIS	1 (0.1%)
INCREASED CAPILLARY FRAGILITY	1 (0.1%)
MESENTERIC OCCLUSION	1 (0.1%)
MYOCARDIAL INFARCT	1 (0.1%)
PALPITATION	1 (0.1%)
POSTURAL HYPOTENSION	1 (0.1%)
SYNCOPE	1 (0.1%)
THROMBOPHLEBITIS	1 (0.1%)
THROMBOSIS	1 (0.1%)
VASODILATATION	1 (0.1%)
DIGESTIVE SYSTEM	
ANY AE	82 (4.1%)
GASTROINTESTINAL HEMORRHAGE	14 (0.7%)
DIARRHEA	9 (0.5%)
VOMITING	9 (0.5%)
HEPATIC FAILURE	8 (0.4%)
MUCOSITIS	7 (0.4%)
LIVER FUNCTION TESTS ABNORMAL	6 (0.3%)
NAUSEA	4 (0.2%)
VENOOCCLUSIVE LIVER DISEASE	4 (0.2%)
GASTROINTESTINAL DISORDER	3 (0.2%)
LIVER DAMAGE	3 (0.2%)
GASTROINTESTINAL CARCINOMA	2 (0.1%)
INTESTINAL OBSTRUCTION	2 (0.1%)
PANCREATITIS	2 (0.1%)
RECTAL HEMORRHAGE	2 (0.1%)
STOMATITIS	2 (0.1%)
ANOREXIA	1 (0.1%)
BILE DUCT DISORDER	1 (0.1%)
CHOLECYSTITIS	1 (0.1%)
CHOLELITHIASIS	1 (0.1%)
COLITIS	1 (0.1%)
DYSPHAGIA	1 (0.1%)
ENTERITIS	1 (0.1%)
ENTEROCOLITIS	1 (0.1%)
GASTRITIS	1 (0.1%)
GASTROENTERITIS	1 (0.1%)
GUM/ORAL HEMORRHAGE	1 (0.1%)
HEMATEMESIS	1 (0.1%)

N= number of patients in integrated safety database

n(%)- number and percentage of patients with SAE (serious adverse event)

(1) Patients could have more than one SAE reported

Clinical Review
 Mary E. Singer, M.D., Ph.D.
 Micafungin sodium for Esophageal Candidiasis
 Mycamine (Micafungin sodium)

Table 47. (continued) Incidence of Serious Adverse Events in Patients (from applicant's Appendix 8.1.2, Clinical Safety Summary, Update, July, 2004

BODY SYSTEM (1) COSTART TERM	n (%)	Micafungin (N=1980)
HEPATOMEGALY	1 (0.1%)	
INTESTINAL PERFORATION	1 (0.1%)	
JAUNDICE	1 (0.1%)	
RECTAL DISORDER	1 (0.1%)	
STOMACH ULCER HEMORRHAGE	1 (0.1%)	
VIRAL HEPATITIS	1 (0.1%)	
NERVOUS SYSTEM		
ANY AE	72 (3.6%)	
CONVULSION	18 (0.9%)	
INTRACRANIAL HEMORRHAGE	7 (0.4%)	
CONFUSION	6 (0.3%)	
ENCEPHALOPATHY	6 (0.3%)	
MENINGITIS	6 (0.3%)	
THINKING ABNORMAL	6 (0.3%)	
CEREBRAL HEMORRHAGE	5 (0.3%)	
COMA	5 (0.3%)	
DELIRIUM	4 (0.2%)	
CEREBROVASCULAR ACCIDENT	3 (0.2%)	
NEUROPATHY	3 (0.2%)	
STUPOR	3 (0.2%)	
HEMIPLEGIA	2 (0.1%)	
ACUTE BRAIN SYNDROME	1 (0.1%)	
ANXIETY	1 (0.1%)	
BRAIN ABSCESS	1 (0.1%)	
BRAIN EDEMA	1 (0.1%)	
CNS NEOPLASIA BENIGN	1 (0.1%)	
DEMENTIA	1 (0.1%)	
DIZZINESS	1 (0.1%)	
FLACCID PARALYSIS	1 (0.1%)	
HEADACHE	1 (0.1%)	
HYPERTONIA	1 (0.1%)	
SPEECH DISORDER	1 (0.1%)	
SUBARACHNOID HEMORRHAGE	1 (0.1%)	
VERTIGO	1 (0.1%)	
WITHDRAWAL SYNDROME	1 (0.1%)	
HEMIC AND LYMPHATIC SYSTEM		
ANY AE	63 (3.2%)	
LEUKOPENIA	16 (0.8%)	
THROMBOCYTOPENIA	13 (0.7%)	
ACUTE MYELOBLASTIC LEUKEMIA	6 (0.3%)	

N= number of patients in integrated safety database

n(%)- number and percentage of patients with SAE (serious adverse event)

(1) Patients could have more than one SAE reported

Clinical Review
 Mary E. Singer, M.D., Ph.D.
 Micafungin sodium for Esophageal Candidiasis
 Mycamine (Micafungin sodium)

Table 47. (continued) Incidence of Serious Adverse Events in Patients (from applicant's Appendix 8.1.2, Clinical Safety Summary, Update, July, 2004

BODY SYSTEM (1) COSTART TERM	Micafungin (N=1980) n(%)
ANEMIA	6 (0.3%)
COAGULATION DISORDER	6 (0.3%)
CYANOSIS	3 (0.2%)
LEUKEMIA	3 (0.2%)
PANCYTOPENIA	3 (0.2%)
HEMOLYSIS	2 (0.1%)
LYMPHADENOPATHY	2 (0.1%)
LYMPHOMA	2 (0.1%)
ACUTE LYMPHOBLASTIC LEUKEMIA	1 (0.1%)
CHRONIC LYMPHOCYTIC LEUKEMIA	1 (0.1%)
CHRONIC MYELOCYTIC LEUKEMIA	1 (0.1%)
ERYTHROCYTES ABNORMAL	1 (0.1%)
HYPOCHROMIC ANEMIA	1 (0.1%)
LEUKOCYTOSIS	1 (0.1%)
THROMBOTIC THROMBOCYTOPENIC PURPURA	1 (0.1%)
METABOLIC AND NUTRITIONAL DISORDERS	
ANY AE	63 (3.2%)
BILIRUBINEMIA	11 (0.6%)
CREATININE INCREASED	8 (0.4%)
DEHYDRATION	8 (0.4%)
HYPOKALEMIA	8 (0.4%)
ACIDOSIS	7 (0.4%)
BUN INCREASED	6 (0.3%)
HYPERGLYCEMIA	4 (0.2%)
HYPERVOLEMIA	4 (0.2%)
RESPIRATORY ACIDOSIS	4 (0.2%)
ALKALINE PHOSPHATASE INCREASED	3 (0.2%)
HYPERKALEMIA	3 (0.2%)
ELECTROLYTE ABNORMALITY	2 (0.1%)
HYPONATREMIA	2 (0.1%)
SGOT INCREASED	2 (0.1%)
AMYLASE INCREASED	1 (0.1%)
EDEMA	1 (0.1%)
ENZYMATIC ABNORMALITY	1 (0.1%)
HEALING ABNORMAL	1 (0.1%)
HYPOGLYCEMIA	1 (0.1%)
HYPOPHOSPHATEMIA	1 (0.1%)
HYPOVOLEMIA	1 (0.1%)
LACTIC DEHYDROGENASE INCREASED	1 (0.1%)
SGPT INCREASED	1 (0.1%)

N= number of patients in integrated safety database

n(%)- number and percentage of patients with SAE (serious adverse event)

(1) Patients could have more than one SAE reported

Clinical Review
 Mary E. Singer, M.D., Ph.D.
 Micafungin sodium for Esophageal Candidiasis
 Mycamine (Micafungin sodium)

Table 47. (continued) Incidence of Serious Adverse Events in Patients (from applicant's Appendix 8.1.2, Clinical Safety Summary, Update, July, 2004

BODY SYSTEM (1) COSTART TERM	n (%)	Micafungin (N=1980)
UROGENITAL SYSTEM		
ANY AE	58 (2.9%)	
KIDNEY FAILURE	27 (1.4%)	
ACUTE KIDNEY FAILURE	10 (0.5%)	
HEMORRHAGIC CYSTITIS	5 (0.3%)	
HEMATURIA	4 (0.2%)	
KIDNEY FUNCTION ABNORMAL	3 (0.2%)	
OLIGURIA	3 (0.2%)	
URINARY TRACT INFECTION	3 (0.2%)	
KIDNEY TUBULAR NECROSIS	2 (0.1%)	
ANURIA	1 (0.1%)	
CARCINOMA RENAL	1 (0.1%)	
PENIS DISORDER	1 (0.1%)	
SKIN AND APPENDAGES		
ANY AE	12 (0.6%)	
RASH	4 (0.2%)	
HERPES ZOSTER	3 (0.2%)	
FURUNCULOSIS	1 (0.1%)	
HERPES SIMPLEX	1 (0.1%)	
MACULOPAPULAR RASH	1 (0.1%)	
SKIN NECROSIS	1 (0.1%)	
URTICARIA	1 (0.1%)	
SPECIAL SENSES		
ANY AE	8 (0.4%)	
RETINITIS	2 (0.1%)	
ABNORMAL VISION	1 (0.1%)	
DIPLOPIA	1 (0.1%)	
EAR DISORDER	1 (0.1%)	
EAR PAIN	1 (0.1%)	
MIOSIS	1 (0.1%)	
PAPILLEDEMA	1 (0.1%)	
MUSCULOSKELETAL SYSTEM		
ANY AE	3 (0.2%)	
ARTHRALGIA	2 (0.1%)	
JOINT DISORDER	1 (0.1%)	

N= number of patients in integrated safety database

n(%)- number and percentage of patients with SAE (serious adverse event)

(1) Patients could have more than one SAE reported

Those serious adverse events considered drug-related were reported in 3.6 % (72/1980) patients, and are shown in the table below. The most drug-related common serious adverse events were bilirubinemia (0.3%), hypokalemia (0.2%), leukopenia (0.2%), thrombocytopenia (0.2%), atrial fibrillation (0.2%), hypotension (0.2%), dyspnea (0.2%), hypoxia (0.2%), allergic reaction (0.2%), and rash (0.2%).

