

## Clinical Review

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

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

significance level, 201 patients per treatment group would provide 80% power to demonstrate that micafungin is non-inferior to fluconazole with a non-inferiority margin of 10%.

Because a MFAS was added in the protocol amendment, the number of patients in each treatment group was increased to 230, to ensure that at least 201 treated patients per group had confirmed EC, based on an 11 % difference in the FAS and MFAS populations in the FG463-21-09 study.

## Analysis Sets

**Full Analysis Set (FAS):** All randomized patients who received at least one dose of study drug. This was the primary efficacy set as defined by the Applicant. The FAS was also the Safety Set.

**Modified Full Analysis Set (MFAS):** All randomized patients who received at least one dose of study drug and had confirmed EC at baseline. Analysis of this set for efficacy was considered a supportive analysis by the Applicant.

**Per Protocol Set (PPS):** All randomized patients who received at least one dose of study drug, had confirmed EC at baseline, who had both baseline and EOT endoscopy, and who had no major protocol deviations. Analysis of this set for efficacy was considered a secondary analysis by the Applicant.

## Study Results

### Patient Disposition

A total of 776 patients were screened to obtain the 523 patients who were randomized in the study at 35 investigational sites in South Africa, Brazil, and Peru. Most (71%) patients were enrolled in South Africa, followed by Brazil (17%) and Peru (12%).

The study populations are summarized in the table below. A total of 265 patients were randomized to micafungin, and 5 patients did not receive study drug; while 258 patients were randomized to fluconazole and all randomized patients received at least one dose of study drug.

Table 5. Summary of Patient Disposition (Applicant's Table 1, study report)

Parameter	Treatment Group	
	Micafungin (n=265)	Fluconazole (n=258)
All Randomized Patients	265 (100.0%)	258 (100.0%)
Full Analysis Set (Safety Set)	260 (98.1%)	258 (100.0%)
Modified Full Analysis Set	230 (83.0%)	215 (83.3%)
Per Protocol Set	189 (71.3%)	192 (74.4%)

Patient base: all randomized patients.

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**Reasons for Exclusion from the Per Protocol Set**

A total of 189/265 (71.3%) patients who received micafungin and 192/258 (74.4%) patients who received fluconazole were included in the Per Protocol Set. Reasons for exclusion in the PPS are shown in the table below. The most frequent reason for exclusion was lack of confirmed EC at baseline in both treatment groups, 51/265 (19.2%) of those who received micafungin, and 48/258 (18.6%) of those who received fluconazole.

Table 6. Reasons for Exclusion from the Per Protocol Set (Applicant’s Table 2, study report)

Reason	Treatment Group	
	Micafungin (n=265)	Fluconazole (n=258)
Received <10 doses of study drug	22 (8.3%)	13 (5.0%)
Did not have confirmed esophageal candidiasis at baseline	51 (19.2%)	48 (18.6%)
Did not have a baseline and/or end of therapy endoscopy performed	25 (9.4%)	21 (8.1%)
Had additional major protocol deviations	2 (0.8%)	3 (1.2%)

Patient base: all randomized patients.

Additional major protocol deviations included in Table \_ above, included EOT endoscopy performed 2 days prior to last dose of study drug (1 micafungin patient); concomitant Herpes simplex or cytomegalovirus esophagitis (1 micafungin patient and 1 fluconazole patient); ≥ 3 prior episodes of EC (1 fluconazole patient); and unacceptable use of prior or concomitant medications (1 fluconazole patient).

*Medical Officer Comments: The overall proportion of patients excluded from the PPS was similar for both treatment groups, and the reasons for exclusions were proportionately similar.*

**Study Completion**

Seventy seven (77%) of micafungin-treated patients completed the study in comparison to 83% of fluconazole-treated patients. Patient status at the end-of-study is shown in the following table.

Table 7. Patient Status at End of Study (Applicant’s Table 4, study report)

Status	Treatment Group	
	Micafungin (n=265)	Fluconazole (n=258)
Completed Study	204 (77.0%)	214 (83.0%)
Death	30 (11.3%)	28 (10.8%)
Lost to follow-up	22 (8.3%)	14 (5.4%)
Other	9 (3.4%)	7 (2.8%)

Patient base: all randomized patients.

n=total number of patients randomized to each treatment group.

Other: study drug was not administered (5 micafungin patients), amendment 1 was not approved at the time the patient completed the study, so 4-week posttreatment visit was not included (2 micafungin patients and 2 fluconazole patients), baseline infection was not confirmed (1 micafungin patient), and withdrawal of consent (1 micafungin patient).

Source: Table 13.1.1 and Appendix 14.4.1.1.

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*Medical Officer Comments: The proportions of patients who died and who were lost to follow-up were similar for the two treatment groups.*

### Treatment discontinuation

In the micafungin treatment group, 232/260 (89.2%) patients completed therapy in comparison to 234/258 (90.7%) patients in the fluconazole treatment group.

The reasons for treatment discontinuation are shown in the table below.

Table 8. Treatment Discontinuation (adapted from Applicant's Table 5, study report)

	Micafungin N=260	Fluconazole N=258
Completed Therapy	232 (89.2)	234 (90.7)
Discontinued Therapy	28 (10.8)	24 (9.3)
Reasons for Treatment Discontinuation:		
Discontinuation due to Adverse Event:	17 (6.5)	12 (4.7)
- Drug-related adverse event	6 (2.3)	1 (0.4)
- Adverse event resulting in death	10 (3.8)	9 (3.5)
Discontinuation due to withdrawn consent	2 (0.8)	0
Discontinuation due to non-compliance with protocol	5 (1.9)	4 (1.6)
Lack of efficacy	2 (0.8)	6 (2.3)
Other	2 (0.8)	2 (0.8)

N= number of patients in FAS

Other: Herpes virus infection (1 micafungin patient); non-compliance (1 micafungin patient); concomitant Herpes esophagitis (1 fluconazole patient); patient too ill to participate (1 fluconazole patient)

*Medical Officer Comments: A somewhat higher proportion of patients who received micafungin required study drug discontinuation due to adverse events in comparison to those who received fluconazole, 6.5% and 4.7%, respectively. Additionally, more of the adverse events resulting in drug discontinuation were considered drug-related in the micafungin treatment group; while the overall proportion of discontinuations due to adverse events which resulted in death were similar for both groups.*

### Patient Demographics

Overall, most patients enrolled in this study were black, 356/518 (68.3%) and female, 271/518 (52.3%). The patient distribution by race and gender was similar for both treatment groups, although a somewhat higher proportion of female patients received fluconazole. This difference was not statistically significant. The mean age for patients in both treatment groups was approximately 37 years old. Patient demographic data is shown in the following table.

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Table 9. Patient Demographics (Applicant's Table 6, study report)

Parameter	Treatment Group	
	Micafungin (n=260)	Fluconazole (n=258)
Race		
Caucasian	38 (14.6%)	35 (13.6%)
Black	176 (67.7%)	178 (69.0%)
Mestizo	32 (12.3%)	29 (11.2%)
Other	14 (5.4%)	16 (6.2%)
Gender		
Male	131 (50.4%)	116 (45.0%)
Female	129 (49.6%)	142 (55.0%)
Age (years)		
Mean ± SD	37.2 ± 10.59	37.5 ± 11.16
Range	17.0 to 80.0	17.0 to 87.0

Patient base: all randomized patients who received at least one dose of study drug (Full Analysis Set).  
 n=total number of patients in each treatment group.  
 SD: standard deviation.  
 Other includes verbatim terms of Cape Colored (4 micafungin and 2 fluconazole patients), Colored (6 micafungin and 5 fluconazole patients), Mixed/Mixed Race (2 micafungin and 1 fluconazole patients), Mulatto (1 micafungin and 7 fluconazole patients), and Multiracial (1 micafungin patient).

**Underlying Disease**

Most patients in each of the treatment groups had underlying HIV disease (suspected or confirmed). A total of 245/260 (94.2%) patients had HIV in the micafungin group, and 241/258 (93.4%) patients had HIV in the fluconazole group. Baseline CD<sub>4</sub> counts for patients with HIV are shown in the table below.

Table 10. HIV Disease Status for Patients in Study 03-7-005

Parameter	Micafungin Patients with HIV N=245	Fluconazole Patients with HIV N=241
*Mean CD <sub>4</sub> Count ± SD	109 ± 191 cells/mm <sup>3</sup>	110 ± 182 cells/mm <sup>3</sup>
*Median CD <sub>4</sub> count	39	37
*CD <sub>4</sub> count range	0-1609	0-1419
Patients receiving Antiretroviral Therapy	22/245 (9.0%)	30/241 (12.4%)

\*data derived directly from database

*Medical Officer Comments: Although the mean CD<sub>4</sub> counts were similar between treatment groups, there was a wide range of CD<sub>4</sub> counts within each group. The median CD<sub>4</sub> count was low (37-39 cells/mm<sup>3</sup>) for each treatment group, indicating a highly immunocompromised population among patients with HIV.*

**Other Underlying Diseases**

Overall, 32 patients in this study (15 patients who received micafungin and 17 who received fluconazole) had underlying diseases other than HIV, as shown in the following table.

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Table 11. Primary Underlying Disease (adapted from Applicant's Table 13.2.2, study report)

Primary Underlying Disease	Micafungin N=260	Fluconazole N=258	Total N=518
HIV	245 (94.2)	241 (93.4)	486 (93.8)
Diabetes mellitus	4 (1.5)	1 (0.4)	5 (1.0)
Bacterial sepsis	0	1 (0.4)	1 (0.2)
Malignancy	4 (1.5)	9 (3.5)	13 (2.5)
Immune disorder	1 (0.4)	1 (0.4)	2 (0.4)
Lung disorder	3 (1.2)	1 (0.4)	4 (0.8)
Other	3 (1.2)	4 (1.6)	7 (1.4)

*Medical Officer Comments: proportionately more patients in the fluconazole group had malignancy listed as the primary underlying disease 3.5%, in comparison to 1.5% in the micafungin group. Depending on whether these patients were receiving chemotherapy or transplant, the fluconazole group may have had more sicker patients overall than those in the micafungin group; however the number of patients with malignancy was small (9 in fluconazole and 4 in micafungin group), and overall efficacy outcome for each group would not be expected to differ significantly on this basis.*

**Baseline Esophageal Candidiasis**

Baseline endoscopic mucosal grade, mean EC symptom grade score, and number of prior EC episodes was similar in both treatment groups at baseline, as shown in the next table. Most patients had a mucosal grade of 1 or 2 at baseline; while 75/260 (28.8%) micafungin-treated and 63/259 (24.4%) fluconazole-treated patients had severe EC at baseline. Most patients in each treatment group had no prior episodes of EC.

Table 12. Characteristics of Esophageal Candidiasis at Baseline (adapted from Applicant's Table 7, study report)

Parameter	Micafungin N=260	Fluconazole N=258
Baseline Mucosal Grade:		
1	87 (33.5)	96 (37.2)
2	98 (37.7)	99 (38.4)
3	75 (28.8)	63 (24.4)
Total EC Symptom Grade:		
Mean ± SD	4.2 ± 1.84	4.3 ± 1.98
Range	1.0 to 9.0	1.0 to 9.0
Number of Prior EC Episodes		
0	225 (86.5)	225 (87.2)
1	25 (9.6)	23 (8.9)

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2	7 (2.7)	6 (2.3)
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SD= standard deviation

**Medical Officer Comments:** In the applicant's analysis, no significant difference was noted between treatment groups for baseline mucosal grade (p-value= 0.499).

### Oropharyngeal Candidiasis at Baseline

The incidence of OPC at baseline was similar in the micafungin group, 88.5% (230/260), and the fluconazole group, 88.8% (229/258) at baseline. Mean OPC grades were also similar at baseline in the micafungin (mean 4.2 ± 2.86) and fluconazole (mean 4.2 ± 2.80) groups.

### Fungal Cultures at Baseline

*Candida albicans* was the most common organism identified at baseline, found in 233/236 (98.7 %) micafungin-treated patients with a positive culture, and in 226/227 (99.6 %) fluconazole-treated patients with a positive culture. Culture results were negative in 29/260 (11.2%) patients randomized to micafungin, and in 31/258 (12.1%) of those randomized to fluconazole. Other *Candida* species were found in 12/260 (4.6%) patients randomized to micafungin, and 13/258 (5.0%) of those randomized to fluconazole. Most of these organisms were co-isolated with *C. albicans*. Baseline fungal culture data is shown in the table below.