Clinical Review

Mary E. Singer, M.D., Ph.D.

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

Table.48. Incidence of Drug-Related Serious Adverse Events in Patients who received Micafungin (Applicant's Appendix 8.8, 120 day Safety Update)

BODY SYSTEM (1) FK463
COSTART TERM (N=1980)

-----	-----
ALL SYSTEMS	72 (3.6%)
METABOLIC AND NUTRITIONAL DISORDERS	
ANY AE	16 (0.8%)
BILIRUBINEMIA	5 (0.3%)
HYPOKALEMIA	4 (0.2%)
ALKALINE PHOSPHATASE INCREASED	3 (0.2%)
CREATININE INCREASED	3 (0.2%)
SGOT INCREASED	2 (0.1%)
BUN INCREASED	1 (0.1%)
HYPONATREMIA	1 (0.1%)
SGPT INCREASED	1 (0.1%)
HEMIC AND LYMPHATIC SYSTEM	
ANY AE	13 (0.7%)
LEUKOPENIA	4 (0.2%)
THROMBOCYTOPENIA	4 (0.2%)
PANCYTOPENIA	2 (0.1%)
ANEMIA	1 (0.1%)
COAGULATION DISORDER	1 (0.1%)
CYANOSIS	1 (0.1%)
HEMOLYSIS	1 (0.1%)
CARDIOVASCULAR SYSTEM	
ANY AE	12 (0.6%)
ATRIAL FIBRILLATION	3 (0.2%)
HYPOTENSION	3 (0.2%)
HYPERTENSION	2 (0.1%)
HEART ARREST	1 (0.1%)
PALPITATION	1 (0.1%)
PERIPHERAL VASCULAR DISORDER	1 (0.1%)
THROMBOPHLEBITIS	1 (0.1%)
VASODILATATION	1 (0.1%)
RESPIRATORY SYSTEM	
ANY AE	9 (0.5%)
DYSPNEA	4 (0.2%)
HYPOXIA	3 (0.2%)
PULMONARY EMBOLUS	2 (0.1%)
BODY AS A WHOLE	
ANY AE	8 (0.4%)

Clinical Review
Mary E. Singer, M.D., Ph.D.
Micafungin sodium for Esophageal Candidiasis
Mycamine (Micafungin sodium)

Table.48 (continued) Incidence of Drug-Related Serious Adverse Events in Patients who received Micafungin (Applicant's Appendix 8.8, 120 day Safety Update)

BODY SYSTEM (1) COSTART TERM	FK463 (N=1980)
-----	-----
ALLERGIC REACTION	3 (0.2%)
FEVER	2 (0.1%)
AIDS	1 (0.1%)
ANAPHYLACTOID REACTION	1 (0.1%)
CHILLS	1 (0.1%)
NERVOUS SYSTEM	
ANY AE	8 (0.4%)
DELIRIUM	2 (0.1%)
ANXIETY	1 (0.1%)
CEREBRAL HEMORRHAGE	1 (0.1%)
CONFUSION	1 (0.1%)
DEMENTIA	1 (0.1%)
MENINGITIS	1 (0.1%)
NEUROPATHY	1 (0.1%)
DIGESTIVE SYSTEM	
ANY AE	7 (0.4%)
DIARRHEA	1 (0.1%)
LIVER DAMAGE	1 (0.1%)
LIVER FUNCTION TESTS ABNORMAL	1 (0.1%)
NAUSEA	1 (0.1%)
PANCREATITIS	1 (0.1%)
RECTAL HEMORRHAGE	1 (0.1%)
VOMITING	1 (0.1%)
SKIN AND APPENDAGES	
ANY AE	5 (0.3%)
RASH	4 (0.2%)
URTICARIA	1 (0.1%)
UROGENITAL SYSTEM	
ANY AE	3 (0.2%)
ACUTE KIDNEY FAILURE	2 (0.1%)
KIDNEY FAILURE	1 (0.1%)

Serious Adverse Events in Fluconazole-Controlled Studies

The overall incidence of serious adverse events in the fluconazole-controlled studies was 15.9% (148/932) in micafungin-treated and 13.3% (105/787) in fluconazole-treated patients. The more common serious adverse events in these studies were sepsis (2.0% micafungin and 1.9% fluconazole), pneumonia (1.6% micafungin and 1.3% fluconazole), fever (1.5% micafungin and 0.8% fluconazole), hypotension (1.5% micafungin and 0.4% fluconazole), respiratory failure (1.4% micafungin and 0.6% fluconazole), and atrial fibrillation (1.0% micafungin and 0.3% fluconazole).

Serious Drug-Related Adverse Events in Fluconazole-Controlled Studies

To summarize serious drug-related adverse events across all fluconazole-controlled studies, events are tabulated by study and patient in the table below. Events in this category that occurred in more than one patient, and more often in micafungin-treated patients included delirium, allergic reaction, rash, and hypoxia/decreased oxygen saturation.

Clinical Review
 Mary E. Singer, M.D., Ph.D.
 Micafungin sodium for Esophageal Candidiasis
 Mycamine (Micafungin sodium)

Table 49. Summary of Serious Drug-Related Adverse Events in Fluconazole-Controlled Studies

Study	Study Drug/Dose (mg/day)	N	n	Adverse Event (COSTART Term)
03-7-005	Micafungin 150	260	1	AIDS
	Micafungin 150		2	Delirium
	Fluconazole 200	258	1	Asthenia; delirium
FG463-21-09	Micafungin 50	185	1	Chills, hypotension; vomiting
	Micafungin 100		1	Dementia
	Micafungin 100		2	Allergic reaction
	Micafungin 100		1	Anaphylactoid reaction
	Micafungin 150		1	Leukopenia
	Micafungin 150		1	Rash
	Fluconazole 200	60	1	Gastrointestinal anomaly; flu syndrome; vaginal hemorrhage; vaginitis
	Fluconazole 200		1	Leukopenia
97-0-041	Micafungin 50	62	1	Atrial fibrillation
	Micafungin 200 mg		1	Pancreatitis
98-0-050	Micafungin 50	425	2	Bilirubinemia*
			1	Hypoxia; cerebral infarction; infection; seizure
			2	Rash
			1	Sepsis*
	Fluconazole 400	457	1	Lung disorder; sweating; diarrhea; asthenia; tachycardia; pain; dizziness; nausea; dyspnea; abdominal pain; neck pain
			1	Dyspnea; vasodilatation
			2	Elevated liver function tests
			1	Hepatitis, nonspecific
			2	Bilirubinemia
			1	Increased ALT; increased AST
			1	Hepatic failure
			1	Subdural hematoma

* N= number of patients who received at least one dose study drug ; n = number of patients who experienced adverse event; *Note that Table 13.5.6.1 (original 21-506 submission) did not

Clinical Review

Mary E. Singer, M.D., Ph.D.

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

include 1 micafungin-treated patient with bilirubinemia and one with sepsis found in the adverse event database.

Medical Officer Comments: The applicant did not summarize drug-related adverse events for fluconazole-controlled studies. The most common serious adverse events among micafungin-treated patients were rash (3 patients), allergic reaction, delirium, and bilirubinemia, each in 2 patients; while the most common serious adverse events among patients treated with fluconazole were elevated liver function tests, bilirubinemia, dyspnea, and asthenia, each in 2 patients.

Serious Adverse Events by Age, Race, Gender

The applicant compiled serious adverse events by age group (<16 years; 16- < 65 years; and > 65 years old). The overall incidence of serious adverse events was highest in those patients less than 16 years old, 35.2% (86/224), followed by those > 65 years old, 30.7% (50/163), then by those between the ages of 16-65 years old, 26.6% (418/1573).

Serious Adverse Events by Race

The overall incidence of serious adverse events was lowest in black patients, 20.0% (101/504) in comparison to Caucasian, 31.8% (390/1228), and to “other” races, 25.4% (63/248). As noted previously in the section on “Deaths”, these differences may be due in part to the underlying disease. Most black patients in these studies had HIV/AIDS, and the incidence of serious adverse events among patients with HIV/AIDS was lower than among patients with hematologic malignancy/HSCT, or among patients with other conditions (16.9%, 33.7%, and 33.5%, respectively).

Serious Adverse Events by Gender

No significant gender difference was noted in the overall incidence of serious adverse events, 28.3% (319/1127) in male patients, and 27.5% (235/853) in female patients. The overall serious adverse event profile was also similar for males and females.

7.1.3 Dropouts and Other Significant Adverse Events

Adverse events that led to discontinuation of micafungin occurred in 251 of 2402 (10.4%) subjects and in 245 of 1980 (12.4%) patients. Adverse events resulting in study drug discontinuation judged to be drug-related occurred in 73/2402 (3.0%) subjects, and in 68/1980 (3.4%) patients. The most common Narrative summaries for drug-related adverse events resulting in micafungin discontinuation are provided in the individual reports for studies FG463-21-09, 97-7-003, and 03-7-005 in the Appendix, section 10, this review.

7.1.3.1. Overall profile of dropouts

Reasons for patient withdrawal from the clinical studies are shown in the table below. The incidence of withdrawal due to adverse events varied by study, but in the fluconazole-controlled

Clinical Review

Mary E. Singer, M.D., Ph.D.