Table 13. Baseline Fungal Culture Data (FAS) (medical officer's analysis from database)

Baseline <i>Candida</i> isolate (s)	Micafungin N=260 n (%)	Fluconazole N=258 n (%)
No organism isolated	31 (11.9)	27 (10.5)
<i>Candida albicans</i>	222 (85.4)	218 (84.5)
<i>C. albicans</i> and <i>C. glabrata</i>	5	4
<i>C. albicans</i> , <i>C. glabrata</i> , and <i>C. krusei</i>	1	1
<i>C. albicans</i> and <i>C. inconspicua</i>	1	0
<i>C. albicans</i> and <i>C. tropicalis</i>	1	1
<i>C. albicans</i> and <i>C. krusei</i>	0	2
<i>C. albicans</i> , <i>C. glabrata</i> , <i>Candida sp.</i> , and <i>C. tropicalis</i>	0	1
<i>C. kefyr</i>	1	0
<i>Candida species</i>	3	2
<i>C. parapsilosis</i>	0	1

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N= number of patients in FAS

n (%) = number and proportion of patients with isolate or combination of isolates at baseline

*Medical Officer Comments: The number of non-ablicans Candida isolates in each treatment group was low, and conclusions regarding the use of micafungin for treatment of non-albicans isolates will be limited. Additionally, the applicant noted in the study summary that 3 patients had non-Candida fungi isolated at baseline (Saccharomyces cerevisiae and Trichosporon beiglei each in 1 micafungin and 1 fluconazole patient; and Cryptococcus neoformans in 1 fluconazole patient). These patients were not located in the database.*

### Prior Antifungal Therapy

The use of systemic antifungal therapy within 14 days of receipt of the first dose of study medication was reported in 11/260 (4.2%) micafungin-treated, and 7/258 (2.7%) fluconazole-treated patients. Non-systemic (topical) antifungal therapy was reported in 10/260 (3.8%), and 16/258 (6.2%) micafungin- and fluconazole-treated patients, respectively.

*Medical Officer Comments: A similar proportion of patients in the micafungin group, 21/260 (8.1%) patients and in the fluconazole group, 23/258 (8.9%) patients received either topical or systemic antifungal therapy in the 2 weeks preceding the first dose of study medication. Because patients were excluded if they received topic antifungal therapy within 48 hours or systemic therapy within 72 hours of receiving the first dose of study medication, the use of prior antifungal therapy probably did not influence efficacy outcomes.*

### Concomitant Antifungal Therapy

The use of antifungal therapy during the study is shown in the following table .

Table 14. Concomitant Antifungal Therapy

Antifungal Therapy	Micafungin N=260	Fluconazole N=258
<b>During Treatment with Study Drug</b>		
Systemic	0	2 (0.8)
Non-systemic (topical)	1 (0.4)	3 (1.2)
<b>During Post-treatment Period</b>		
Systemic	44 (16.9)	30 (11.6)
Non-systemic (topical)	14 (5.4)	8 (3.1)

*Medical Officer Comments: If a patient required a systemic or topical antifungal agent during the treatment period (dosing with study drug), the patient was to be*

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*discontinued from study drug therapy. More patients in the fluconazole group required treatment with another antifungal agent in the treatment period.*

*Antifungal therapy was not prohibited in the post-treatment period, and the proportion of patients who received systemic antifungal therapy during this time frame was higher for those who received micafungin than those who received fluconazole. The use of systemic antifungal therapy during the post-treatment period may confound the analysis of relapse, unless patients who received antifungal medications during this time were counted as relapses.*

### Other Concomitant Medication

Antibacterial agents were used concomitantly in 130/260 (50%) micafungin-treated, and in 116/258 (45%) fluconazole-treated patients. Antituberculous medication use was also similar in each group, with concomitant use in 50/260 (19.2%) micafungin-treated, and 55 (21.3%) in fluconazole-treated patients. Systemic antiviral agents (including antiretroviral agents) were used concomitantly in 27/260 (10.4%) micafungin-treated, and in 33/258 (12.8%) fluconazole-treated patients.

*Medical Officer Comments: The concomitant use of antibacterial, antituberculous, and antiviral drugs was similar in both treatment groups, and the use of other concomitant medications was also similar for the two treatment groups.*

### Efficacy

#### Primary Endpoint- Endoscopic Response at End-of-Therapy

Endoscopic cure (success) was achieved in 228/260 (87.7%) of patients treated with micafungin and in 227/258 (88.0%) of patients treated with fluconazole. The 95% confidence interval around the treatment difference of -0.3% (micafungin minus fluconazole cure rates) was [-5.9%, 5.3%]. Because the lower limit of the confidence interval was < 10%, micafungin was shown to be non-inferior to fluconazole for this primary endpoint in the FAS. Similar cure rates were observed in the MFAS, and higher cure rates in the PPS. For all three analyses, the lower limit of the confidence interval was within the bounds of the pre-specified non-inferiority margin of 10%.

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Table 15. Endoscopic Response at End-of-Therapy (Applicant's Table 8, report summary)

Treatment Outcome	Treatment		Treatment Difference	95% CI for the Difference
	Micafungin	Fluconazole		
Full Analysis Set	n=260	n=258		
Success	228 (87.7%)	227 (88.0%)	-0.3%	[-5.9%, 5.3%]
Failure	32 (12.3%)	31 (12.0%)		
Mucosal Grade >0	7 (2.7%)	10 (3.9%)		
Not Evaluable	25 (9.6%)	21 (8.1%)		
Modified Full Analysis Set	n=220	n=215		
Success	191 (86.8%)	188 (87.4%)	-0.6%	[-6.9%, 5.7%]
Failure	29 (13.2%)	27 (12.6%)		
Mucosal Grade >0	6 (2.7%)	10 (4.7%)		
Not Evaluable	23 (10.5%)	17 (7.9%)		
Per Protocol Set	n=189	n=192		
Success	183 (96.8%)	182 (94.8%)	2.0%	[-2.0%, 6.0%]
Failure	6 (3.2%)	10 (5.2%)		
Mucosal Grade >0	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 confirmed esophageal candidiasis 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.

Endoscopic cure: mucosal grade=0 at end of therapy.

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

95% Confidence Interval: the 95% CI for the difference in success is based on the large sample normal approximation.

*Medical Officer Comments: In the FAS and MFAS, the most common reason for treatment failure in both treatment groups was patient non-evaluability, which was due primarily to premature discontinuation due to adverse events.*

**Secondary Efficacy Endpoints**

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**Clinical Response at EOT**

The applicant defined clinical success as “cleared” or “improved” for symptoms of EC (odynophagia, dysphagia, and retrosternal pain). Clinical failure included “unchanged”, “worse”, and not evaluable. Clinical success is shown in the table below.

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Table.16 Clinical Success at EOT (“Cleared” or “Improved”) (adapted from Applicant’s Table 8, study report)

Clinical Response	Micafungin	Fluconazole	Treatment Difference*	95% Confidence Interval
FAS	N=260	N=258		
Success	245 (94.2)	244 (94.6)	-0.3 %	[-4.3%, 3.6%]
Cleared	239 (91.9)	237 (91.9)	0	
Improved	6 (2.3)	7 (2.7)	-0.4 %	
MFAS	N=220	N=215		
Success	206 (93.6)	206 (95.8)	-2.2 %	[-6.4%, 2.0%]
Cleared	200 (90.9)	199 (92.6)	-1.7 %	
Improved	6 (2.7)	7 (3.3)	-0.6 %	
PPS	N=189	N=192		
Success	187 (98.9)	189 (98.4)	0.5 %	[-1.8%, 2.8%]
Cleared	184 (97.4)	183 (95.3)	-1.5 %	
Improved	3 (1.6)	6 (3.1)	-0.5%	

N= number of patients in analysis set

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

**Medical Officer Comment:** Most patients with clinical success in both treatment groups had resolution of clinical symptoms (“cleared”), 91.9% in each treatment group in the FAS. If patients whose clinical symptoms had only improved were considered clinical failure, the clinical success rates would still be > 90% for both treatment groups for each analysis set. Efficacy results from this secondary endpoint support the conclusions drawn from the primary outcome measure, endoscopic cure at EOT.

Clinical failure was predominantly due to patient non-evaluability in the FAS analysis sets, with 13/15 (87%) failures due to non-evaluability in the micafungin group, and 10/14 (71%) failures due to non-evaluability in the fluconazole group. In the FAS 1/258 (0.4%) patients treated with fluconazole had symptoms that were worse than baseline; while none of the 260 (0%) micafungin treated patients had worsening or symptomatic progression at the end-of therapy. Two of 260 (0.8%) micafungin-treated patients and 3/258 (1.2%) fluconazole-treated patients had EC symptoms that were unchanged at the EOT.

#### Overall Therapeutic Response

Overall therapeutic success was defined by the applicant as Clinical Success (“cleared” or “improved”), plus mucosal response (endoscopic response in comparison to baseline) of “cleared” or “improved” at the end of therapy. Overall Therapeutic Response is shown in the table below.

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Table 17. Overall Therapeutic Response at EOT (adapted from Applicant's Tables 13.4.4.1.1, 13.4.4.1.2, and 13.4.4.1.3)

Overall Therapeutic Response	Micafungin	Fluconazole	Treatment Difference	95% Confidence Interval
FAS	N=260	N=258		
Success	227 (87.3)	225 (87.2)	0.1	[-5.6%, 5.8%]
Failure	33 (12.7)	33 (12.8)		
MFAS	N= 220	N=215		
Success	190 (86.4)	187 (87.0)	-0.6	[-7.0%, 5.8%]
Failure	30 (13.6)	28 (13.0)		
PPS	N=189	N=192		
Success	182 (96.3)	181 (94.3)	2.0%	[-2.2%, 6.3%]
Failure	7 (3.7)	11 (5.7)		

N= number of patients in analysis set

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

*Medical Officer Comments: The Applicant analyzed EC relapse in patients with overall therapeutic success. However, in the medical officer's opinion, only patients with overall therapeutic cure, defined as those patients with an endoscopic grade of 0 and clinically "cleared" at the end-of-treatment would be more appropriate for relapse evaluation, as shown below.*

These data were re-analyzed using the definition above for overall therapeutic cure, endoscopic cure (grade 0) plus clinical cure ("cleared"), as shown in the table below. These data support the conclusions drawn from the primary efficacy analysis.

Table 18. Overall Therapeutic Cure at EOT in FAS (Analysis by Medical Officer and Statistical Reviewer)

	Micafungin N=260	Fluconazole N=258	Treatment Difference (Micafungin- Fluconazole)	95% Confidence Interval
	n (%)	n (%)		
Overall Therapeutic Cure*	223 (85.8)	220 (85.3)	0.5	[-5.6, +6.6%]

\* Overall therapeutic cure was defined as patients with endoscopic grade 0 and clinical "cleared" at EOT.

n (%) = number and proportion of patients with overall therapeutic cure.

*Medical Officer Comments: The proportion of patients with overall therapeutic "cure" did not differ significantly from the proportion with overall therapeutic*

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

### Incidence of Relapse

Relapse was assessed at 2 weeks and 4 weeks post-treatment for patients who had overall therapeutic success (endoscopic grade 0 plus clinically “cleared” or “improved”). This analysis was performed by the applicant in two ways: excluding missing values and including missing values as failures (relapse). These analyses are shown in Tables 19 and 20 below.

Table 19. Incidence of Relapse during Post-treatment Period (excluding Missing Values) (applicant’s Table 10, report summary)

Posttreatment Visit	Treatment Group		P-Value
	Micafungin	Fluconazole	
<b>Full Analysis Set</b>			
Relapse at 2-Week Visit	13/205 (6.3%)	8/208 (3.8%)	0.313
Relapse at 4-Week Visit <sup>1</sup>	17/185 (9.2%)	14/188 (7.4%)	0.498
Relapse through Week 4 Visit <sup>2</sup>	30/198 (15.2%)	22/195 (11.3%)	0.257
<b>Modified Full Analysis Set</b>			
Relapse at 2-Week Visit	9/170 (5.3%)	7/171 (4.1%)	0.743
Relapse at 4-Week Visit <sup>1</sup>	13/154 (8.4%)	13/154 (8.4%)	0.821
Relapse through Week 4 Visit <sup>2</sup>	22/163 (13.5%)	20/160 (12.5%)	0.721
<b>Per Protocol Set</b>			
Relapse at 2-Week Visit	9/164 (5.5%)	7/165 (4.2%)	0.767
Relapse at 4-Week Visit <sup>1</sup>	12/148 (8.1%)	12/148 (8.1%)	0.918
Relapse through Week 4 Visit <sup>2</sup>	21/157 (13.4%)	19/154 (12.3%)	0.786

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

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.

<sup>1</sup>Patients that relapsed at the 2-week posttreatment visit are not included in the 4-week posttreatment analysis.

<sup>2</sup>Patients that were not a relapse at week 2 and did not have a 4-week assessment are excluded from the analysis.

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Table 20. Incidence of Relapse during the Post-treatment Period (including Missing Values as Relapses) (Applicant's Table 11, study report)

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 <sup>1</sup>	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 <sup>1</sup>	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 <sup>1</sup>	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.

<sup>1</sup>Patients that relapsed at the 2-week posttreatment visit are not included in the 4-week posttreatment analysis.

*Medical Officer Comments: Relapse data was re-analyzed below evaluating only patients who had both clinical and endoscopic cure, rather than those with clinical and endoscopic cure or improvement. In the medical officer's opinion, patients who did not have complete resolution of EC at the end-of-therapy, were not appropriate for relapse evaluation.*

The statistical reviewer evaluated relapse in patients with overall therapeutic success (using the definition of "cleared" for both clinical and endoscopic responses), counting patients as relapses if relapse evaluation was not performed, if the patient died or was lost to follow-up, or if the patient received systemic antifungal therapy post-treatment. This analysis is shown in the following table.