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

studies the incidence of micafungin discontinuation due to adverse events was similar to that observed with fluconazole.

Table 50. Reasons for Patient Withdrawal by Study (Applicant's Appendices 2.7.4.5.1, 2.7.4.5.2, and 2.7.4.5.3)

		98-0-046/ FC463-21-01 (N=326)	98-0-047/ FC463-21-02 (N=353)	97-7-003 (N=120)	99-0-063 (N=13)	FC463-21-03 (N=36)	98-0-043 (N=77)	FC0003 (N=70)
COMPLETE THERAPY		118 (36.2%)	222 (62.9%)	91 (75.8%)	12 (100.0%)	24 (66.7%)	52 (67.5%)	49 (70.0%)
TOTAL WITHDRAWAL		208 (63.8%)	131 (37.1%)	29 (24.2%)	0	12 (33.3%)	25 (32.5%)	19 (27.1%)
ADVERSE EVENT	TOTAL	95 (28.8%)	71 (20.1%)	16 (13.3%)	0	0	2 (2.6%)	9 (12.9%)
	DID NOT RESULT IN DEATH	18 (5.5%)	30 (8.5%)	8 (6.7%)	0	0	2 (2.6%)	0
	RESULTED IN DEATH	68 (20.9%)	41 (11.6%)	8 (6.7%)	0	0	0	9 (12.9%)
LACK OF EFFICACY		74 (22.7%)	35 (9.9%)	3 (2.5%)	0	11 (30.6%)	19 (24.7%)	9 (12.9%)
ADMINISTRATIVE	TOTAL	48 (14.7%)	25 (7.1%)	10 (8.3%)	0	1 (2.8%)	4 (5.2%)	1 (1.4%)
	PATIENT WITHDREW CONSENT	9 (2.8%)	9 (2.5%)	7 (5.8%)	0	1 (2.8%)	1 (1.3%)	1 (1.4%)
	PATIENT NON-COMPLIANCE WITH PROTOCOL	1 (0.3%)	1 (0.3%)	1 (0.8%)	0	0	0	0
	OTHER	38 (11.7%)	15 (4.2%)	2 (1.7%)	0	0	3 (3.9%)	0

		98-0-050		97-0-041 (1)		FC463-21-09	
		FC463 (N=425)	FLUCONAZOLE (N=457)	FC463 (N=62)	FLUCONAZOLE (N=12)	FC463 (N=185)	FLUCONAZOLE (N=60)
COMPLETE THERAPY		319 (75.1%)	310 (67.8%)	44 (71.0%)	7 (58.3%)	157 (84.9%)	52 (86.7%)
TOTAL WITHDRAWAL		106 (24.9%)	147 (32.2%)	18 (29.0%)	5 (41.7%)	28 (15.1%)	8 (13.3%)
ADVERSE EVENT	TOTAL	18 (4.2%)	33 (7.2%)	2 (3.2%)	0	15 (8.1%)	4 (6.7%)
	DID NOT RESULT IN DEATH	13 (3.1%)	27 (5.9%)	2 (3.2%)	0	14 (7.6%)	3 (5.0%)
	RESULTED IN DEATH	5 (1.2%)	6 (1.3%)	0	0	1 (0.5%)	1 (1.7%)
LACK OF EFFICACY		75 (17.6%)	107 (23.4%)	15 (24.2%)	5 (41.7%)	1 (0.5%)	0
ADMINISTRATIVE	TOTAL	13 (3.1%)	7 (1.5%)	1 (1.6%)	0	12 (6.5%)	4 (6.7%)
	PATIENT WITHDREW CONSENT	4 (0.9%)	3 (0.7%)	1 (1.6%)	0	3 (1.6%)	1 (1.7%)
	PATIENT NON-COMPLIANCE WITH PROTOCOL	1 (0.2%)	0	0	0	1 (0.5%)	2 (3.3%)
	OTHER	8 (1.9%)	4 (0.9%)	0	0	8 (4.3%)	1 (1.7%)

		03-7-005		01-0-124	
		FC463 (N=260)	FLUCONAZOLE (N=258)	FC463 (N=51)	PLACEBO (N=51)
COMPLETE THERAPY		232 (89.2%)	234 (90.7%)	32 (62.7%)	33 (64.7%)
TOTAL WITHDRAWAL		28 (10.8%)	24 (9.3%)	19 (37.3%)	18 (35.3%)
ADVERSE EVENT	TOTAL	17 (6.5%)	12 (4.7%)	7 (13.7%)	4 (7.8%)
	DID NOT RESULT IN DEATH	7 (2.7%)	3 (1.2%)	3 (5.9%)	0
	RESULTED IN DEATH	10 (3.8%)	9 (3.5%)	4 (7.8%)	4 (7.8%)
LACK OF EFFICACY		2 (0.8%)	5 (1.9%)	3 (5.9%)	9 (17.6%)
ADMINISTRATIVE	TOTAL	9 (3.5%)	5 (1.9%)	9 (17.6%)	5 (9.8%)
	PATIENT WITHDREW CONSENT	2 (0.8%)	0	0	0
	PATIENT NON-COMPLIANCE WITH PROTOCOL	5 (1.9%)	4 (1.6%)	1 (2.0%)	0
	OTHER	2 (0.8%)	1 (0.4%)	8 (15.7%)	5 (9.8%)

Best Possible Copy

7.1.3.2 Adverse events associated with dropouts

The most common adverse events leading to micafungin discontinuation were shock in 26/2402 (1.1%) subjects, respiratory failure in 19/2402 (0.8%) subjects, pneumonia in 17/2402 (0.7%) subjects, sepsis in 12/2402 (0.5%) subjects, and rash in 12/2402 (0.5%) subjects. Six volunteers experience adverse events which resulted in discontinuation of micafungin, including phlebitis (1 subject), fever (3 subjects), and rash (2 subjects). The incidence of adverse events which resulted in micafungin discontinuation is shown in the following table.

Clinical Review

Mary E. Singer, M.D., Ph.D.

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

Table 51. Incidence of Adverse Events Resulting in Micafungin Discontinuation (Applicant's

Appendix 9.1.1, 120-day Safety Update)

BODY SYSTEM (1) FK463
COSTART TERM (N=2402)

ALL SYSTEMS 251(10.4%)

RESPIRATORY SYSTEM

ANY AE	61(2.5%)
RESPIRATORY FAILURE	19(0.8%)
PNEUMONIA	17(0.7%)
DYSPNEA	5(0.2%)
LUNG HEMORRHAGE	4(0.2%)
RESPIRATORY DISTRESS SYNDROME	4(0.2%)
HYPOXIA	2(0.1%)
LUNG EDEMA	2(0.1%)
LUNG FIBROSIS	2(0.1%)
PULMONARY TUBERCULOSIS REACTIVATED	2(0.1%)
EMPHYSEMA	1(0.0%)
HEMOPTYSIS	1(0.0%)
LUNG DISORDER	1(0.0%)
PULMONARY EMBOLUS	1(0.0%)

CARDIOVASCULAR SYSTEM

ANY AE	47(2.0%)
SHOCK	26(1.1%)
HEART ARREST	3(0.1%)
ATRIAL FIBRILLATION	2(0.1%)
HEART FAILURE	2(0.1%)
HYPOTENSION	2(0.1%)
PERIPHERAL VASCULAR DISORDER	2(0.1%)
SUBDURAL HEMATOMA	2(0.1%)
ARRHYTHMIA	1(0.0%)
CONGESTIVE HEART FAILURE	1(0.0%)
DEEP THROMBOPHLEBITIS	1(0.0%)
ELECTROCARDIOGRAM ABNORMAL	1(0.0%)
INCREASED CAPILLARY FRAGILITY	1(0.0%)
MYOCARDIAL INFARCT	1(0.0%)
PALPITATION	1(0.0%)
PHLEBITIS	1(0.0%)

BODY AS A WHOLE

ANY AE	43(1.8%)
SEPSIS	12(0.5%)
ALLERGIC REACTION	7(0.3%)
FEVER	5(0.2%)
AIDS	4(0.2%)
ABDOMINAL PAIN	2(0.1%)

ANAPHYLACTOID REACTION	2(0.1%)
TUBERCULOSIS REACTIVATED	2(0.1%)
ABSCESS	1(0.0%)
CACHEXIA	1(0.0%)
CARCINOMA	1(0.0%)
CHILLS	1(0.0%)
DRUG LEVEL INCREASED	1(0.0%)
GRAFT VERSUS HOST DISEASE	1(0.0%)
PERITONITIS	1(0.0%)
RELAPSE OF PRIMARY MALIGNANCY	1(0.0%)
TUBERCULOSIS AGGRAVATED	1(0.0%)

NERVOUS SYSTEM

ANY AE	25(1.0%)
--------	-----------

Clinical Review

Mary E. Singer, M.D., Ph.D.

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

INTRACRANIAL HEMORRHAGE	5(0.2%)
MENINGITIS	4(0.2%)
CEREBRAL HEMORRHAGE	3(0.1%)
CONVULSION	3(0.1%)
DELIRIUM	3(0.1%)
HEADACHE	2(0.1%)
ACUTE BRAIN SYNDROME	1(0.0%)
BRAIN EDEMA	1(0.0%)
COMA	1(0.0%)
DEMENTIA	1(0.0%)
VERTIGO	1(0.0%)

DIGESTIVE SYSTEM

ANY AE	21(0.9%)
LIVER FUNCTION TESTS ABNORMAL	9(0.4%)
GASTROINTESTINAL HEMORRHAGE	2(0.1%)
HEPATITIS, NONSPECIFIC	2(0.1%)
ANOREXIA	1(0.0%)
CHOLESTATIC JAUNDICE	1(0.0%)
DIARRHEA	1(0.0%)
HEPATIC FAILURE	1(0.0%)
LIVER DAMAGE	1(0.0%)
NAUSEA	1(0.0%)
VENOOCCLUSIVE LIVER DISEASE	1(0.0%)
VOMITING	1(0.0%)

METABOLIC AND NUTRITIONAL DISORDERS

ANY AE	18(0.7%)
BILIRUBINEMIA	7(0.3%)

ALKALINE PHOSPHATASE INCREASED	3(0.1%)
CREATININE INCREASED	3(0.1%)
SGOT INCREASED	2(0.1%)
ACIDOSIS	1(0.0%)
ENZYMATIC ABNORMALITY	1(0.0%)
RESPIRATORY ACIDOSIS	1(0.0%)

HEMIC AND LYMPHATIC SYSTEM

ANY AE	14(0.6%)
LEUKOPENIA	5(0.2%)
THROMBOCYTOPENIA	4(0.2%)
PANCYTOPENIA	2(0.1%)
CHRONIC LYMPHOCYTIC LEUKEMIA	1(0.0%)
COAGULATION DISORDER	1(0.0%)
LEUKEMIA	1(0.0%)

SKIN AND APPENDAGES

ANY AE	14(0.6%)
RASH	12(0.5%)
URTICARIA	2(0.1%)

UROGENITAL SYSTEM

ANY AE	5(0.2%)
KIDNEY FAILURE	4(0.2%)
ACUTE KIDNEY FAILURE	1(0.0%)

MUSCULOSKELETAL SYSTEM

ANY AE	3(0.1%)
ARTHRALGIA	3(0.1%)

In the fluconazole-controlled studies, 52 of 932 (5.6%) of patients treated with micafungin and 49 of 787 (6.2%) treated with fluconazole experienced an adverse event that resulted in treatment discontinuation. These events are tabulated in the following table.

Clinical Review

Mary E. Singer, M.D., Ph.D.

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

Table 52. Incidence of Adverse Events resulting in Drug Discontinuation in Fluconazole-Controlled Studies (Applicant's Appendix 9.1.3, 120-day Safety Update)

BODY SYSTEM (1) COSTART TERM	FK463 (N=932)	FLUCONAZOLE (N=787)
ALL SYSTEMS	52 (5.6%)	49 (6.2%)
DIGESTIVE SYSTEM		
ANY AE	3 (0.3%)	11 (1.4%)
LIVER FUNCTION TESTS ABNORMAL	1 (0.1%)	5 (0.6%)
HEPATIC FAILURE	1 (0.1%)	2 (0.3%)
LIVER DAMAGE	0	2 (0.3%)
DIARRHEA	0	1 (0.1%)
HEPATITIS, NONSPECIFIC	0	1 (0.1%)
VOMITING	1 (0.1%)	0
METABOLIC AND NUTRITIONAL DISORDERS		
ANY AE	4 (0.4%)	8 (1.0%)
BILIRUBINEMIA	3 (0.3%)	4 (0.5%)
HYPERVOLEMIA	0	1 (0.1%)
HYPOKALEMIA	0	1 (0.1%)
KETOSIS	0	1 (0.1%)
SGPT INCREASED	0	1 (0.1%)
CREATININE INCREASED	1 (0.1%)	0
RESPIRATORY SYSTEM		
ANY AE	8 (0.9%)	8 (1.0%)
PNEUMONIA	4 (0.4%)	3 (0.4%)
RESPIRATORY FAILURE	0	2 (0.3%)
DYSPNEA	0	1 (0.1%)
LUNG HEMORRHAGE	0	1 (0.1%)
RESPIRATORY DISTRESS SYNDROME	1 (0.1%)	1 (0.1%)
LUNG EDEMA	1 (0.1%)	0
PULMONARY TUBERCULOSIS REACTIVATED	2 (0.2%)	0
NERVOUS SYSTEM		
ANY AE	7 (0.8%)	7 (0.9%)
CEREBROVASCULAR ACCIDENT	0	1 (0.1%)
CONVULSION	0	1 (0.1%)
DEMENTIA	1 (0.1%)	1 (0.1%)
DIZZINESS	0	1 (0.1%)
HEADACHE	0	1 (0.1%)
MENINGITIS	3 (0.3%)	1 (0.1%)
PSYCHOSIS	0	1 (0.1%)
DELIRIUM	2 (0.2%)	0
INTRACRANIAL HEMORRHAGE	1 (0.1%)	0
CARDIOVASCULAR SYSTEM		
ANY AE	9 (1.0%)	6 (0.8%)
SHOCK	2 (0.2%)	2 (0.3%)
SUBDURAL HEMATOMA	0	2 (0.3%)
HEART ARREST	1 (0.1%)	1 (0.1%)
HEART FAILURE	0	1 (0.1%)
ARRHYTHMIA	1 (0.1%)	0
ATRIAL FIBRILLATION	2 (0.2%)	0
HYPOTENSION	1 (0.1%)	0
INCREASED CAPILLARY FRAGILITY	1 (0.1%)	0

Clinical Review

Mary E. Singer, M.D., Ph.D.

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

PALPITATION	1 (0.1%)	0
UROGENITAL SYSTEM		
ANY AE	1 (0.1%)	4 (0.5%)
KIDNEY FAILURE	1 (0.1%)	2 (0.3%)
ACUTE KIDNEY FAILURE	0	1 (0.1%)
KIDNEY FUNCTION ABNORMAL	0	1 (0.1%)
BODY AS A WHOLE		
ANY AE	9 (1.0%)	2 (0.3%)
SEPSIS	0	2 (0.3%)
AIDS	1 (0.1%)	0
ALLERGIC REACTION	3 (0.3%)	0
ANAPHYLACTOID REACTION	2 (0.2%)	0
CHILLS	1 (0.1%)	0
TUBERCULOSIS AGGRAVATED	1 (0.1%)	0
TUBERCULOSIS REACTIVATED	1 (0.1%)	0
HEMIC AND LYMPHATIC SYSTEM		
ANY AE	2 (0.2%)	2 (0.3%)
LEUKOPENIA	1 (0.1%)	2 (0.3%)
PANCYTOPENIA	1 (0.1%)	0
SKIN AND APPENDAGES		
ANY AE	8 (0.9%)	1 (0.1%)
RASH	7 (0.8%)	1 (0.1%)
URTICARIA	1 (0.1%)	0
MUSCULOSKELETAL SYSTEM		
ANY AE	1 (0.1%)	0
ARTHRALGIA	1 (0.1%)	0

Adverse events resulting in micafungin discontinuation were less frequent in patients who received ≥ 150 mg/day micafungin for at least 10 days, 4.8% (29/606), in comparison to those who received a lower dose or shorter duration of therapy, 12.4% (222/1796). The adverse event profile was similar for both dosing groups.

Medical Officer Comment: This difference was likely due to differences in underlying disease. The majority of patients who received a minimum of 150 mg/day for at least 10 days were those with HIV/AIDS; while those who received lower doses or durations of therapy were more likely to have an underlying hematological malignancy, or had received a HSCT.

Drug-Related Adverse Events Resulting in Discontinuation

Adverse events considered drug-related occurred in 73 of 2402 (3.0%) of micafungin-treated subjects, and in 68/1980 (3.4%) of micafungin-treated patients. The following table shows the incidence of adverse events in micafungin-treated subjects. The most common drug-related adverse events resulting in micafungin discontinuation were rash (0.5%), allergic reaction (0.3%), abnormal liver function tests (0.3%), and bilirubinemia (0.2%).

Clinical Review
 Mary E. Singer, M.D., Ph.D.
 Micafungin sodium for Esophageal Candidiasis
 Mycamine (Micafungin sodium)

Table 53. Drug-Related Adverse Events in Micafungin-Treated Subjects (adapted from Applicant's Appendix 9.2.1, Clinical Summary of Safety, Update, July, 2004)

BODY SYSTEM (1)	FK463 (N=2402)
ALL SYSTEMS	73(3.0%)
SKIN AND APPENDAGES	
ANY AE	14(0.6%)
RASH	12(0.5%)
URTICARIA	2(0.1%)
BODY AS A WHOLE	
ANY AE	13(0.5%)
ALLERGIC REACTION	7(0.3%)
ANAPHYLACTOID REACTION	2(0.1%)
FEVER	2(0.1%)
AIDS	1(0.0%)
CHILLS	1(0.0%)
METABOLIC AND NUTRITIONAL DISORDERS	
ANY AE	13(0.5%)
BILIRUBINEMIA	6(0.2%)
ALKALINE PHOSPHATASE INCREASED	3(0.1%)
CREATININE INCREASED	2(0.1%)
ENZYMATIC ABNORMALITY	1(0.0%)
SGOT INCREASED	1(0.0%)
DIGESTIVE SYSTEM	
ANY AE	11(0.5%)
LIVER FUNCTION TESTS ABNORMAL	7(0.3%)
ANOREXIA	1(0.0%)
HEPATITIS, NONSPECIFIC	1(0.0%)
LIVER DAMAGE	1(0.0%)
NAUSEA	1(0.0%)
HEMIC AND LYMPHATIC SYSTEM	
ANY AE	8(0.3%)
LEUKOPENIA	3(0.1%)
THROMBOCYTOPENIA	3(0.1%)
PANCYTOPENIA	2(0.1%)
NERVOUS SYSTEM	
ANY AE	6(0.2%)
DELIRIUM	2(0.1%)
CEREBRAL HEMORRHAGE	1(0.0%)
CONVULSION	1(0.0%)
DEMENTIA	1(0.0%)
HEADACHE	1(0.0%)
CARDIOVASCULAR SYSTEM	
ANY AE	4(0.2%)
ATRIAL FIBRILLATION	1(0.0%)
PALPITATION	1(0.0%)
PERIPHERAL VASCULAR DISORDER	1(0.0%)
PHLEBITIS	1(0.0%)
MUSCULOSKELETAL SYSTEM	
ANY AE	2(0.1%)
ARTHRALGIA	2(0.1%)
RESPIRATORY SYSTEM	

Clinical Review

Mary E. Singer, M.D., Ph.D.