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Table 21. Relapse at 2- and 4- weeks Post-treatment in Patients with Overall Therapeutic Response in MFAS (Statistical Reviewer’s Analysis from Database)

Parameter	Micafungin	Fluconazole	Treatment difference [95% confidence interval]
<b>Two Weeks Post-treatment</b>	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	
<b>Total Relapse (relapse, not evaluated, or AFT use post-treatment)</b>	<b>40 (17.9)</b>	<b>30 (13.6)</b>	<b>4.3 [-2.5,11.1]</b>
<b>Four Weeks Post-treatment</b>	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	
<b>Total Relapse (relapse, not evaluated, or AFT use post-treatment)</b>	<b>33 (17.9)</b>	<b>32 (16.7)</b>	<b>1.2 [-6.4, 8.9]</b>
<b>Cumulative Relapse at 4 weeks</b>	<b>73/223 (32.7)</b>	<b>62/220 (28.2)</b>	<b>4.5 [-4.0, 13.1]</b>

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: Relapse rates in this analysis were somewhat higher in comparison to those reported by the applicant in Table 20 above, because patients who received systemic antifungal therapy post-treatment were all counted as having relapse in this analysis. A few of these patients received systemic antifungal prophylaxis post-treatment, but were counted as relapses because any systemic antifungal therapy would confound the analysis of relapse. Although not statistically different from the fluconazole treatment group, relapse rates at 2 weeks, 4 weeks or cumulative rate at 4 weeks were only slightly higher for the micafungin treatment group. Treatment of EC with either micafungin or fluconazole while clearly efficacious at the EOT, resulted in relapse (cumulative) in about one-third of patients by 4 weeks post-treatment. This is not wholly*

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*unexpected in patients who were not receiving antiretroviral therapy or antifungal prophylaxis.*

**Mycological Response at EOT**

In the MFAS, patients who had confirmed esophageal candidiasis, 188/22 (85.4%) of patients treated with micafungin, and 181/215 (84.2%) of those treated with fluconazole had mycological eradication or colonization at the end-of-therapy. The applicant’s analysis is shown in the next table. The overall mycological response rate is similar to the endoscopic response rate if eradication and colonization are combined.

Table 22. Mycological Response at End-of-Therapy (Applicant’s Table 17, study report)

Mycological Response	Treatment Group	
	Micafungin	Fluconazole
<b>Full Analysis Set</b>		
n	260	258
Eradication	179 (68.8%)	189 (73.3%)
Persistence (Colonization)	42 (16.2%)	31 (12.0%)
Persistence (Presumed Colonization)	7 (2.7%)	8 (3.1%)
Persistence (Invasive)	8 (3.1%)	10 (3.9%)
Not Evaluable	24 (9.2%)	20 (7.8%)
<b>Modified Full Analysis Set</b>		
n	220	215
Eradication	148 (67.3%)	155 (72.1%)
Persistence (Colonization)	40 (18.2%)	26 (12.1%)
Persistence (Presumed Colonization)	4 (1.8%)	3 (3.7%)
Persistence (Invasive)	6 (2.7%)	10 (4.7%)
Not Evaluable	22 (10.0%)	16 (7.4%)
<b>Per Protocol Set</b>		
n	189	192
Eradication	141 (74.6%)	149 (77.6%)
Persistence (Colonization)	38 (20.1%)	25 (13.0%)
Persistence (Presumed Colonization)	4 (2.1%)	8 (4.2%)
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 Comment:** *Combination of the categories mycological eradication and colonization is appropriate, because EC is an invasive fungal disease, and many patients will remain colonized but asymptomatic after effective therapy. The applicant did not explain presumed colonization and those patients were not counted among those with eradication or colonization at EOT in this analysis.*

Further analysis was performed using the MFAS to correlate the primary endpoint, endoscopic response to mycological response. These data are shown in the table below. Overall 188/220 (85.5%) micafungin-treated patients were both endoscopically cured and had mycological eradication or colonization, in comparison to 184/215 (85.6%) fluconazole-treated patients. Discordant results were observed in 8 patients in the micafungin group and in 9 patients in the fluconazole group.

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**Table 23. Correlation of Mycological and Endoscopic Response at EOT (MFAS)  
(medical officer's analysis)**

Micafungin-treated Patients N= 220	Endoscopic Success EOT	Endoscopic Failure EOT
Mycological Success*	188 (85.5)	4 (discordant)
Mycological failure	4 (discordant)	24 (11.4)
Fluconazole-treated Patients N= 215		
Mycological Success*	184 (85.6)	5 (discordant)
Mycological Failure	4 (discordant)	22 (10%)

Endoscopic success= grade 0

Endoscopic failure = > grade 0 or not evaluated

Mycological Success = eradication or persistence (colonization), or presumed colonization

Mycological Failure = persistence( invasive), not evaluated

The mycological response at EOT (eradication, colonization, or persistent invasion) is shown by endoscopic response at EOT for each treatment group to further evaluate reasons for discordance between mycological and endoscopic response, in the table below.

**Table 24. Correlation of Endoscopic and Mycological Response at EOT in MFAS  
(Medical Officer's Analysis from database)**

Endoscopic Response EOT	Mycological Eradication EOT	Mycological Colonization EOT	Mycological Persistence (invasive) EOT	Mycological Colonization (presumed) EOT	Not Evaluated EOT
<b>Micafungin-treated Patients N= 220</b>					
Success	145 (65.9)	39 (17.7)	3 (1.4)	4 (1.8)	0
Failure*	3 (1.4)	1 (0.5)	3 (1.4)	0	22 (10.0)
<b>Fluconazole-treated Patients N=215</b>					
Success	151 (70.2)	25 (11.6)	4 (1.9)	8 (3.7)	0
Failure*	4 (1.9)	1 (0.5)	6 (2.8)	0	16 (7.4)

\*endoscopic failure included any patient with endoscopic grade > 0, or not evaluated at EOT

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**Medical Officer Comments:** Reasons for discordant outcomes are not clear, but only 8 micafungin-treated and 9 fluconazole-treated patients had discordant outcomes overall. For patients with mycological success, but endoscopic failure, only 1 patient in each group was reported as not evaluated endoscopically (and counted as endoscopic failure). For a patient to be evaluated for mycologic response, endoscopy was required to obtain esophageal brushing for culture, histology and cytology, so it is not clear why these patients did not have an endoscopic response recorded. However, overall conclusions would not be changed because this occurred in only 2 patients. For patients with mycological failure, but endoscopic success, all of the patients with discordant outcomes had been evaluated mycologically.

### Mycological Response by baseline *Candida* isolates

At baseline, only 12 micafungin-treated patients, and 13 fluconazole-treated patients had non-*albicans* *Candida* isolates at baseline. Four of the 12 micafungin-treated patients had a single *Candida* isolate at baseline (1 patient with *C. kefyr* and 3 with *Candida* sp.); while the others had mixed infections with *C. albicans* and other *Candida* species. In addition, 4 of the 13 fluconazole-treated patients had a single *Candida* isolate at baseline (1 patient with *C. krusei*, 1 patient with *C. parapsilosis*, and 2 patients with *Candida* sp.); while the others had mixed infections with *C. albicans* and other *Candida* species. Outcomes at end-of-therapy and at 2- and 4-weeks post-treatment are shown for patients with non-*albicans* isolates in the table below.

Twenty seven patients in the fluconazole treatment group and 31 patients in the micafungin treatment group had no organism isolated at baseline in the FAS. Outcomes for these patients are not included in this analysis.

Table 25. Outcomes by baseline *Candida* isolate (FAS) (medical officer analysis from database)

Patient number	Baseline isolate	Endo- scopic Cure EOT	Overall Therapeutic Response EOT*	Mycological Response EOT	Relapse week 2 PT	Relapse week 4 PT
<b>Fluconazole- treated patients</b>						
2545001	<i>C.albicans</i> <i>C. krusei</i>	Cleared	Success	Eradication	No	No
0314500	<i>C.albicans</i> <i>C.glabrata</i>	Unchanged	Failure	Persistent invasive	N/A	N/A
03145014	<i>C.albicans</i> <i>C.glabrata</i>	Cleared	Success	Eradication	No	No
03235002	<i>C. krusei</i>	Cleared	Success	Colonization	No	No
03235003	<i>C.albicans</i> <i>C.glabrata</i> <i>C.tropicalis</i> <i>Candida</i> sp.	Unchanged	Failure	Persistent invasive	N/A	N/A

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03235006	<i>C.albicans</i> <i>C.tropicalis</i>	Unchanged	Failure	Persistent invasive	N/A	N/A
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Table 25. (continued) Outcomes by baseline *Candida* isolate (FAS) (medical officer analysis from database)

03235018	<i>C.albicans</i> <i>C.krusei</i>	Cleared	Success	Eradication	No	Yes
10305004	<i>C.albicans</i> <i>C.glabrata</i>	Cleared	Success	Colonization	No	No
10375002	<i>Candida sp.</i>	Not evaluated	Failure	Not evaluated	Not done	Not done
10375004	<i>Candida sp.</i>	Cleared	Success	Persistent invasive	Yes	Yes
10545002	<i>C.albicans</i> <i>C.glabrata</i>	Not evaluated	Failure	Eradication	No	No
10685009	<i>C.parapsilosis</i>	Cleared	Success	Colonization (presumed)	No	No
11635002	<i>C.albicans</i> <i>C.glabrata</i> <i>C.krusei</i>	Cleared	Success	Colonization	No	No
<b>Micafungin- treated Patients</b>						
0325015	<i>C.albicans</i> <i>C.glabrata</i>	Not evaluated	Failure	Not evaluated	Not done	Not done
03245011	<i>C.albicans</i> <i>C.inconspicua</i>	Cleared	Success	Eradication	No	No
03245014	<i>C.albicans</i> <i>C.glabrata</i> <i>C.krusei</i>	Cleared	Success	Colonization	No	Yes
10375001	<i>Candida sp.</i>	Cleared	Success	Eradication	No	No
10375003	<i>Candida sp.</i>	Cleared	Success	Colonization	No	No
10435002	<i>C.albicans</i> <i>C.tropicalis</i>	Cleared	Success	Eradication	No	No
10475001	<i>C.albicans</i> <i>C.glabrata</i>	Cleared	Success	Colonization	No	No
10705059	<i>C.kefyr</i>	Cleared	Success	Eradication	No	No
10745044	<i>Candida sp.</i>	Cleared	Success	Eradication	No	No
11645004	<i>C.albicans</i> <i>C.glabrata</i>	Unchanged	Failure	Persistent invasive	Not done	Not done
11645001	<i>C.albicans</i> <i>C.glabrata</i>	Cleared	Success	Colonization	No	No
11645006	<i>C.albicans</i> <i>C.glabrata</i>	Cleared	Success	Colonization	No	No

PT= post-treatment

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Outcomes at end-of-therapy and at 2-and 4-weeks post treatment for patients with baseline *C. albicans* alone or with non-*albicans Candida* are compared in the following table.

Table 26. Summary of Outcomes for Patients with *Candida albicans* vs. non-*albicans Candida* isolates at baseline (FAS) (Medical Officer's Analysis from database)

	Micafungin N=222 ( <i>C.albicans</i> )	Micafungin N= 12 (non- <i>albicans Candida</i> )	Fluconazole N=218 ( <i>C.albicans</i> )	Fluconazole N=13 (non- <i>albicans Candida</i> )
Endoscopic Cure EOT	195 (87.8)	10 (76.9)	195 (89.4)	8 (61.5)
Overall treatment success	194 (87.3)	10 (76.9)	193 (88.5)	8 (61.5)
Mycological eradication or colonization	196 (88.2)	10 (76.9)	196 (89.9)	8 (61.5)

*Medical Officer Comments: This was a subset analysis, subject to all the inherent limitations of post-hoc analyses, and the number of patients with non-*albicans* isolates in this study was too small to draw any firm conclusions about the treatment of esophageal candidiasis in patients with non-*albicans Candida* isolates at baseline. However, for the primary endpoint, endoscopic cure, mycological eradication, and overall treatment success, overall outcomes for patients with non-*albicans* isolates were lower within each treatment group than for those with *Candida albicans*.*

**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.

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**Table 27. Endoscopic, Clinical, and Mycological Outcomes for Esophageal Candidiasis at End-of-Treatment**

Treatment Outcome*	MYCAMINE 150 mg/day N=260	Fluconazole 200 mg/day N=258	% Difference† (95% CI)
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

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**Ororopharyngeal Candidiasis (OPC) Outcomes**

The change in total clinical signs and symptom score of oropharyngeal candidiasis from baseline to end-of-therapy was a secondary endpoint in this study. The OPC clinical signs and symptoms score was discussed above. The mean and median OPC score at baseline, and at the end-of-therapy were similar for the two treatment groups.

Table 28. Changes in Total Clinical Signs and Symptom Score of OPC from Baseline to End-of-Therapy (Applicant's Table 15)

Scheduled Visit	Treatment Group	
	Micafungin	Fluconazole
<b>Baseline</b>		
n	259	256
Mean ± SD	4.2 ± 2.86	4.2 ± 2.80
Median	4.0	4.0
Range	0 to 12	0 to 12
<b>End of Therapy</b>		
n	249	249
Mean ± SD	0.2 ± 0.55	0.2 ± 0.89
Median	0.0	0.0
Range	0 to 4	0 to 11
<b>Change from Baseline</b>		
n	248	248
Mean ± SD	-3.9 ± 2.74	-3.9 ± 2.80
Median	-4.0	-4.0
Range	-12 to 0	-12 to 1

Patient base: all randomized patients who received at least one dose of study drug (Full Analysis Set).  
 n=total number of patients in each treatment group.  
 SD: standard deviation.

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*Medical Officer Comments: For clinicians, a more useful outcome measure for treatment of OPC would be overall percentage of patients with baseline OPC with/without OPC at EOT and 2- and 4-weeks post-treatment. This analysis is shown below.*

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*

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*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 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 CD<sub>4</sub> count, however, independently predicted treatment outcome regardless of treatment.

*Medical Officer Comments: The finding that baseline CD<sub>4</sub> count predicted the primary treatment outcome is not unexpected. Patients with lower CD<sub>4</sub> 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.*

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### Safety Analysis

#### Drug Exposure

Drug exposure in the full analysis set is shown in the following table. The mean and median number of days for both micafungin and fluconazole treatment groups was approximately 14 days. The mean and median cumulative dose of fluconazole was higher than that for micafungin because of the difference in dosing (200 mg/day for the former, and 150 mg/day for the latter).

Table 29. Drug Exposure in FAS (adapted from Table 13.3.1)

Parameter	Micafungin N=260	Fluconazole N=258
Duration (days):		
Mean ± std. deviation	14.3±3.68	14.7±3.62
Median	14.0	14.0
Range (min. to max. days)	1-33	2-29
Cumulative dose (mg):		
Mean ± std. deviation	2121.9± 544.85	2904.7±717.58
Median	2100	2800
Range (min. to max. in mg)	150-4800	400-5600

FAS= full analysis set

N= number of patients in FAS

Std. deviation= standard deviation of the mean

#### Adverse Events

Adverse events in this study are summarized in the table below.

Table 30. Summary of Safety in Study 03-7-005

Safety Parameter	Micafungin N= 260	Fluconazole N= 258
	n (%)	n (%)
Any AE	202 (77.7)	186 (72.1)
Any Drug-Related AE	72 (27.7)	55 (21.3)
Any SAE	35 (13.5)	24 (9.3)
Any Drug-Related SAE	3 (1.2)	1 (0.4)
Discontinuation due to AE	16 (6.2)	10 (3.9)
Discontinuation due to drug-related AE	6 (2.3)	2 (0.8)
Deaths	30 (11.5)	28 (10.9)

AE= adverse event; SAE= serious adverse event

N= number of patients in safety set (FAS)

n= number of patients with AE, SAE or death

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The most common adverse events in micafungin-treated patients were phlebitis (15.4%), fever (13.1%), diarrhea (10.4%), pneumonia (9.6%), and headache (8.5%). Common adverse events which occurred in at least 5% of patients in either treatment group are shown in the following table.

Table 31. Incidence of Most Common\* Adverse Events in Study (adapted from Table 19, study report 03-7-005)

Body System COSTART Code	Treatment Group		P-Value
	Micafungin (n=260)	Fluconazole (n=258)	
Any Adverse Event	202 (77.7%)	186 (72.1%)	0.156
<b>Body as a Whole</b>			
Abdominal Pain	12 (4.6%)	20 (7.8%)	0.148
Fever	34 (13.1%)	22 (8.5%)	0.119
<b>Cardiovascular System</b>			
Phlebitis	40 (15.4%)	12 (4.7%)	<0.001
<b>Digestive System</b>			
Diarrhea	27 (10.4%)	29 (11.2%)	0.779
Nausea	20 (7.7%)	23 (8.9%)	0.636
Vomiting	18 (6.9%)	18 (7.0%)	1.000
<b>Hemic and Lymphatic System</b>			
Anemia	11 (4.2%)	19 (7.4%)	0.137
Leukopenia	16 (6.2%)	12 (4.7%)	0.561
<b>Nervous System</b>			
Headache	22 (8.5%)	21 (8.1%)	1.000
Insomnia	9 (3.5%)	13 (5.0%)	0.393
<b>Respiratory System</b>			
Pneumonia	25 (9.6%)	13 (5.0%)	0.063
<b>Skin and Appendages</b>			
Rash	17 (6.5%)	7 (2.7%)	0.058

Patient base: all randomized patients who received at least one dose of study drug (Safety Set).

\*Common: experienced by at least 5% of the patients in either treatment group.

n=total number of patients in each treatment group in the Safety Set.

P-value is based on Fisher's Exact test.

Within a body system, patients may have reported more than one event.

Source: Table 13.5.1 and Appendix 14.4.4.1.

*Medical Officer Comments: A number of adverse events occurred more frequently in micafungin-treated patients. The applicant reported that the p-value was < 0.10 for phlebitis, pneumonia, and rash, as well as for other less common events including thrombophlebitis and chills.*

## Drug-Related Adverse Events

A total of 72/260 (27.7%) patients who received micafungin and 55/258 (21/3%) patients who received fluconazole had a drug-related adverse event as determined by the investigator. The most common micafungin-related adverse events which were more

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frequent in the micafungin group than the fluconazole group were phlebitis (3.8%), rash (4.2%), leukopenia (3.8%), headache (2.7%), chills (2.3%), and abdominal pain (2.3%).

The incidence of common drug-related adverse events is shown in the table below.

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Table 32. Incidence of Common\* Drug-Related adverse events (Applicant's Table 20, Study Report)

Body System COSTART Code	Treatment Group	
	Micafungin (n=260)	Fluconazole (n=258)
Any Adverse Event	72 (27.7%)	55 (21.3%)
<b>Body as a Whole</b>		
Abdominal Pain	6 (2.3%)	4 (1.6%)
Chills	6 (2.3%)	0 (0.0%)
Fever	5 (1.9%)	1 (0.4%)
Procedural Complication	5 (1.9%)	3 (1.2%)
<b>Cardiovascular System</b>		
Phlebitis	10 (3.8%)	6 (2.3%)
<b>Digestive System</b>		
Liver Function Tests Abnormal	3 (1.2%)	1 (0.4%)
Nausea	6 (2.3%)	7 (2.7%)
Vomiting	3 (1.2%)	4 (1.6%)
<b>Hemic and Lymphatic System</b>		
Anemia	4 (1.5%)	4 (1.6%)
Leukopenia	10 (3.8%)	3 (1.2%)
Thrombocytopenia	3 (1.2%)	4 (1.6%)
<b>Metabolic and Nutritional Disorders</b>		
Alkaline Phosphatase Increased	4 (1.5%)	3 (1.2%)
Hypomagnesemia	0 (0.0%)	3 (1.2%)
Lactic Dehydrogenase Increased	3 (1.2%)	3 (1.2%)
SGOT increased	2 (0.8%)	4 (1.6%)
SGPT Increased	1 (0.4%)	5 (1.9%)
<b>Nervous System</b>		
Headache	7 (2.7%)	4 (1.6%)
Somnolence	1 (0.4%)	7 (2.7%)
<b>Skin and Appendages</b>		
Pruritus	4 (1.5%)	4 (1.6%)
Rash	11 (4.2%)	5 (1.9%)

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Patient base: all randomized patients who received at least one dose of study drug (Safety Set).

Common: experienced by at least 1% of the patients in either treatment group.

Related: at least possibly related in the opinion of the investigator.

n=total number of patients in each treatment group in the Safety Set.

SGOT: serum glutamic oxaloacetic transaminase; SGPT: serum glutamic pyruvic transaminase.

Procedural complication: includes burning at infusion site (1 micafungin patient) and inflammation at drip site (4 micafungin patients and 3 fluconazole patients).

Within a body system, patients may have reported more than one event.

*Medical Officer Comments: Drug-related adverse events were more common in patients who received micafungin than in those who received fluconazole. Those events that occurred more frequently in micafungin-treated patients were abdominal pain, chills, fever, procedural complication, phlebitis, abnormal liver function tests, leukopenia, increased alkaline phosphatase, headache, and rash.*

### Deaths

A total of 30 of 260 (11.5%) patients in the micafungin treatment group died during the study; while 28 of 258 (10.9%) patients died in the fluconazole group. Except for two patients in each treatment group, the deaths occurred in the post-treatment study period. Only one death in each group was attributed to study drug as having a "possible" relationship (Micafungin-treated patient 10655006 described in narrative summary below). No deaths in the study were attributed to fungal infection in either treatment arm.

The following table lists the primary causes of death in the study. Narrative summaries for each patient who received micafungin, and who died study in the study are provided below.

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Table 33. Primary Causes of Death in Study 005 (adapted from applicant's Tables 21 and 13.5.11)

Primary Cause of Death (COSTART Term)	Micafungin N=260	Fluconazole N=258
	n (%)	n (%)
Any Cause	30 (11.5)	28 (10.9)
Pneumonia	6 (2.3)	5 (1.9)
Pulmonary tuberculosis, reactivated	5 (1.9)	2 (0.8)
Tuberculosis, reactivated	4 (1.5)	1 (0.4)
AIDS	4 (1.5)	6 (2.3)
Acute Kidney failure	2 (0.8)	1 (0.4)
Heart failure	2 (0.8)	3 (1.2)
Apnea	1 (0.4)	0 (0)
Arrhythmia	1 (0.4)	0 (0)
Kidney failure	1 (0.4)	2 (0.8)
Respiratory distress syndrome	1 (0.4)	0 (0)
Respiratory failure	1 (0.4)	0 (0)
Sepsis	1 (0.4)	2 (0.8)
Shock	1 (0.4)	3 (1.2)
Anemia	0 (0)	1 (0.4)
Hypokalemia	0 (0)	1 (0.4)
Lung edema	0 (0.4)	1 (0.4)

N= number of patients in FAS

n (%)= number and percentage of patients

**Medical Officer Comments:** Most deaths in both treatment arms were secondary to infection (pneumonia or tuberculosis, or AIDS). Deaths due to tuberculosis were more common in the micafungin group, than in the fluconazole-treated group; while the baseline numbers of TB cases were similar in both groups, 38 in the micafungin group, and 36 in the fluconazole group. Additionally, deaths due to respiratory adverse events, including respiratory failure, apnea and ARDS, although infrequent were reported in the micafungin treatment arm, but not in the fluconazole arm of the study.

The primary and contributing causes of death, as well as other adverse events and laboratory abnormalities that occurred in patients who died in this study are shown in the table below. Notably, acute liver failure was considered a contributing factor in the death of 1 micafungin-treated patient who died of MDR tuberculosis. Renal failure and heart failure were considered contributing factors in the death of a patient treated with micafungin who died of pneumonia. Similarly, anemia was considered a contributing factor in the death of 3 micafungin-treated patients.

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Table 34. Deaths in Study03-7-005 Patients who received Micafungin 150 mg/day

Site	Patient Number	CD4 Count Cells/mm <sup>3</sup>	Cumulative Dose (mg)	Treatment Duration (days)	Day of Death	Primary Cause	Contributing Factors	Related? (investigator assessment)
0254	5016	13	2850	19	19	Renal failure	(TB) (neutropenia)	No
0254	5018	2	450	3	6	Respiratory failure	HIV	No
0323	5015	24	1500	10	11	Septic shock	None	No
0323	5021	10	2100	14	20	Interstitial pneumonia	None	No
1044	5008	13	2100	14	26	Miliary TB	Cachexia	No
1057	5015	17	2100	14	28	Pulmonary tuberculosis	HIV	No
1057	5026	844	2100	14	24	Heart failure	HIV	Unlikely
1057	5041	8	2100	14	21	Pulmonary tuberculosis	HIV	Unlikely
1057	5045	16	300	2	3	Pulmonary tuberculosis	HIV	Unlikely
1057	5046	181	2100	14	17	Heart failure	HIV	Unlikely
1062	5002	0	150	1	2	Ventricular fibrillation	HIV; severe electrolyte abnormality	No

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Table 34. (continued) Deaths in Study 03-7-005 Patients who received Micafungin 150 mg/day

Site	Patient Number	CD4 count (cells/mm <sup>3</sup> )	Cumulative Dose (mg)	Treatment Duration (days)	Day of Death	Primary Cause	Contributing Factors	Related? (investigator assessment)
1065	5006	0	1800	12	13	Progression of HIV	None	Possible
1066	5003	Not done	2100	14	29	Pulmonary tuberculosis	HIV progression	No
1066	5017	Not done	2100	14	26	Broncho-pneumonia	None	No
1066	5018	Not done	2100	14	17	Worsening of HIV	Anemia of chronic disease	No
1066	5036	Not done	2100	14	31	Pulmonary tuberculosis	HIV progression	No
1066	5037	Not done	2400	16	17	Pneumonia	HIV progression; heart failure; renal failure	No

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Table 34. (continued) Deaths in Study 03-7-005 Patients who received Micafungin 150 mg/day

Site	Patient Number	CD4 count (cells/mm <sup>3</sup> )	Cumulative Dose (mg)	Treatment Duration (days)	Day of Death	Primary Cause	Contributing Factors	Related? (investigator assessment)
1070	5004	Not done	2100	14	19	<i>Pneumocystis carinii</i> pneumonia (PCP)	None	No
1070	5010	Not done	2100	14	19	Worsening of tuberculosis (Multi-organ failure by autopsy)	None	No
1070	5024	Not done	2100	14	39	Acute renal failure	Worsening anemia	No
1070	5047	12	1950	13	14	PCP	None	No
1074	5031	148	1350	9	17	Acute renal failure	HIV; "consuming Zulu traditional medications"	No

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Table 34. (continued) Deaths in Study 03-7-005 Patients who received Micafungin 150 mg/day

Site	Patient Number	CD4 count (cells/mm <sup>3</sup> )	Cumulative Dose (mg)	Treatment Duration (days)	Day of Death	Primary Cause	Contributing Factors	Related? (investigator assessment)
1074	5035	97	750	5	17	Multi-drug resistant tuberculosis	Acute liver failure	No
1075	5007	225	1050	7	8	Respiratory failure	Suspected pulmonary tuberculosis; HIV	No
1075	5009	9	3150	21	27	Worsening of HIV	Anemia	No
1163	5004	30	2100	14	29	Sepsis	Tuberculosis	No
1164	5004	67	750	5	6	Adult respiratory distress syndrome	Kaposi's sarcoma, stage IV	No
1164	5009	29	750	5	34	Tuberculous meningitis multifactorial shock	Septic shock; hypovolemic shock	No
1165	5005	Not done	2100	14	35	Worsening HIV	None	No
1165	5009	57	900	10	13	Pneumonia	HIV	No

**Medical Officer Comments:** Notably, all but two of the patients who died in the micafungin treatment group had CD4 counts below 200, and most were below 50, indicating severe immunosuppression. Additionally, most of these patients were not receiving antiretroviral therapy, and as such, would be expected to have a very poor prognosis with regard to life expectancy due to multiple complications of AIDS. Only one of the deaths in this group was considered possibly related to micafungin by the investigator. Most of the cases are complex in patients with opportunistic infections, malignancy, and metabolic abnormalities, and thus are highly confounded for the analysis of potential relationship to micafungin, and in the narrative summaries provided below, I have noted whether I agree with the investigator's determination of relatedness to micafungin.