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

ANY AE 1(0.0%)
HYPOXIA 1(0.0%)

UROGENITAL SYSTEM

ANY AE 1(0.0%)
ACUTE KIDNEY FAILURE 1(0.0%)

In the fluconazole-controlled studies, 2.9% (27/932) micafungin-treated and 2.2% (17/787) fluconazole-treated patients experienced a drug-related adverse event resulting in drug-discontinuation. The table below summarizes those events for comparison of micafungin and fluconazole. The profile for drug-related adverse events resulting in discontinuation differed somewhat between treatment groups. In micafungin-treated patients, the most common events in this category included rash, bilirubinemia and allergic reaction, delirium and anaphylactoid reaction. In patients who received fluconazole, the most common events in this category included abnormal liver function tests, liver damage, and bilirubinemia.

Table 54. Drug-Related Adverse Events Resulting in Drug Discontinuation in Fluconazole-Controlled Studies (adapted from Applicant's Appendix 9.2.3, Clinical Summary of Safety, Update, July, 2004)

BODY SYSTEM (1) COSTART TERM	FK463 (N=932)	FLUCONAZOLE (N=787)
-----	-----	-----
ALL SYSTEMS	27 (2.9%)	17 (2.2%)
DIGESTIVE SYSTEM		
ANY AE	1 (0.1%)	9 (1.1%)
LIVER FUNCTION TESTS ABNORMAL	1 (0.1%)	5 (0.6%)
LIVER DAMAGE	0	2 (0.3%)
HEPATIC FAILURE	0	1 (0.1%)
HEPATITIS, NONSPECIFIC	0	1 (0.1%)
METABOLIC AND NUTRITIONAL DISORDERS		
ANY AE	4 (0.4%)	3 (0.4%)
BILIRUBINEMIA	3 (0.3%)	2 (0.3%)
HYPERVOLEMIA	0	1 (0.1%)
CREATININE INCREASED	1 (0.1%)	0
NERVOUS SYSTEM		
ANY AE	3 (0.3%)	2 (0.3%)
DIZZINESS	0	1 (0.1%)
HEADACHE	0	1 (0.1%)
DELIRIUM	2 (0.2%)	0
DEMENTIA	1 (0.1%)	0
HEMIC AND LYMPHATIC SYSTEM		
ANY AE	1 (0.1%)	1 (0.1%)
LEUKOPENIA	0	1 (0.1%)
PANCYTOPENIA	1 (0.1%)	0
RESPIRATORY SYSTEM		
ANY AE	0	1 (0.1%)
DYSPNEA	0	1 (0.1%)
SKIN AND APPENDAGES		
ANY AE	8 (0.9%)	1 (0.1%)
RASH	7 (0.8%)	1 (0.1%)
URTICARIA	1 (0.1%)	0

Clinical Review

Mary E. Singer, M.D., Ph.D.

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

BODY AS A WHOLE

ANY AE	7 (0.8%)	0
AIDS	1 (0.1%)	0
ALLERGIC REACTION	3 (0.3%)	0
ANAPHYLACTOID REACTION	2 (0.2%)	0
CHILLS	1 (0.1%)	0

CARDIOVASCULAR SYSTEM

ANY AE	2 (0.2%)	0
ATRIAL FIBRILLATION	1 (0.1%)	0
PALPITATION	1 (0.1%)	0

MUSCULOSKELETAL SYSTEM

ANY AE	1 (0.1%)	0
ARTHRALGIA	1 (0.1%)	0

7.1.3.3 Other significant adverse events

Adverse Events Resulting in Dose Interruption or Reduction

Adverse events that resulted in dose reduction or interruption were uncommon, occurring in 60 of 1980 (3.0%) micafungin-treated patients. The most common adverse events in this category were laboratory abnormalities, including increased AST (0.4%), increased creatinine (0.3%), abnormal liver function tests (0.3%), bilirubinemia (0.2%), leukopenia (0.2%), as shown in the table below.

Table 55. Adverse Events Resulting in Micafungin Dose Interruption or Reductions in all Micafungin-Treated Patients (Applicant's Appendix 10, 120-day Safety Update)

BODY SYSTEM (1)	FK463	
COSTART TERM	(N=1980)	
-----	-----	
ALL SYSTEMS	60 (3.0%)	
METABOLIC AND NUTRITIONAL DISORDERS		
ANY AE	21 (1.1%)	
SGPT INCREASED	7 (0.4%)	
CREATININE INCREASED	5 (0.3%)	
BILIRUBINEMIA	3 (0.2%)	
SGOT INCREASED	2 (0.1%)	
ALKALINE PHOSPHATASE INCREASED	1 (0.1%)	
BUN INCREASED	1 (0.1%)	
CREATININE CLEARANCE DECREASED	1 (0.1%)	
HYPERVOLEMIA	1 (0.1%)	
LACTIC DEHYDROGENASE INCREASED	1 (0.1%)	
PERIPHERAL EDEMA	1 (0.1%)	
WEIGHT LOSS	1 (0.1%)	
DIGESTIVE SYSTEM		
ANY AE	9 (0.5%)	
LIVER FUNCTION TESTS ABNORMAL	5 (0.3%)	
ANOREXIA	2 (0.1%)	
NAUSEA	2 (0.1%)	
GASTROINTESTINAL HEMORRHAGE	1 (0.1%)	
BODY AS A WHOLE		
ANY AE	8 (0.4%)	
ASTHENIA	2 (0.1%)	
ABDOMINAL PAIN	1 (0.1%)	

Clinical Review
 Mary E. Singer, M.D., Ph.D.
 Micafungin sodium for Esophageal Candidiasis
 Mycamine (Micafungin sodium)

ALLERGIC REACTION	1 (0.1%)
CHILLS	1 (0.1%)
FEVER	1 (0.1%)
INFECTION	1 (0.1%)
PROCEDURAL COMPLICATION	1 (0.1%)
SEPSIS	1 (0.1%)
CARDIOVASCULAR SYSTEM	
ANY AE	8 (0.4%)
ARRHYTHMIA	2 (0.1%)
BRADYCARDIA	1 (0.1%)
HEART ARREST	1 (0.1%)
HYPERTENSION	1 (0.1%)
HYPOTENSION	1 (0.1%)
PALPITATION	1 (0.1%)
PHLEBITIS	1 (0.1%)
VASODILATATION	1 (0.1%)
SKIN AND APPENDAGES	
ANY AE	8 (0.4%)
PRURITUS	2 (0.1%)
RASH	2 (0.1%)
HERPES SIMPLEX	1 (0.1%)
MACULOPAPULAR RASH	1 (0.1%)
PETECHIAL RASH	1 (0.1%)
SKIN DISORDER	1 (0.1%)
URTICARIA	1 (0.1%)
HEMIC AND LYMPHATIC SYSTEM	
ANY AE	7 (0.4%)
LEUKOPENIA	3 (0.2%)
ANEMIA	1 (0.1%)
CYANOSIS	1 (0.1%)
HEMOLYSIS	1 (0.1%)
THROMBOCYTOPENIA	1 (0.1%)
RESPIRATORY SYSTEM	
ANY AE	4 (0.2%)
DYSPNEA	1 (0.1%)
HYPOXIA	1 (0.1%)
PNEUMONIA	1 (0.1%)
PULMONARY EMBOLUS	1 (0.1%)
NERVOUS SYSTEM	
ANY AE	3 (0.2%)
ANXIETY	1 (0.1%)
DELIRIUM	1 (0.1%)
PARESTHESIA	1 (0.1%)
SPECIAL SENSES	
ANY AE	1 (0.1%)
TINNITUS	1 (0.1%)
UROGENITAL SYSTEM	
ANY AE	1 (0.1%)
KIDNEY FAILURE	1 (0.1%)

Medical Officer Comments: The effect of dose reduction or interruption in these cases was not analyzed by the applicant. If an adverse event resolved or improved with dose-reduction or interruption, attribution to study drug would be more straightforward.

Other significant adverse events not meeting the definition of serious, and not leading to death or modification of therapy are discussed in the Special Studies section, 7.1.12, by organ system.

Clinical Review

Mary E. Singer, M.D., Ph.D.

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

7.1.4 Other Search Strategies

Preclinical studies (summarized in section 3.2), and postmarketing adverse events in Japan (summarized in section 7.1.17) were reviewed in addition to the safety database for the clinical studies, for potential safety signals with micafungin.

The medical officer's review of caspofungin (Cancidas®) and the package insert, were also reviewed for comparison to micafungin, in addition to literature searches by the Applicant and the medical reviewers for potential toxicities related to echinocandins in general, and to micafungin.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

For all studies in the safety database, treatment-emergent adverse events were defined as any adverse event that occurred during the treatment period, any pre-existing condition that worsened during the treatment period, or any adverse event that occurred within 72 hours after last study drug administration.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

Adverse events were coded by body system using a modified Coding Symbols for Thesaurus of Adverse Reaction Terms (COSTART) dictionary in the safety database. Additionally, for studies 03-7-005 and 98-0-050, and 01-0-124, adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA version 5.0).

Several of the COSTART terms used to identify an adverse event could refer to the same event. These events are better discussed in the section on adverse events by organ system or syndrome. Additionally individual adverse events of significant clinical concern are discussed separately subsequently.