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### Narrative Summary for Death in Micafungin-treated Patient Possibly Related to Study Drug

**Patient 10655006** was a 33 year-old black South African male with HIV and a CD4 count of 0 cells/mm<sup>3</sup>. He was not receiving antiretroviral therapy. He received micafungin 150 mg/day for 12 days for EC. Baseline conditions included suspected tuberculosis, cachexia, hypokalemia, oral leukoplakia, SIADH, chest pain and insomnia. At the time of study enrollment the patient was receiving metoclopramide, augmentin and cotrimoxazole, which were continued. Adverse events reported during micafungin treatment included anorexia and arthralgia. Micafungin was stopped on day 12 due to HIV progression and the patient died on day 13. The cause of death was reported as progression of HIV, and no autopsy was performed. The investigator considered the death possibly related to micafungin. Additional concomitant medications included rifabutin, amitriptyline, amikacin, paracetamol, potassium chloride, zolpidem, clothiapine, cyproheptadine and diclofenac (topical). The patient also received a blood transfusion on day 11 due to hemoglobin incorrectly reported as 7.4 g/dL. Laboratory values obtained during the study are shown in the table below. Additionally, AST, ALT, total bilirubin and alkaline phosphatase were normal at baseline and during treatment.

#### Laboratory Values\* for Patient 10655006

Study Day	WBC (x 10 <sup>9</sup> )	Hemoglobin (g/dL)	Platelets (x 10 <sup>9</sup> )	BUN (mg/dL)	Creatinine (mg/dL)	Albumin (g/dL)
Baseline	2.7	12	174	42	1.2	1.8
Day 8	2.9	13	98	23	1.1	2.8

\*normal laboratory values are shown in Appendix 10.

*Medical Officer Comments: The only significant laboratory value reported was a decreased platelet count of 98 on day 8. No additional laboratory values were available. Death due to HIV disease itself is uncommon, and is usually related to an opportunistic infection, malignancy, or complication related to treatment. The details provided in the case report form and narrative summary are insufficient to judge whether this death was related to micafungin or to some other event not reported.*

### Narrative Summaries for All Deaths in Micafungin-Treated Patients

**Patient 02545016** was a 35 year-old black male from South Africa with HIV and a CD4 count of 13 cells/mm<sup>3</sup>. He was not receiving antiretroviral therapy. The patient received micafungin 150 mg/day for 19 days for EC. Baseline conditions included cachexia, tuberculosis, nausea, anemia and fever. On study day 19, the patient developed severe, intractable vomiting and the patient was hospitalized for dehydration. At that time, laboratory evaluation revealed neutropenia, elevated LDH (7280 U/L) and renal failure (BUN 64 mg/dL) and creatinine 2.8 mg/dL (BUN and creatinine were normal at baseline). The patient died the same day, and the cause of death was reported as kidney failure. No

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autopsy was performed, and the investigator considered the death unrelated to micafungin. Other adverse events during the study included phlebitis, and hypoproteinemia. Concomitant medications included metoclopramide, augmentin, ibuprofen, paracetamol, cough expectorant, diclofenac, Immunity one (nutritional supplement), prochlorperazine, albumin, ringer's lactate, chlorpromazine, and Ensure (nutritional supplement). Laboratory evaluations during the study for this patient are shown in the table below. Additionally, AST and ALT were elevated on study day 19 (417 and 55 U/L, respectively) from normal values (28 and 15 U/L) at baseline; while alkaline phosphatase and bilirubin remained normal throughout the study.

Laboratory Values\* for Patient 02545016

Study Day	WBC (x 10 <sup>9</sup> )	ANC cells/mm <sup>3</sup>	Hemoglobin g/dL	Platelets (x 10 <sup>9</sup> )	BUN (mg/dL)	Creatinine (mg/dL)	LDH (U/L)
Baseline	3.3	2734	8.5	152	13	0.8	
Day 7	5.3	4641	8.2	342	56	2.2	
Day 14	6.5	6051	6.7	342	24	1.2	
Day 19	9.2	368**	6.7	111	64	2.8	7280

\*normal laboratory values are shown in Appendix 10.

\*\*patient had 4% neutrophils, 90% bands, so ANC was actually 8648 if band forms were counted as neutrophils

***Medical Officer Comments:** This patient was seriously ill with untreated tuberculosis, and significant anemia at baseline. Renal insufficiency was noted on day 7, and was reported as a serious adverse event on day 19 when the patient was hospitalized with severe vomiting and dehydration. The renal failure certainly may have resulted from dehydration or sepsis. The patient was leukopenic at baseline, and re-evaluation of the hematology data suggests that the patient was not actually neutropenic, but had a preponderance of neutrophil band forms on the differential count, which suggests the presence of a significant bacterial infection. The elevated LDH in the absence of bilirubinemia was not likely due to hemolysis, but could suggest significant pulmonary disease, and although the AST was elevated on day 19, in the absence of bilirubinemia, significant hepatocellular disease is less likely. In the absence of autopsy data, the cause of death in this patient remains obscure. I would agree with the investigator that the death in this patient was probably not related to micafungin.*

**Patient 02545018** was a 33 year-old black female from South Africa with HIV, and a CD4 count of 2 cells/mm<sup>3</sup>. The patient was not receiving antiretroviral therapy. Significant baseline conditions included vomiting, incoordination, neuropathy, cough, anemia, leukopenia, hypoproteinemia, and *Herpes simplex* (HSV) infection. The patient received micafungin 150 mg/day for 3 days for EC. Micafungin was discontinued on day 3 due to esophageal HSV. Concomitant medications included gentian violet (topical), metoclopramide, vitamin B complex, cotrimoxazole, amthocaine cream (topical), paracetamol, ibuprofen, Immunity One (nutritional supplement), and diclofenac. On day

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2, fever was reported as an adverse event, and on day 4 kidney failure (not considered a serious adverse event) was noted. The patient experienced severe apnea and respiratory collapse on day 6 and died. Cause of death was reported as apnea, and was not considered related to micafungin. No autopsy was performed. Laboratory evaluations for this patient are shown in the table below. AST, ALT, alkaline phosphatase and bilirubin were normal at baseline and study day 4. No additional laboratory data was available.

### Laboratory Values\* for Patient 02545018

Study Day	WBC (x 10 <sup>9</sup> )	ANC cells/mm <sup>3</sup>	Hemoglobin g/dL	Platelets (x 10 <sup>9</sup> )	BUN mg/dL	Creatinine g/dL	Albumin g/dL
Baseline	1.7	1333	6.5	278	10	0.8	1.4
Day 4	0.6	513	6.6	272	37	3.5	1.3

\*normal laboratory values are shown in Appendix 10.

***Medical Officer Comments:** Additional laboratory abnormalities reported in the database included an elevated calcium at baseline and week 1 (10.3 and 10.5, respectively), and low magnesium (1.9 at baseline and week 1). This patient had significant anemia at baseline, and developed severe neutropenia (ANC < 500 cells/mm<sup>3</sup>) during the study which was not listed as an adverse event. This patient had many conditions which may have been a factor in her death, including neutropenia, anemia, and renal failure. Although apnea may have been the primary cause of death, the underlying condition which resulted in apnea is not clear.*

**Patient 03235015** was a 62 year old mestizo female from Peru with HIV and a CD4 count of 24 cells/mm<sup>3</sup>. Significant baseline conditions included pneumonia, pneumothorax, gastritis, colitis, diarrhea, hypoproteinemia, anemia, abnormal WBCs, urinary tract infection, anorexia and insomnia. The patient received micafungin 150 mg/day for 10 days for EC. Micafungin was discontinued on day 10 due to septic shock, and the patient died on day 11 due to septic shock. No autopsy was performed, and the death was not considered related to micafungin. Other adverse events reported during the study were thrombocytopenia, and hypocalcemia (neither was considered serious or drug-related). Concomitant medications included ranitidine, hyoscyamine, potassium chloride, sodium chloride, cotrimoxazole, metoclopramide, ceftriaxone, sucralfate, amikacin, furosemide, calcium gluconate, ketorolac, and metamizole. Laboratory data for this patient is shown in the table below. AST, ALT, alkaline phosphatase and total bilirubin were normal at baseline and day 10, except for mild elevation of AST (66 U/L) on day 10.

### Laboratory Values\* for Patient 0325015

Study Day	WBC (x 10 <sup>9</sup> )	Hemoglobin g/dL	Platelets (x 10 <sup>9</sup> )	BUN mg/dL	Creatinine mg/dL	Albumin g/dL	Calcium mg/dL	Mg g/dL
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Baseline	26.4	8.9	216	19	0.7	1.3	6.9	1.4
Day 7	16.4	8.4	50	24	1.0	1.0	7.0	1.1
Day 10	13.2	6.1	20	36	1.9	0.7	6.3	1.1

\*normal laboratory values are shown in Appendix 10.

**Medical Officer Comments:** *This patient was seriously ill with sepsis, anemia which worsened during treatment, with no evidence of hemolysis (normal bilirubin and LDH), severe thrombocytopenia which developed during treatment, renal insufficiency, (both of which could be attributed to sepsis), hypocalcemia, and hypomagnesemia. I would agree with the investigator that the death in this patient was not likely related to micafungin.*

**Patient 03235021** was a 33 year-old mestizo female from Peru with HIV and a CD4 count of 10 cells/mm<sup>3</sup>. She received micafungin 150 mg/day for 14 days for EC. Conditions reported at baseline included chronic diarrhea, nausea, cough, gastritis, cachexia, lymphopenia, hypoproteinemia, and hypokalemia. Adverse events reported during the study included Herpes zoster, stomatitis, duodenitis, interstitial pneumonia and progression of HIV. None of these events were considered related to micafungin. Respiratory insufficiency was reported on study day 20, and CXR showed a diffuse alveolar infiltrate. The patient died on study day 29 due to interstitial pneumonia. No autopsy was performed and the death was not considered related to micafungin. Concomitant medications included cotrimoxazole, ceftriaxone, acyclovir, clarithromycin, hydrocortisone, prednisone, isoniazid, rifampin, ethambutol, and pyrazinamide, and metronidazole. Laboratory abnormalities noted on review of the database are shown in the table below. Additionally, AST and ALT were mildly elevated on day 28, from a normal baseline, at 123 U/L and 59 U/L, respectively; while total bilirubin remained in the normal range.

### Laboratory Values\* for Patient 03235021

Study Day	WBC (x 10 <sup>9</sup> )	Hemoglobin g/dL	Platelets (x 10 <sup>9</sup> )	Sodium mmol/L	Postassium mmol/L	LDH U/L	Albumin g/dL
Baseline	3.3	12	344	127	2.1	475	2.0
Day 7	4.7	13	288	136	3.2	671	1.9
Day 14	2.7	12	232	129	4.2	801	1.3
Day 29	1.9	10	59	126	3.8	1161	1.3

\*normal laboratory values are shown in Appendix 10.

**Medical Officer Comment:** *This patient developed interstitial pneumonia and was treated for bacterial pneumonia, tuberculosis, and presumably Pneumocystis, although the dose of bactrim used was not provided in the case report form (CRF). She also developed worsening leukopenia and new thrombocytopenia during the study. At baseline she had hyponatremia, which persisted, and hypokalemia, which normalized during the study. The increasing LDH in this*

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*patient may have been related to the pneumonia. I would agree with the investigator that the death in this patient was not related to micafungin.*

**Patient 10445008** was a 45 year-old Caucasian male from Brazil with HIV and a CD4 count of 13 cells/mm<sup>3</sup>. He was not receiving antiretroviral therapy. Baseline conditions included cerebral toxoplasmosis, disseminated tuberculosis, psoriasis, oral *Herpes simplex*, and prurigo. The patient received micafungin 150 mg/day for 14 days for EC. On day 19, reactivated tuberculosis was noted as an adverse event, and the patient became comatose and died on day 26. The cause of death was reported as military tuberculosis, and cachexia. Autopsy revealed disseminated tuberculosis. The death was not considered related to micafungin. Phlebitis was also noted as an adverse event during treatment with micafungin. Concomitant medications included omeprazole, metoclopramide, dipirone, heparin, phenytoin, folinic acid, sulfadiazine, pyramethamine, isoniazid, rifampin, pyrazinamide, zidovudine, lamivudine, efavirenz, stavudine, thiabendazole, cisapride, ivermectin, oxacillin, diazepam, dopamine, and epinephrine. A number of laboratory abnormalities were noted during the study, and are shown in the table below. Additional laboratory abnormalities included progressive hypoalbuminemia, hyponatremia and both hypokalemia and hyperkalemia during the study. Renal function remained normal throughout the study.

### Laboratory Values\* for Patient 10445008

Study day	WBC (x 10 <sup>9</sup> )	Hemoglobin g/dL	Platelets (x 10 <sup>9</sup> )	AST U/L	ALT U/L	Total bilirubin mg/dL	LDH U/L	Alkaline phosphatase U/L
Baseline	2.4	9.0	239	50	74	0.4	224	514
Day 8	2.0	9.0	330	179	227	0.8	332	646
Day 14	2.5	7.4	61	43	81	1.2	368	741
Day 26	3.3	8.9	21	5670	1760	4.1	3795	249

\*normal laboratory values are shown in Appendix 10.

*Medical Officer Comments: Unquestionably this patient died of disseminated tuberculosis, but he also developed a number of significant laboratory abnormalities during the study, including anemia, thrombocytopenia, and significant transaminase and bilirubin elevation.. The patient received multiple concomitant medications with known hepatotoxicity (isoniazid, rifampin, pyrazinamide, antiretroviral medications, etc.) and the disseminated tuberculosis probably involved the liver as well. I would agree that the death in this patient was not related to micafungin.*

**Patient 10575015** was a 38 year-old black South African male with HIV and a CD4 count of 17 cells/mm<sup>3</sup>. He was not receiving antiretroviral therapy. He receiving micafungin 150 mg/day for 14 days for EC. At baseline, the patient also had asthma, pulmonary tuberculosis, cachexia, dehydration, and anemia. Concomitant medications included rifafour E 200 (isoniazid, rifampin, pyrazinamide, and ethambutol), ventolin, and becotide , as well as amoxil, ibuprofen, panado , vitamin B, cough syrup, and lomotil.

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During the study, the patient experience cellulitis (possibly related to micafungin infusion), asthenia, hiccups, and increased cough. On day 28, reactivated tuberculosis and HIV progression were reported as adverse events, and the patient died on day 28 due to pulmonary tuberculosis. Laboratory abnormalities during the study included a decrease in hemoglobin from 9.3 g/dL at baseline to 7.8 g/dL (day 7 and 14), increase in AST from 100 U/L at baseline to 417 U/L (day 14), moderate increase in ALT from 122 U/L at baseline to 164 U/L (day 14), decreased albumin from 2.6 g/dL at baseline to 1.6 g/dL (day 14), decreased sodium from 130 mmol/L at baseline to 126 mmol/L (day 14), increased LDH from 928 U/L at baseline to 2081 U/L on day 14, and mild hypercalcemia (9.6 mg/dL at baseline to 10.2 mg/dL day 14). BUN, creatinine and total bilirubin remained normal.

*Medical Officer Comments: Although no autopsy was performed it appears likely that the patient died secondary to tuberculosis, and given the time difference between stopping micafungin (day 14) and death (day 28), I would agree that the death was most likely not related to micafungin.*

**Patient 10575026** was a 63 year-old black South African female with suspected HIV. CD4 count at baseline was 844 cells/mm<sup>3</sup>. Baseline conditions included anorexia, cachexia, peripheral edema, depression and an abnormal pulmonary examination. She received micafungin 150 mg/day for 14 days for EC. The patient was receiving no other medications at the time of enrollment. During the study, the patient developed deep venous thrombosis (DVT), weakness and depression. For the DVT, she received aspirin and clexane. On day 23, heart failure was reported, and worsening HIV on day 24. The patient died day 24 due to heart failure. No autopsy was performed, and the death was considered unlikely related to micafungin. The significant laboratory abnormality noted were elevated calcium at baseline (10.6mg/dL) and day 15 (10.5 mg/dL) decreased platelets from 199 x 10<sup>9</sup> at baseline to 109 x 10<sup>9</sup> (day 7), decreased sodium from 137 mmol/L at baseline to 127 mmol/L day 15, and increased LDH from 731 U/L at baseline to 940 U/L on day 15. A mild elevation of AST was noted (35 U/L at baseline to 67 U/L on day 15), and bilirubin was only slightly elevated at 1.2 mg/dL (baseline) and 1.1 mg/dL (day 15).

*Medical Officer Comments: This patient had presumed HIV, but a CD4 count within normal range, which can occur in patients co-infected with HTLV-1 or in those who were splenectomized, and neither was mentioned in the CRF or narrative summary provided by the applicant. Malignancy could be suspected given her cachexia, and baseline hypercalcemia, and one could speculate that the patient was predisposed to a DVT for this reason. However, the etiology of heart failure in this patient is not specified. I would agree with the investigator that the death was unlikely related to micafungin given the time course of events.*

**Patient 10575041** was a 34 year-old black male from South Africa with HIV and a CD4 count of 8 cells/mm<sup>3</sup>. He was not receiving antiretroviral therapy. The only baseline condition reported was cachexia. He received micafungin 150 mg/day for 14 days for EC.

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Concomitant medications included vitamin B complex, bactrim, proidium (), scopex () and normal saline. Pulmonary tuberculosis was reported on day 20, and worsening HIV disease on day 21. The patient died on day 21 due to pulmonary tuberculosis. No autopsy was performed and the death was considered unrelated to micafungin. The only significant laboratory abnormalities noted on review of the database were a slightly decreased hemoglobin (from 10.5 g/dL at baseline to 9.3 g/dL on day 15), and decreased sodium (from 132 mmol/L at baseline to 126 mmol/L on day 15).

*Medical Officer Comments: I would concur with the investigator that this death does not appear related to micafungin.*

**Patient 10575045** was a 36 year old black South African male with HIV, and a CD4 count of 16 cells/mm<sup>3</sup>. He was not receiving antiretroviral therapy. Baseline conditions included asthenia, anorexia, an abnormal pulmonary examination, cachexia, dehydration, depression, diarrhea, hyporeflexia, and tuberculosis. He received micafungin 150 mg/day for 2 days for EC. Concomitant medications included vitamin B complex, normal saline, loperamide and rifafour E-200 (isoniazid, rifampin, pyrazinamide, and ethambutol). The patient developed diarrhea (presumably worsening), and worsening of pulmonary tuberculosis and HIV disease, and 3 died on study day 3. Pulmonary tuberculosis was the reported cause of death. No autopsy was performed and the death was not considered related to micafungin. Only baseline laboratories were available for this patient. Laboratory abnormalities included baseline anemia (hemoglobin 9.1 g/dL), hyponatremia (sodium 131mmol/L),elevated LDH (594 U/L), and mild elevation of BUN (22 mg/dL).

*Medical Officer Comments: No further details are provided in the narrative summary provided by the applicant, as to how the patient died. Although I think it is unlikely that micafungin was related to death in this patient, the temporal relationship of the death to micafungin treatment raises that possibility.*

**Patient 10575046** was a 31 year-old black South African male with HIV, and a CD4 count of 181 cells/mm<sup>3</sup>. Significant baseline conditions included astheniam anorexia, abnormal pulmonary examination, cachexia, abnormal kidney function, dehydration, tachycardia, and anemia. He received micafungin 150 mg/day for 14 days for EC. Concomitant medications included vitamin B complex, normal saline, scopex (), proidium (), bactrim, and lasix. Adverse events included impaired renal function (worsening), and diarrhea. Neither was considered related to micafungin. On day 17, heart failure, kidney failure, and respiratory failure were reported as serious adverse events. The patient died on day 17 due to multiple organ failure (per the CRF). No autopsy was performed, and the death was not considered related to micafungin. Laboratory data for this patient is provided in the table below. Additional abnormalities included decreased albumin (1.9 g/dL at baseline to 1.7 g/dL on day 14), and increased LDH (465 U/L at baseline and 1195 U/L on day 14). Total bilirubin remained normal throughout the study.

Laboratory Values\* for Patient 10575046

Study	WBC	Hemoglobin	Platelets	BUN	Creatinine	Sodium	Calcium
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Mycamine (Micafungin sodium)

Day	(x 10 <sup>9</sup> )	g/dL	(x 10 <sup>9</sup> )	mg/dL	mg/dL	mmol/L	Mg/dL
Baseline	10.7	9.6	359	92	3.5	123	10.4
Day 7	11.9	8.6	302	157	6.5	126	10.4
Day 14	15	9.7	268	205	6.0	138	10.5

\*normal laboratory values are shown in Appendix 10.

*Medical Officer Comments: At baseline, this patient had renal failure, anemia, hyponatremia, and hypercalcemia. I would agree that the death in this patient was not likely related to micafungin.*

**Patient 10625002** was a 35 year-old black female from South Africa with HIV, and a CD4 count of 0 cells/mm<sup>3</sup>. Baseline conditions included lymphopenia, hypokalemia, gastroenteritis, cachexia, hypocalcemia, “flu syndrome”, electrolyte abnormality, hyponatremia, hypomagnesemia, and dehydration. She received micafungin 150 mg/day for 1 day for EC. On the first day of treatment, the patient developed worsening electrolyte abnormalities, worsening of HIV, and ventricular fibrillation. The patient died on day 2 due to ventricular fibrillation (CRF). No autopsy was performed and the death was not considered related to micafungin. Concomitant medications included prednisone, ampicillin, purbac (bactrim), gentamicin, panado, slow-K, Klacid XL, and potassium chloride. Baseline laboratory values for this patient are shown in the table below.

Baseline laboratory values\* for Patient 10625002

Laboratory Parameter	Laboratory Value
WBC	9.0 x 10 <sup>9</sup>
Hemoglobin	10.4 g/dL
Platelets	167 x 10 <sup>9</sup>
BUN	34 mg/dL
Creatinine	3.6 mg/dL
Sodium	126 mmol/L
Potassium	1.7 mmol/L
Magnesium	1.3 mg/dL
Calcium	9.6 mg/dL
Albumin	2.3 g/dL
AST	48 U/L
ALT	23 U/L
Total bilirubin	0.6 mg/dL
Alkaline phosphatase	72 U/L
LDH	688 U/L

\*normal laboratory values are shown in Appendix 10.

*Medical Officer Comments: This patient clearly had renal failure, as well as severe electrolyte abnormalities which would predispose her to a ventricular*

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*arrhythmia, particularly the potassium level of 1.7 at baseline. I would agree that the death in this patient was not likely related to micafungin.*

**Patient 10655006** was reviewed in the section above, “Narrative Summaries for Deaths Possibly Related to Micafungin”.

**Patient 10665003** was a 34 year-old South African black female with HIV. No CD4 count was obtained, and the patient was not receiving antiretroviral therapy. Baseline conditions included tuberculosis, diarrhea, weight loss, dehydration, and fever. The patient received micafungin 150 mg/day for 14 days for EC. During treatment the patient experienced cystitis, worsening pulmonary tuberculosis, fever, nausea, vomiting and worsening hyponatremia. The patient was found comatose on day 29, and died that day due to pulmonary tuberculosis and progression of HIV disease. No autopsy was performed, and the death was not considered related to micafungin. Concomitant medications included Ringer’s lactate, cozide, loperamide, ciprofloxacin, ceftriaxone, maxolon, voltaren and panado. Pertinent laboratory data for this patient is provided in the table below. Other abnormalities included increased LDH (1609 U/L at baseline, and 2203 U/L day 28), decreased AST (145 U/L to 77 U/L), ALT (64 U/L to 21 U/L), increased alkaline phosphatase (66 U/L to 311 U/L) and bilirubin (1.0 mg/dL to 1.2 mg/dL) from baseline to day 28.

### Laboratory Values\* for Patient 10665003

Study day	WBC x 10 <sup>9</sup>	Hemoglobin g/dL	Platelets x 10 <sup>9</sup>	BUN mg/dL	Creatinine mg/dL	Sodium mmol/L	Calcium Mg/dL
Baseline	8.5	9.0	155	22	1.8	132	10.3
Day 7	6.7	8.1	105	10	0.8	138	10.4
Day 14	10.1	8.7	127	9	0.9	129	10.5
Day 28	14.4	7.4	353	85	4.5	144	10.5

\*normal laboratory values are shown in Appendix 10.

***Medical Officer’s Comments:** At baseline the patient had anemia, mild thrombocytopenia, mild renal insufficiency and hypercalcemia. On the day prior to death, the patient was found comatose, and she had renal failure, and worsening anemia. She was not hyperkalemic. I would agree that any relationship of this death to micafungin is unlikely.*

**Patient 10665017** was a 26 year-old black female from South Africa with HIV. CD4 count was not measured. Baseline conditions included anemia, fever, and deteriorating vision. She received micafungin 150 mg/day for 14 days for EC. Concomitant medications included metoclopramide, cyclizine, voltaren, stopayne, paracetamol (acetaminophen), ceftriaxone, depo-provera, vitamin B complex and clavmox. During micafungin treatment the patient developed a urinary tract infection, nausea, and pneumonia. The patient died on day 26 due to pneumonia. No autopsy was performed and the death was not attributed to micafungin. Significant laboratory values are shown in

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the table below. AST and ALT were mildly elevated at baseline, 107 U/L and 131 U/L, respectively and were 64 U/L and 31 U/L, respectively on day 13.