7.1.5.3 Incidence of common adverse events

The incidence of adverse events in all subjects (patients and volunteers) was 84.4% (2028/2402), and in all patients was 92.1% (1824/1980). The most common adverse events in subjects who received micafungin were diarrhea (26%), nausea (25.7%), vomiting (24.4%), fever (23.6%), and leukopenia (20.9%). The adverse event profile in patients was similar to that of subjects, with the most common adverse events in patients including diarrhea (31.2%), nausea (29.7%), vomiting (29.2%), fever (28.2%), leukopenia (25.3%), thrombocytopenia (23.4%), mucositis (22.9%), hypokalemia (22.5%), headache (21.5%), and abdominal pain (21.2%).

Clinical Review
 Mary E. Singer, M.D., Ph.D.
 Micafungin sodium for Esophageal Candidiasis
 Mycamine (Micafungin sodium)
 7.1.5.4 Common adverse event tables

Table _ summarizes the common (occurring in $\geq 2\%$ subjects) adverse events in subjects and patients in micafungin safety database. Those events that occurred in more subjects (patients plus volunteers) than patients are those that occurred in volunteers. These are highlighted in bold font in the table below.

Table 56. Incidence of Common* Adverse Events in Micafungin-treated Patients and Subjects** (adapted from Applicant's Appendices 2.7.4.3.1 and 2.7.4.3.2, 120 day Safety, Update, July 2004)

Adverse Event Body System COSTART Term	Subjects N=2402	Patients N=1980
	n (%)	n (%)
Body as a Whole		
Fever	566 (23.6)	559 (28.2)
Abdominal pain	433 (18.0)	420 (21.2)
Infection	354 (14.7)	354 (17.9)
Procedural complication	352 (14.7)	317 (16.0)
Asthenia	311 (12.9)	296 (14.9)
Sepsis	293 (12.2)	293 (14.8)
Chills	240 (10.0)	238 (12.0)
Pain	213 (8.9)	206 (10.4)
Back pain	168 (7.0)	158 (8.0)
Abdomen enlarged	114 (4.7)	114 (5.8)
Allergic reaction	106 (4.4)	106 (5.4)
Graft vs. host disease	77 (3.2)	77 (3.2)
Transfusion reaction	75 (3.1)	75 (3.8)
Face edema	73 (3.0)	72 (3.6)
Flu syndrome	54 (2.2)	47 (2.4)
Digestive System		
Diarrhea	625 (26.0)	618 (31.2)
Nausea	617 (25.7)	589 (29.7)
Vomiting	586 (24.4)	579 (29.2)
Mucositis	454 (18.9)	454 (22.9)
Anorexia	335 (13.9)	331 (16.7)
Constipation	304 (12.7)	301 (15.2)
Dyspepsia	194 (8.1)	188 (9.5)
Rectal disorder	145 (6.0)	145 (7.3)
Liver function tests abnormal	105 (4.4)	88 (4.4)
Dry mouth/nose	88 (3.7)	85 (4.3)
Stomatitis	71 (3.0)	69 (3.5)
Jaundice	62 (2.6)	62 (3.1)

Clinical Review
 Mary E. Singer, M.D., Ph.D.
 Micafungin sodium for Esophageal Candidiasis
 Mycamine (Micafungin sodium)

Dysphagia	49 (2.0)	49 (2.5)
Gastrointestinal hemorrhage	47 (2.0)	47 (2.4)
Gastroenteritis	44 (1.8)	44 (2.2)
Melena	44 (1.8)	44 (2.2)
Ileus	42 (1.7)	42 (2.1)
Gastritis	41 (1.7)	41 (2.1)
Gastrointestinal disorder	40 (1.7)	40 (2.0)
Metabolic and Nutritional Disorders		
Hypokalemia	448 (18.7)	446 (22.5)
Hypomagnesemia	387 (16.1)	387 (19.5)
Edema	214 (8.9)	214 (10.8)
Peripheral edema	204 (8.5)	201 (10.2)
Hypocalcemia	173 (7.2)	173 (8.7)
Hyperglycemia	166 (6.9)	166 (8.4)
Bilirubinemia	162 (6.7)	161 (8.1)
Hypervolemia	155 (6.5)	155 (7.8)
Hypophosphatemia	145 (6.0)	145 (7.3)
Hyponatremia	132 (5.5)	132 (6.7)
Hypoproteinemia	126 (5.2)	126 (6.4)
ALT increased	136 (5.7)	121 (6.1)
AST increased	135 (5.6)	124 (6.3)
Hyperkalemia	110 (4.6)	110 (5.6)
Alkaline phosphatase increased	103 (4.3)	103 (5.2)
Creatinine increased	89 (3.7)	89 (4.5)
BUN increased	76 (3.2)	76 (3.8)
Dehydration	76 (3.2)	76 (3.8)
Acidosis	68 (2.8)	68 (3.4)
Hypernatremia	58 (2.4)	58 (2.9)
Lactic dehydrogenase increased	44 (1.8)	44 (2.2)
Hypoglycemia	41 (1.7)	41 (2.1)
Hyperchloremia	39 (1.6)	39 (2.0)
Nervous System		
Headache	463 (19.3)	426 (21.5)
Insomnia	276 (11.5)	274 (13.8)
Anxiety	184 (7.7)	184 (9.3)
Dizziness	146 (6.1)	129 (6.5)
Confusion	119 (5.0)	119 (6.0)
Depression	87 (3.6)	87 (4.4)
Somnolence	87 (3.6)	86 (4.3)
Agitation	75 (3.1)	75 (3.8)

Clinical Review
 Mary E. Singer, M.D., Ph.D.
 Micafungin sodium for Esophageal Candidiasis
 Mycamine (Micafungin sodium)

Tremor	72 (3.0)	70 (3.5)
Paresthesia	82 (3.4)	69 (3.5)
Nervousness	65 (2.7)	64 (3.2)
Respiratory System		
Cough increased	249 (10.4)	245 (12.4)
Dyspnea	221 (9.2)	219 (11.1)
Lung disorder	162 (6.7)	162 (8.2)
Pneumonia	159 (6.6)	159 (8.0)
Epistaxis	158 (6.6)	156 (7.9)
Rhinitis	161 (6.7)	151 (7.6)
Pharyngitis	135 (5.6)	125 (6.3)
Respiratory failure	83 (3.5)	83 (4.2)
Hypoxia	77 (3.2)	77 (3.9)
Asthma	75 (3.1)	75 (3.8)
Hyperventilation	65 (2.7)	65 (3.3)
Pleural effusion	63 (2.6)	63 (3.2)
Sinusitis	57 (2.4)	54 (2.7)
Hiccup	53 (2.2)	53 (2.7)
Hemoptysis	49 (2.0)	49 (2.5)
Lung edema	40 (1.7)	40 (2.0)
Hemic and Lymphatic System		
Leukopenia	501 (20.9)	501 (25.3)
Thrombocytopenia	465 (19.4)	464 (23.4)
Anemia	313 (13.0)	311 (15.7)
Petechia	83 (3.5)	82 (4.1)
Ecchymosis	87 (3.6)	80 (4.0)
Leukocytosis	48 (2.0)	48 (2.40)
WBC abnormal	41 (1.7)	41 (2.1)
Cardiovascular System		
Hypotension	239 (10.0)	239 (12.1)
Tachycardia	225 (9.4)	223 (11.3)
Hypertension	200 (8.3)	200 (10.1)
Chest pain	155 (6.5)	150 (7.6)
Vasodilatation	114 (4.7)	97 (4.9)
Phlebitis	97 (4.0)	97 (4.9)
Shock	53 (2.2)	53 (2.7)
Bradycardia	52 (2.2)	52 (2.6)
Skin and appendages		
Rash	396 (16.5)	381 (19.2)

Clinical Review

Mary E. Singer, M.D., Ph.D.

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

Pruritis	181 (7.5)	176 (8.9)
Skin disorder	106 (4.4)	106 (5.4)
Sweating	77 (3.2)	72 (3.6)
Maculopapular rash	66 (2.7)	62 (3.1)
Dry skin	59 (2.5)	55 (2.8)
Herpes simplex	57 (2.4)	55 (2.8)
Alopecia	48 (2.0)	47 (2.4)
Skin ulcer	45 (1.9)	45 (2.3)
Urticaria	43 (1.8)	43 (2.2)
Urogenital System		
Hematuria	117 (4.9)	114 (5.8)
Oliguria	78 (3.2)	78 (3.9)
Urinary tract infection	79 (3.3)	78 (3.9)
Dysuria	75 (3.1)	74 (3.7)
Kidney failure	50 (2.1)	50 (2.5)
Urinary incontinence	46 (1.9)	46 (2.3)
Kidney function abnormal	42 (1.7)	42 (2.1)
Musculoskeletal system		
Arthralgia	136 (5.7)	135 (6.8)
Myalgia	60 (2.5)	56 (2.8)
Bone pain	55 (2.3)	55 (2.8)
Special Senses		
Abnormal vision	42 (1.7)	42 (2.1)
Dry eyes	40 (1.7)	40 (2.0)
Ear pain	40 (1.7)	39 (2.0)

* Common Adverse event defined as $\geq 2\%$ in patients or subjects

N= number of patients or subjects (or both)

n (%) = number and percentage of patients and/or subjects with adverse event (patients could experience more than 1 adverse event within a body system)

***Medical Officer Comments:** Those adverse events that occurred in volunteers as well as in patients may be more likely to be drug-related, except for those conditions that occur commonly in healthy individuals (eg. rhinitis and pharyngitis). The caveat here is that some of the volunteers were not healthy, but had underlying renal failure (9 volunteers) or moderate hepatic insufficiency (9 volunteers).*

Common Adverse Events in Fluconazole-Controlled Studies

The incidence of adverse events in the fluconazole-controlled studies (03-7-005 (EC), FG463-21-09(EC), 98-0-050 (prophylaxis) and 97-0-041 (prophylaxis) was 91.6% (854/932) in micafungin-treated patients, and 90.3% (711/787) in fluconazole-treated patients. The most common ($\geq 10\%$ in either treatment arm) adverse events are shown in the table below. For those events that occurred at a rate of $\geq 10\%$ in either treatment arm, the incidence was higher in the

Clinical Review

Mary E. Singer, M.D., Ph.D.