Laboratory Values\* for Patient 10665017

Study Day	WBC x 10 <sup>9</sup>	Hemoglobin g/dl	Platelets x 10 <sup>9</sup>	BUN mg/dL	Creatinine mg/dL	Total bilirubin mg/dL	LDH U/L	Albumin g/dL
Baseline	5.0	7.1	204	6	0.7	0.5	1170	2.2
Day 7	9.2	5.5	161	10	0.8	0.5	1199	1.6
Day 13	12.2	5.5	158	8	0.8	0.7	14442	1.7

\*normal laboratory values are shown in Appendix 10.

*Medical Officer Comments: This patient had severe anemia at baseline, which worsened during micafungin treatment. Because bilirubin remained normal, hemolysis seems unlikely. I would agree that the death was probably not related to micafungin, given the 2 week period between last dose of micafungin and death.*

**Patient 10665018** was a 52 year-old black female from South Africa with HIV. No CD4 count was obtained, and the patient was not receiving antiretroviral therapy. Baseline conditions included hypertension, bronchitis, anemia, and fever. She received micafungin 150 mg/day for 14 days for EC. Concomitant medications included ciprofloxacin, napacod, voltaren, panado, ferrous sulfate, and cyclizine. During treatment the patient developed nausea, and worsening of anemia and HIV disease. The patient died on day 17 due to worsening HIV and anemia. No autopsy was performed and the death was not attributed to micafungin. Pertinent laboratory data for this patient is shown in the table below.

Laboratory Values\* for Patient 10665018

Study day	WBC x 10 <sup>9</sup>	Hemoglobin g/dL	Platelets x 10 <sup>9</sup>	BUN mg/dL	Creatinine mg/dL	Sodium mmol/L	Potassium mmol/L
Baseline	5.9	6.6	372	42	1.8	126	5.5
Day 7	8.8	6.3	215	13	1.0	129	5.1
Day 14	5.4	5.4	156	13	0.9	124	4.7
	AST U/L	ALT U/L	Alkaline phosphatase U/L	Total bilirubin mg/dL	Calcium mg/dL	LDH U/L	Albumin g/dL
Baseline	90	34	249	0.7	10.8	2083	2.0
Day 7	57	27	488	0.4	10.6	2030	1.9
Day 14	72	23	415	0.6	9.5	2472	1.7

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\*normal laboratory values are shown in Appendix 10.

**Medical Officer Comments:** *This patient had severe anemia at baseline which worsened during micafungin treatment. She also had hyponatremia which worsened during therapy; while her baseline renal insufficiency and hypercalcemia improved presumably with hydration. LDH was elevated at baseline and continued to rise during therapy and alkaline phosphatase was high at baseline and increased over time. Bilirubin remained normal; while AST and ALT decreased during the treatment period. The investigator did not attribute worsening anemia to micafungin, although there was certainly a temporal relationship. No further details are provided regarding the actual death, and with all the confounding factors in this case, I would agree that the death was not likely related to micafungin.*

**Patient 10665036** was a 59 year-old black female from South Africa with HIV. CD4 count was not obtained, and the patient was not receiving antiretroviral therapy. Baseline conditions included fever, dehydration, diarrhea, muscle weakness (CRF), and anemia. She received micafungin 150 mg/day for 14 days. Concomitant medications included fluconazole (starting day 18 for persistent EC, stopayne, panado, loperamide, cyclizine, cifran (ciprofloxacin), voltaren, maxolon, Ringer's lactate, and rifafour (isoniazid, rifampin, pyrazinamide, and ethambutol). During treatment with micafungin she developed nausea and pneumonia (day 10). She was subsequently diagnosed with tuberculosis on day 17. The patient died on day 31 due to pulmonary tuberculosis. Laboratory values for this patient are provided in the table below.

### Laboratory Values\* for Patient 10665036

Study day	WBC x 10 <sup>9</sup>	Hemoglobin g/dL	Platelets x 10 <sup>9</sup>	BUN mg/dL	Creatinine mg/dL	Sodium mmol/L	Potassium mmol/L
Baseline	2.5	9.0	89	9	0.8	121	3.1
Day 7	6.5	9.5	127	16	0.6	134	4.4
Day 13	5.6	7.6	150	19	1.2	140	4.2
Day 26	5.1	7.2	24	51	1.7	142	3.8
	AST U/L	ALT U/L	Total bilirubin mg/dL	Alkaline phosphatase U/L	Albumin g/dL	Calcium mg/dL	LDH U/L
Baseline	159	55	0.6	67	1.5	9.9	975
Day 7	67	34	0.5	100	1.5	10.2	899
Day 14	194	50	0.7	118	1.2	10.5	986
Day 26	83	31	0.8	216	0.9	11.2	973

\*normal laboratory values are shown in Appendix 10.

**Medical Officer Comments:** *This patient had anemia at baseline which worsened during treatment with micafungin. Additionally, thrombocytopenia was noted at baseline, and worsened on day 26. Multiple metabolic abnormalities were noted during treatment including renal insufficiency, and hypercalcemia (progressive).*

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*The hyponatremia and hypokalemia at baseline improved over time. Both LDH and alkaline phosphatase increased during and after treatment; while AST and ALT decreased. Bilirubin remained within normal range. I would agree that the death is most likely unrelated to micafungin.*

**Patient 10665037** was a 29 year-old South African black female with HIV. CD4 count was not obtained, and the patient was not receiving antiretroviral therapy. Baseline conditions included asthenia, convulsion, anemia, and fever. The patient received micafungin 150 mg/day for EC for 16 days, at which time micafungin was discontinued due to pneumonia. Concomitant medications included panado, stopayne, voltaren, cifran (ciprofloxacin), purbac (bactrim), and ativan. Other adverse events during treatment were anxiety, heart failure (serious), renal failure (serious), and HIV progression (serious). The patient died on day 17 due to pneumonia. No autopsy was performed, and the death was not considered related to micafungin. Heart failure, renal failure, and HIV progression were considered contributing conditions. Laboratory data for this patient is shown in the table below.

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 Mycamine (Micafungin sodium)

Laboratory Values\* for Patient 10665037

Study day	WBC x 10 <sup>9</sup>	Hemoglobin g/dL	Platelets x 10 <sup>9</sup>	BUN mg/dL	Creatinine mg/dL	Sodium mmol/L	Calcium mg/dL
Baseline	4.8	6.7	166	7	0.7	133	9.8
Day 7	10.9	5.0	326	15	0.9	135	9.8
Day 14	14.0	6.0	222	16	0.8	140	11.0
	AST U/L	ALT U/L	Total bilirubin mg/dL	Alkaline phosphatase U/L	LDH U/L	Magnesium mg/dL	Albumin g/dL
Baseline	94	70	0.8	80	1514	2.2	1.9
Day 7	68	29	0.8	71	1318	1.7	1.3
Day 14	108	29	1.0	319	2480	1.7	1.3

\*normal laboratory values are shown in Appendix 10.

*Medical Officer Comments: The patient had severe anemia at baseline, which worsened during treatment. Additionally, during treatment the patient developed hypercalcemia, increased alkaline phosphatase and LDH, hypomagnesemia and hypoalbuminemia. AST was mildly elevated at baseline and day 14; while ALT, which was mildly elevated at baseline, decreased, and bilirubin remained normal during treatment. I would agree with the investigator that the death was most likely not related to micafungin.*

**Patient 10705004** was a 43 year-old South African male with suspected HIV. CD4 count was not obtained, and the patient was not receiving antiretroviral therapy. Baseline conditions included *Pneumocystis jirovecii* (formerly *carinii*) pneumonia (PCP). Concomitant medications included cozole (bactrim), multivitamins, paracetamol (), iron sulfate, vitamin B complex, a cough medication, and bactrim for treatment of PCP. The patient received micafungin 150 mg/day for 14 days for EC. The patient died on day 19 due to worsening PCP. The only significant laboratory abnormality noted on review of the database was sodium, which was low at baseline (127 mmol/L), and decreased to 119 mmol/L(day 7) and 122 mmol/L(day 14). Additionally, LDH rose from 764 U/L at baseline to 1319 U/L by day 14. He was mildly anemic (hemoglobin 11.1g/dL) at baseline and throughout study, and no other hematologic abnormalities were observed. AST was mildly elevated at baseline (53 U/L), and remained in that range throughout the study (68 U/L on day 14). ALT was minimally elevated at baseline (40 U/L), and was normal at the end-of-therapy; and alkaline phosphatase remained normal throughout the study. Bilirubin was normal except for a transient elevation (1.2 mg/dL) on day 7.

*Medical Officer Comments: I would agree with the investigator that the death was probably not related to micafungin, but rather to PCP.*

**Patient 10705010** was a 39 year-old black South African female with suspected HIV. CD4 count was not measured, and the patient was not receiving antiretroviral therapy. Baseline conditions included pulmonary tuberculosis, diarrhea, anemia, and pneumonia

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Mycamine (Micafungin sodium)

(PCP). The patient received micafungin 150 mg/day for 14 days for EC. Concomitant medications included rifampin (isoniazid, rifampin, pyrazinamide, and ethambutol), vitamin B complex, ferrous sulfate, cotrim (bactrim), gatifloxacin, midazolam, and xylocaine (topical anesthetic). She also received a blood transfusion (day 9). During treatment dehydration and worsening of PCP (serious) were reported as adverse events. Acute renal failure was reported as an adverse event on day 19, and was considered possibly related to micafungin. The patient died on day 36 due to worsening tuberculosis. According to the applicant autopsy was not performed and the death was not attributed to micafungin. Laboratory data for this patient are shown in the table below.

### Laboratory Values\* for Patient 10705010

Study day	WBC x 10 <sup>9</sup>	Hemoglobin g/dL	Platelets x 10 <sup>9</sup>	BUN mg/dL	Creatinine mg/dl	Alkaline phosphatase U/L	LDH U/L
Baseline	5.3	3.3	413	11	1.9	83	455
Day 8	7.9	3.5	340	19	3.2	82	482
Day 14	5.7	7.1	254	23	3.0	137	2085
Day 28	8.1	5.2	134	108	6.0	101	919
	Sodium mmol/L	Potassium mmol/L	Calcium mg/dL	Albumin g/dL	Total bilirubin mg/dL	AST U/L	ALT U/L
Baseline	131	4.7	10.5	2.2	0.6	22	10
Day 8	130	6.2	11.0	1.9	0.8	38	14
Day 14	137	7.9	12.3	2.2	3.9	69	15
Day 28	135	5.9	10.8	2.6	0.6	114	62

\*normal laboratory values are shown in Appendix 10.

**Medical Officer Comments:** This patient developed renal failure with hyperkalemia and hypercalcemia during treatment. She was also receiving bactrim, which can cause renal failure, particularly at the high doses required for treatment of Pneumocystis. However, baseline creatinine was modestly elevated and baseline calcium was also abnormal. The patient also had severe anemia at baseline, and required a blood transfusion. Laboratories on day 14 suggest possible hemolysis, with elevated bilirubin, LDH, and potassium, although the patient's hemoglobin and hematocrit had risen from 3.5 and 15%, respectively on day 8 to 7.1 and 25% on day 14. Mild elevations of AST and ALT were noted on day 28 of the study. I would agree with the investigator that this death was not likely attributable to micafungin. Of note, on the case report form, the investigator checked that no autopsy was performed. However, an autopsy was cited with the CRF that described multiple organ failure as the cause of death.

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Mycamine (Micafungin sodium)

**Patient 10705024** was a 34 year-old black South African female with suspected HIV. No CD4 count was obtained, and the patient was not receiving antiretroviral therapy. Baseline conditions included PCP pneumonia. The patient received micafungin 150 mg/day for 14 days. Concomitant medications included multivitamin, ferrous sulfate, xylocaine, depo-provera, cozole (bactrim), ibuprofen, paracetamol, and midazolam. No adverse events were reported during the study. The patient died on day 39 due to acute renal failure, and worsening anemia. No autopsy was performed, and the death was not considered related to micafungin. Pertinent laboratory data for this patient is shown in the table below. Except for minimal elevation of AST (from 27 U/L at baseline to 47 U/L on day 13), other liver function tests, including ALT, bilirubin, and alkaline phosphatase remained normal throughout the study.

### Laboratory Values\* for Patient 10705024

Study day	WBC x 10 <sup>9</sup>	Hemoglobin g/dL	Platelets x 10 <sup>9</sup>	BUN mg/dL	Creatinine mg/dL	Sodium mmol/L	Potassium mmol/L
Baseline	6.5	8.1	229	18	1.4	130	4.6
Day 7	4.1	7.1	190	23	1.6	130	4.5
Day 13	8.2	7.3	151	27	1.3	132	3.6
Day 27	11.1	3.8	50	62	3.6	130	6.6
	Calcium mg/dL	Magnesium mg/dL	LDH U/L				
Baseline	10.6	1.9	764				
Day 7	10.4	1.1	993				
Day 13	10.7	1.6	1304				
Day 27	10.8	1.9	1457				

\*normal laboratory values are shown in Appendix 10.