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

fluconazole-treated group, except for headache, which was seen at a somewhat higher incidence in the micafungin treatment group (26.9% vs. 25%).

Table 57. Incidence of Common Adverse Events* in Fluconazole-Controlled Studies

Adverse Event Body System COSTART Term	Micafungin N=932	Fluconazole N=787
	n (%)	n (%)
Digestive System		
Diarrhea	390 (41.8)	397 (50.4)
Mucositis	366 (39.3)	376 (47.8)
Nausea	363 (38.9)	351 (44.6)
Vomiting	335 (35.9)	337 (42.8)
Anorexia	240 (25.8)	240 (30.5)
Constipation	169 (18.1)	158 (20.1)
Rectal disorder	93 (10.0)	89 (11.3)
Body as a Whole		
Fever	332 (35.6)	291 (37.0)
Abdominal pain	223 (23.9)	197 (25.0)
Asthenia	174 (18.7)	196 (24.9)
Infection	183 (19.6)	167 (21.2)
Procedural complication	156 (16.7)	164 (20.8)
Sepsis	119 (12.8)	133 (16.9)
Chills	124 (13.3)	122 (15.5)
Pain	104 (11.2)	95 (12.1)
Metabolic and Nutritional Disorders		
Hypomagnesemia	238 (25.5)	274 (34.8)
Hypokalemia	239 (25.5)	249 (31.6)
Peripheral edema	112 (12.0)	116 (14.7)
Edema	124 (13.3)	115 (14.6)
Hypervolemia	85 (9.1)	101 (12.8)
Hyperglycemia	78 (8.4)	96 (12.2)
Hypocalcemia	80 (8.6)	93 (11.8)
Hemic and Lymphatic System		
Leukopenia	384 (41.2)	367 (46.6)
Thrombocytopenia	358 (38.4)	337 (42.8)
Anemia	206 (22.1)	215 (27.3)
Nervous System		

Clinical Review
 Mary E. Singer, M.D., Ph.D.
 Micafungin sodium for Esophageal Candidiasis
 Mycamine (Micafungin sodium)

Headache	251 (26.9)	197 (25.0)
Insomnia	183 (19.6)	166 (21.1)
Anxiety	110 (11.8)	97 (12.3)
Dizziness	71 (7.6)	96 (12.2)
Respiratory System		
Cough increased	127 (13.6)	130 (16.5)
Rhinitis	95 (10.2)	94 (11.9)
Lung disorder	84 (9.0)	93 (11.8)
Dyspnea	76 (8.2)	90 (11.4)
Epistaxis	66 (7.1)	90 (11.4)
Cardiovascular system		
Hypertension	103 (11.1)	120 (15.2)
Tachycardia	121 (13.0)	114 (14.5)
Hypotension	95 (10.2)	94 (11.9)
Skin and Appendages		
Rash	229 (24.6)	198 (25.2)
Pruritis	104 (11.2)	105 (13.3)

7.1.5.5 Identifying common and drug-related adverse events

An adverse event was considered to be drug-related if it was assessed by the Investigator as possibly, probably, or definitely related to study drug. Overall, 29.9% (717/2404) subjects (patients and volunteers) experienced an adverse event considered by the investigator to be drug-related; while 29.8% (591/1980) patients had a drug-related adverse event. The most common drug-related adverse events included nausea (2.8%), increased ALT (2.7%), increased AST (2.6%), headache (2.4%), vomiting (2.4%), and increased alkaline phosphatase (2.0%). The most common ($\geq 0.5\%$) drug-related adverse events in micafungin-treated subjects are shown in the table below.

Clinical Review
 Mary E. Singer, M.D., Ph.D.
 Micafungin sodium for Esophageal Candidiasis
 Mycamine (Micafungin sodium)

Table 58. Common Drug-Related* Adverse Events in Subjects† Who Received MYCAMINE in Clinical Trials

Adverse Events ⁽¹⁾ (MedDRA System Organ Class and Preferred Term)	MYCAMINE n (%)
Number of Subjects	2402
Blood and Lymphatic System	
Leukopenia	38 (1.6)
Neutropenia	29 (1.2)
Thrombocytopenia	20 (0.8)
Anemia	19 (0.8)
Gastrointestinal Disorders	
Nausea	67 (2.8)
Vomiting	58 (2.4)
Diarrhea	38 (1.6)
Abdominal pain	23 (1.0)
Abdominal pain upper	11 (0.5)
General Disorders and Administration Site Conditions	
Pyrexia	37 (1.5)
Rigors	23 (1.0)
Injection site pain	21 (0.9)
Hepatobiliary Disorders	
Hyperbilirubinemia	25 (1.0)
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)
Blood creatinine increased	14 (0.6)
Blood urea increased	12 (0.5)
Blood lactate dehydrogenase increased	11 (0.5)
Metabolism and Nutrition Disorders	
Hypokalemia	28 (1.2)
Hypocalcemia	27 (1.1)
Hypomagnesemia	27 (1.1)
Nervous System Disorders	
Headache	57 (2.4)
Dizziness	16 (0.7)
Somnolence	12 (0.5)
Skin and Subcutaneous Tissue Disorders	
Rash	38 (1.6)
Pruritus	18 (0.7)
Vascular Disorders	
Phlebitis	39 (1.6)
Hypertension	14 (0.6)
Flushing	12 (0.5)

Patient base: all randomized patients who received at least 1 dose of trial drug
 Common: Incidence of adverse event $\geq 0.5\%$.

Clinical Review

Mary E. Singer, M.D., Ph.D.

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

*Relationship to drug was determined by the investigator to be possibly, probably, or definitely drug-related.

†Subjects included patients and volunteers

⁽¹⁾Within a system organ class, patients may experience more than 1 adverse event

Medical Officer Comments: We have proposed that this table be included in the final micafungin labeling. Although the clinical safety summaries, including the 120-day Safety Update, and most of the individual study reports used COSTART terminology for coding adverse events, the Applicant proposed drug-related adverse event tables using the MedDRA terminology in their proposed label of 24 August, 2004.

The incidence of drug-related adverse events in subjects and patients is also shown by COSTART terminology in the table below. Those adverse events which occurred in more subjects (patients plus volunteers) than patients were those that also occurred in volunteers, and are highlighted in bold font below.

Table 59. Most Common Drug-Related Adverse Events* in Micafungin-treated patients and subjects in Safety Database (adapted from applicant's Tables 6.1.1 and 6.1.2)

Adverse Event COSTART Terms	Subjects N=2402	Patients N=1980
Metabolic and Nutritional disorders:		
AST increased	64 (2.7)	53 (2.7)
ALT increased	63 (2.6)	48 (2.4)
Alkaline phosphatase increased	49 (2.0)	49 (2.5)
Bilirubinemia	36 (1.5)	35 (1.8)
Hypomagnesemia	32 (1.3)	32 (1.6)
Hypocalcemia	29 (1.2)	29 (1.5)
Hypokalemia	30 (1.2)	28 (1.4)
Digestive System:		
Nausea	69 (2.9)	59 (3.0)
Vomiting	58 (2.4)	54 (2.7)
Diarrhea	48 (2.0)	43 (2.2)
Liver function tests abnormal	46 (1.9)	31 (1.6)
Body as a whole:		
Abdominal pain	42 (1.7)	36 (1.8)
Fever	42 (1.7)	39 (2.0)
Procedural complication	29 (1.2)	8 (0.4)
Chills	26 (1.1)	25 (1.3)
Cardiovascular system:		
Phlebitis	37 (1.5)	26 (1.3)
Vasodilatation	23 (1.0)	15 (0.8)

Clinical Review
 Mary E. Singer, M.D., Ph.D.
 Micafungin sodium for Esophageal Candidiasis
 Mycamine (Micafungin sodium)

Nervous system:		
Headache	56 (2.3)	37 (1.9)
Hemic and Lymphatic System:		
Leukopenia	59 (2.5)	59 (3.0)
Anemia	29 (1.2)	28 (1.4)
Thrombocytopenia	23 (1.0)	22 (1.1)
Skin and appendages:		
Rash	56 (2.3)	49 (2.5)
Pruritis	24 (1.0)	20 (1.0)

≥ 1% in either subjects or patients

Medical Officer Comments: Most of these drug-related adverse events occurred in volunteers except for increased alkaline phosphatase, hypomagnesemia, hypocalcemia, and leukopenia.

Drug-Related Adverse Events in Fluconazole-Controlled Studies

A total of 27.4% (255/932) micafungin-treated patients and 21.5% (169/787) fluconazole-treated patients experienced an adverse event which was considered at least possibly drug-related by the investigator. The most common drug-related events in these studies are shown in the following table. Those events attributed more frequently to micafungin than to fluconazole included nausea, vomiting, abdominal pain, fever, chills, increased alkaline phosphatase, hypokalemia, hypophosphatemia, rash, maculopapular rash, pruritis, leukopenia, anemia, headache, phlebitis, and injection site inflammation. These events are highlighted in bold font in the table below.

Table. 60. Most Common Drug-Related Adverse Events* in Fluconazole-controlled studies (adapted from applicant's appendix 6.1.3, Clinical Summary of Safety, Update, July, 2004)

Adverse Events COSTART Body System and Term	Micafungin N=932 n (%)	Fluconazole N=787 n (%)
Digestive System:		
Nausea	29 (3.1)	23 (2.9)
Diarrhea	21 (2.3)	18 (2.3)
Vomiting	20 (2.1)	11 (1.4)
Liver function tests abnormal	9 (1.0)	13 (1.7)
Body as a whole:		
Abdominal pain	21 (2.3)	12 (1.5)
Fever	20 (2.1)	5 (0.6)
Chills	11 (1.2)	6 (0.8)
Metabolic and nutritional disorders:		
AST increased	16 (1.7)	13 (1.7)

Clinical Review
 Mary E. Singer, M.D., Ph.D.
 Micafungin sodium for Esophageal Candidiasis
 Mycamine (Micafungin sodium)

Bilirubinemia	15 (1.6)	14 (1.8)
Alkaline phosphatase increased	14 (1.5)	5 (0.6)
ALT increased	13 (1.4)	14 (1.8)
Hypokalemia	12 (1.3)	9 (1.1)
Hypophosphatemia	10 (1.1)	4 (0.5)
Skin and appendages:		
Rash	25 (2.7)	12 (1.5)
Maculopapular rash	12 (1.3)	0 (0)
Pruritis	12 (1.3)	7 (0.9)
Hemic and lymphatic system:		
Leukopenia	32 (3.4)	13 (1.7)
Anemia	15 (1.6)	9 (1.1)
Thrombocytopenia	8 (0.9)	10 (1.3)
Nervous system:		
Headache	22 (2.4)	8 (1.0)
Somnolence	8 (0.9)	10 (1.3)
Cardiovascular system:		
Phlebitis	12 (1.3)	6 (0.8)
Injection site reactions:		
Injection site inflammation	17 (1.8)	10 (1.3)

*≥ 1.0% in either treatment group

The following table shows common drug-related adverse events in the pivotal esophageal candidiasis study, 03-7-005. In comparison to patients who received fluconazole, drug-related events which occurred more frequently in micafungin-treated patients included leukopenia, rigors, fever, infusion site inflammation, headache, rash, and phlebitis, as highlighted in the table below.

Clinical Review
Mary E. Singer, M.D., Ph.D.
Micafungin sodium for Esophageal Candidiasis
Mycamine (Micafungin sodium)

Table 61. Common Drug-Related * Adverse Events Among Patients with Esophageal Candidiasis (Study 03-7-005)

Adverse Events ⁽¹⁾ (MedDRA System Organ Class and Preferred Term)	MYCAMINE 150 mg/day	Fluconazole 200 mg/day
Number of Patients	260	258
Blood and Lymphatic System		
Leukopenia	7 (2.7%)	2 (0.8%)
Neutropenia	3 (1.2%)	1 (0.4%)
Thrombocytopenia	3 (1.2%)	4 (1.6%)
Anemia	3 (1.2%)	4 (1.6%)
Lymphopenia	2 (0.8%)	1 (0.4%)
Eosinophilia	0	2 (0.8%)
Gastrointestinal Disorders		
Nausea	6 (2.3%)	7 (2.7%)
Abdominal Pain	5 (1.9%)	4 (1.6%)
Vomiting	3 (1.2%)	4 (1.6%)
General Disorders and Administration Site Conditions		
Rigors	6 (2.3%)	0
Pyrexia	5 (1.9%)	1 (0.4%)
Infusion Site Inflammation	4 (1.5%)	3 (1.2%)
Laboratory Tests		
Blood Alkaline Phosphatase Increased	4 (1.5%)	4 (1.6%)
Aspartate Aminotransferase Increased	2 (0.8%)	4 (1.6%)
Blood Lactate Dehydrogenase Increased	2 (0.8%)	3 (1.2%)
Transaminases Increased	2 (0.8%)	1 (0.4%)
Alanine Aminotransferase Increased	1 (0.4%)	5 (1.9%)
Metabolism and Nutrition Disorders		
Hypomagnesemia	0	3 (1.2%)
Nervous System Disorders		
Headache	7 (2.7%)	3 (1.2%)
Dizziness	1 (0.4%)	2 (0.8%)
Somnolence	1 (0.4%)	7 (2.7%)
Psychiatric Disorders		
Delirium	2 (0.8%)	2 (0.8%)
Skin and Subcutaneous Tissue Disorders		
Rash	8 (3.1%)	5 (1.9%)
Pruritus	3 (1.2%)	3 (1.2%)
Vascular Disorders		
Phlebitis	11 (4.2%)	6 (2.3%)

Patient base: all randomized patients who received at least 1 dose of trial drug

Common: ≥0.5% in either treatment arm.

*Relationship to drug was determined by the investigator to be possibly, probably, or definitely drug-related.

⁽¹⁾ Within a system organ class patients may experience more than 1 adverse event.

Medical Officer Comments: We have proposed that this adverse event table be included in the final product labeling for micafungin in the ADVERSE EVENTS section.

Clinical Review

Mary E. Singer, M.D., Ph.D.

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

The following table shows common drug-related adverse events in the *Candida* prophylaxis study, 98-0-050. Those events more common in the micafungin treatment arm included neutropenia, anemia, febrile neutropenia, thrombocytopenia, vomiting, dyspepsia, hyperbilirubinemia, hypokalemia, hypophosphatemia, decreased appetite, and rash, as highlighted in the table below.

**APPEARS THIS WAY
ON ORIGINAL**

Clinical Review
Mary E. Singer, M.D., Ph.D.
Micafungin sodium for Esophageal Candidiasis
Mycamine (Micafungin sodium)

Table 62. Common Adverse Events Related* to Study Drug in Clinical Study of Prophylaxis of *Candida* Infection in Hematopoietic Stem Cell Transplant Recipients (Study 98-0-050)

Adverse Events ⁽¹⁾ (MedDRA System Organ Class and Preferred Term)	MYCAMINE 50 mg/day n (%)	Fluconazole 400 mg/day n (%)
Number of Patients	425	457
Blood and Lymphatic System Disorders		
Neutropenia	5 (1.2%)	4 (0.9%)
Anemia	4 (0.9%)	3 (0.7%)
Febrile neutropenia	4 (0.9%)	1 (0.2%)
Leukopenia	4 (0.9%)	2 (0.4%)
Thrombocytopenia	4 (0.9%)	5 (1.1%)
Gastrointestinal Disorders		
Nausea	10 (2.4%)	12 (2.6%)
Diarrhea	9 (2.1%)	14 (3.1%)
Vomiting	7 (1.6%)	5 (1.1%)
Abdominal pain	4 (0.9%)	3 (0.7%)
Dyspepsia	3 (0.7%)	1 (0.2%)
Constipation	1 (0.2%)	3 (0.7%)
Hiccups	1 (0.2%)	3 (0.7%)
Abdominal pain upper	0	3 (0.7%)
General Disorders and Administrative Site Conditions		
Pyrexia	4 (0.9%)	5 (1.1%)
Mycosal inflammation	1 (0.2%)	3 (0.7%)
Rigors	1 (0.2%)	5 (1.1%)
Fatigue	0	5 (1.1%)
Hepatobiliary Disorders		
Hyperbilirubinemia	12 (2.8%)	11 (2.4%)
Laboratory Tests		
Alanine aminotransferase increased	4 (0.9%)	9 (2.0%)
Aspartate aminotransferase increased	3 (0.7%)	9 (2.0%)
Liver function tests abnormal	3 (0.7%)	6 (1.3%)
Blood creatinine increased	1 (0.2%)	3 (0.7%)
Drug level increased	1 (0.2%)	3 (0.7%)
Transaminases increased	1 (0.2%)	4 (0.9%)
Metabolism and Nutrition Disorders		
Hypokalemia	8 (1.9%)	8 (1.8%)
Hypophosphatemia	6 (1.4%)	4 (0.9%)
Hypomagnesemia	5 (1.2%)	6 (1.3%)
Hypocalcemia	4 (0.9%)	4 (0.9%)
Appetite decreased	3 (0.7%)	0
Nervous System Disorders		
Headache	4 (0.9%)	4 (0.9%)
Dysgeusia	3 (0.7%)	1 (0.2%)
Dizziness	0	5 (1.1%)
Skin and Subcutaneous Tissue Disorders		

Clinical Review

Mary E. Singer, M.D., Ph.D.

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

Rash	6 (1.4%)	4 (0.9%)
Pruritus	4 (0.9%)	3 (0.7%)
Vascular Disorders		
Flushing	1 (0.2%)	6 (1.3%)
Hypotension	1 (0.2%)	4 (0.9%)

Patient base: all randomized patients who received at least 1 dose of trial drug

Common: $\geq 0.5\%$ in either treatment arm.

*Relationship to drug was determined by the investigator to be possibly, probably, or definitely drug-related.

⁽¹⁾ Within a system organ class patients may experience more than 1 adverse event.

Medical Officer Comments: We have recommended that this table be included in the ADVERSE EVENTS section of the final product labeling for micafungin.

7.1.5.6 Additional analyses and explorations

Drug-Related Adverse Events by Dose

The applicant analyzed drug-related adverse events by dose, comparing subjects who received ≥ 150 mg/day micafungin for ≥ 10 days (or ≥ 3 mg/kg for subjects weighing < 40 kg) to subjects who received lower doses or a shorter duration of micafungin. Overall, 222 of 606 (36.6%) subjects who received a minimum of 150 mg/day micafungin for at least 10 days experienced a drug-related adverse event, in comparison to 495 of 1796 (27.6%) subjects of patients who received a lower dose or duration. The most common drug-related adverse events are shown by micafungin in the table below. Those events which occurred more frequently at the higher dose/duration of micafungin are highlighted in bold font.

**APPEARS THIS WAY
ON ORIGINAL**