**Medical Officer Comments:** *This patient was anemic at baseline, but developed severe anemia by study day 27. Significant thrombocytopenia was also noted on day 27. Additionally, she had mild renal insufficiency at baseline, which progressed through the study period. Hyperkalemia was noted on study day 27. The progressive renal insufficiency and hyperkalemia could be attributed to bactrim, which the patient received for PCP. Also at baseline, the patient had hyponatremia, and hypercalcemia, both of which persisted during and after treatment. LDH increased throughout the study period; while hypomagnesemia was noted during micafungin treatment. I would agree that the death was not related to micafungin given the time course (micafungin was stopped on day 14 and the patient died on day 39).*

**Patient 10705047** was a 43 year-old black female from South Africa with HIV, and a CD4 count of 12 cells/mm<sup>3</sup>. She was not receiving antiretroviral therapy. Baseline conditions included PCP, kyphosis, and chronic diarrhea (from CRF). She received micafungin 150 mg/day for 13 days for EC. Concomitant medications included Setin, pectin K, vitamin B complex, xylocaine, panamol, midazolam, cozole (bactrim),

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stopayne, maxalon, Imodium, atrovent, and valium. Adverse events reported during micafungin treatment included dehydration, anemia, and worsening PCP. The patient died on day 14 due to PCP. No autopsy was performed and the death was not attributed to micafungin. Laboratory values for this patient are shown in the table below. Laboratory data beyond day 7 was not available.

#### Laboratory Values for Patient 10705047

Study day	WBC x 10 <sup>9</sup>	Hemoglobin g/dL	Platelets x 10 <sup>9</sup>	BUN mg/dL	Creatinine mg/dL	Sodium mmol/L	Potassium mmol/L
Baseline	12.4	9.1	549	27	1.4	139	3.0
Day 7	9.9	7.0	447	12	1.2	130	5.8
	Calcium mg/dL	Albumin g/dL	AST U/L	ALT U/L	Total bilirubin mg/dL	Alkaline phosphatase U/L	LDH U/L
Baseline	10.5	1.7	50	43	0.6	494	616
Day 7	9.8	1.3	27	21	0.5	536	565

\*normal laboratory values are shown in Appendix 10.

***Medical Officer Comments:** During treatment, this patient developed worsening anemia, hyponatremia, hyperkalemia, worsening hypoalbuminemia, increasing alkaline phosphatase and LDH. Calcium was elevated at baseline, but normalized during treatment. Likewise, AST and ALT were mildly elevated at baseline but normalized, and bilirubin remained within normal range during the first week of treatment. I would agree with the investigator that the death was most likely not related to micafungin.*

**Patient 10745031** was a 34 year-old South African black male with HIV and a CD4 count of 148. He was not receiving antiretroviral therapy. Baseline conditions included chronic gastroenteritis, normocytic anemia, lymphadenopathy, chronic sinusitis, atypical lower respiratory tract infection, and hypoalbuminemia. He received micafungin 150 mg/day for 9 days for EC. Concomitant medications included spasmogel, scopex, clopamon, immodium, normal saline, ciprobay (ciprofloxacin), bactrim, stilpain, cough syrup, immunocare (nutritional supplement), and lasix. Acute renal failure was reported as a serious adverse event on study day 7, and the patient was started on intravenous fluids and lasix. The patient withdrew consent on study day 9. The patient died on day 17 due to acute kidney failure. On the CRF, the investigator listed a contributing cause of death as “consuming Zulu traditional medication” of unknown composition. No autopsy was performed and the death was not attributed to micafungin. Laboratory data for this patient is shown in the table below.

#### Laboratory Values\* for Patient 10745031

Study Day	WBC x 10 <sup>9</sup>	Hemoglobin g/dL	Platelets x 10 <sup>9</sup>	BUN mg/dL	Creatinine mg/dL	Sodium mmol/L	Potassium mmol/L
Baseline	10.6	10.5	229	42	3.5	131	4.0
Day 7	6.1	10.6	69	75	6.9	128	5.9

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	AST U/L	ALT U/L	Total bilirubin mg/dL	Alkaline phosphatase U/L	LDH U/L	Albumin g/dL	Calcium mg/dL
Baseline	101	85	1.1	217	2348	1.4	10.7
Day 7	649	305	4.3	519	2534	1.1	11.4

\*normal laboratory values are shown in Appendix 10.

***Medical Officer Comments:** This patient had renal insufficiency at baseline, which worsened during the micafungin treatment period. He was receiving bactrim (dose unknown) which can cause renal failure, as well as lasix which could contribute to pre-renal azotemia with volume loss. Additionally, he developed thrombocytopenia, hyperkalemia (possibly secondary to renal failure), increased AST, ALT, total bilirubin, alkaline phosphatase, and LDH, and decreased albumin. He was hyponatremic at baseline and on day 7, and hypercalcemic at baseline, which was worse on day 7. The etiology of the hepatic laboratory abnormalities is not clear. The CRF did not indicate hypotension. It is plausible that either micafungin, bactrim, or the "traditional zulu medication" caused liver dysfunction. Because there was no close temporal relationship between micafungin and death in this case, I would agree that the death was not likely related to micafungin.*

**Patient 10745035** was a 34 year-old black South African male with HIV and a CD4 count of 97 cells/mm<sup>3</sup>. Significant baseline conditions included generalized lymphadenopathy, cachexia, alcohol abuse, acute diarrhea, normocytic anemia, an atypical lower respiratory tract infection, and tuberculosis. He received micafungin 150 mg/day for 5 days. Concomitant medications included rifinah (isoniazid and rifampin), DS-24 (nutritional supplementation), bactrim, stilpain (), cough syrup, voltaren and cruciale (multivitamins). Hepatic failure was reported as a serious adverse event on study day 4, and micafungin was discontinued on day 5 because of liver failure. Subsequently, the patient was hospitalized (day 6) and was diagnosed with multi-drug resistant tuberculosis on day 10. The patient was noted to be severely jaundiced at that time. The patient died on day 17 due to multi-drug resistant tuberculosis, with acute liver failure listed as a contributing condition. No autopsy was performed, and the death was not attributed to micafungin. Laboratory data for this patient is summarized in the table below.

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Study Day	WBC x 10 <sup>9</sup>	Hemoglobin g/dL	Platelets x 10 <sup>9</sup>	BUN mg/dL	Creatinine mg/dL	Sodium mmol/L	Potassium mmol/L
Baseline	9.7	10.9	204	10	0.9	134	4.5
	AST U/L	ALT U/L	Total bilirubin mg/dL	Alkaline phosphatase U/L	Albumin g/dL	Calcium mg/dL	LDH U/L
Baseline	121	65	0.9	264	1.6	10.7	747
Day 5**	66	29	8.3	--	--	--	--

\*normal laboratory values are shown in Appendix 10.

\*\* laboratory data for day 5 was obtained from a non-study lab

**Medical Officer Comments:** *This patient had only modest AST and ALT elevations at baseline, which improved by day 5. However, the patient developed isolated bilirubinemia. The patient had been on anti-tuberculous medications (isoniazid and rifampin) for several months prior to enrollment in the study, so it would be unlikely that they caused bilirubinemia acutely. Voltaren, like other NSAIDS has known potential for hepatotoxicity. I would agree with the investigator that the death was probably not due to micafungin given that micafungin was stopped on day 5 and died on day 17. However, it is possible that micafungin contributed to the bilirubinemia. There was no evidence provided that the patient actually had hepatic failure (such as elevated PT, decreased albumin, or clinical signs and symptoms such as encephalopathy, ascites, etc.).*

**Patient 10755007** was a 51 year-old male from South Africa with HIV and a CD4 count of 225 cells/mm<sup>3</sup>. He was not receiving antiretroviral therapy. Baseline conditions included tremor, anemia, urinary incontinence, fecal incontinence, nausea, thrombocytopenia, hyponatremia, hypoproteinemia, urinary tract infection and emphysema. He received micafungin 150 mg/day for 7 days for EC. Adverse events during treatment were reported as worsening HIV and kidney failure. On day 8, the patient developed suspected pulmonary tuberculosis and respiratory failure, and micafungin was discontinued. He died on day 9 due to respiratory failure. No autopsy was performed and the death was not attributed to micafungin. Laboratory values for this patient are shown in the table below.

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Laboratory Values\* for Patient 10755007

Study day	WBC x 10 <sup>9</sup>	Hemoglobin g/dL	Platelets x 10 <sup>9</sup>	BUN mg/dL	Creatinine mg/dL	Sodium mmol/L	Potassium mmol/L
Baseline	6.1	8.8	62	23	1.5	125	4.2
Day 7	8.0	9.3	37	53	2.7	137	5.6
	AST U/L	ALT U/L	Total bilirubin mg/dL	Alkaline phosphatase U/L	Albumin g/dL	Calcium mg/dL	LDH U/L
Baseline	152	35	0.5	535	1.6	10.0	1856
Day 7	304	54	1.0	805	1.4	10.8	3085

\*normal laboratory values are shown in Appendix 10.

*Medical Officer Comments: At baseline this patient had anemia, thrombocytopenia, mild renal insufficiency, hyponatremia, elevated AST and alkaline phosphatase, hypoalbuminemia and elevated LDH. During treatment, thrombocytopenia worsened, as did the renal insufficiency, AST, alkaline phosphatase, LDH, and low albumin. He developed hyperkalemia, and hypercalcemia. I would agree with the investigator that it is unlikely that this death was related to micafungin.*

**Patient 10755009** was a 32 year-old black male from South Africa with HIV and a CD4 count of 9 cells/mm<sup>3</sup>. At baseline, the patient had hemiplegia, rash, anemia, and hypoproteinemia. He received micafungin 150 mg/day for 21 days for EC. Concomitant medications included diclofenac, and doxycycline. During micafungin treatment, he developed bronchitis, phlebitis, and anemia. The patient died on day 27, and cause of death was reported as worsening of HIV disease. No autopsy was performed and the death was not attributed to micafungin. During micafungin treatment, the patient had no significant renal dysfunction, and hepatic transaminases and bilirubin were normal. Alkaline phosphatase was elevated at baseline (206 U/L) and increased to 296 U/L on day 20. Calcium was normal throughout the course of treatment; while magnesium declined from 2.7 mg/dL at baseline to 1.8 mg/dL on day 20. The patient also developed mild anemia during treatment with micafungin. Baseline hemoglobin was 13.4 g/dL, which dropped to 9.6 g/dL on day 7, and remained stable thereafter. Mild hyponatremia was noted on day 7 (134 mmol/L) and day 14 (129 mmol/L), but sodium was normal on day 20 (137 mmol/L).

*Medical Officer Comments: The cause of death in this patient is not clear. Although he had advanced HIV disease, death is usually secondary to an opportunistic infection, malignancy or complication of treatment. I would agree that the death was probably not related to micafungin.*

**Patient 11635004** was a 44 year-old mestizo female from Peru with HIV and a CD4 count of 30. Baseline conditions were reported as AIDS, "flu syndrome", and gastritis. The patient received micafungin 150 mg/day for 14 days for EC. Concomitant

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medications included cotrimoxazole (for PCP prophylaxis), ranitidine, cefuroxime, metimazole, acetaminophen, sodium chloride solution, kalium, dextrose, and midazolam. She received fluconazole post-treatment with micafungin. The only adverse event reported during micafungin treatment was pulmonary tuberculosis (serious) on day 2. Sepsis was reported on day 29, and the patient died that day. The primary cause of death was reported as sepsis, with pulmonary tuberculosis a contributing factor. The death was not attributed to micafungin. Laboratory abnormalities included hemoglobin of 9.1 g/dL at baseline, which decreased to 7.5 g/dL on day 7, mild hyponatremia, which remained stable throughout the study (baseline 131 U/L), low calcium at baseline (8.3 mg/dL), which continued to decline, and was 6.9 mg/dL on day 20. Albumin was 1.9 g/dL at baseline, and decreased to 1.1 g/dL by day 20. The patient had modest elevations of AST and ALT (105 U/L and 69 U/L at baseline, respectively), which declined during treatment; while bilirubin was normal throughout, and alkaline phosphatase increased from 373 U/L at baseline to 964 U/L on day 20. LDH also increased from 518 U/L to 978 U/L by day 20.

*Medical Officer Comments: Despite all the metabolic abnormalities which occurred during treatment with micafungin, I would agree that this death was not likely related to micafungin.*

**Patient 11645004** was a 28 year-old mestizo male from Peru with HIV and a CD4 count of 67 cells/mm<sup>3</sup>. The only baseline condition reported was disseminated Kaposi's sarcoma. He received micafungin 150 mg/day for 5 days for EC. Concomitant medications included cotrimoxazole, dexamethasone, ceftriaxone, nelfinavir, zidovudine, and didanosine (started day 7), dextrose, prednisone, ciprofloxacin, ceftazidime, and amikacin. The patient developed adult respiratory distress syndrome (ARDS) and worsening of Kaposi's sarcoma on day 6 and micafungin was stopped. The patient died on day 45 due to ARDS and stage IV Kaposi's sarcoma. No autopsy was performed and the death was not attributed to micafungin. No significant laboratory abnormalities were noted except for a mild decrease in hemoglobin from 10.0 g/dL at baseline to 8.4 g/dL on day 19, and mild decrease in magnesium from 2.3 mg/dL to 1.8 mg/dL (day 19).

*Medical Officer Comments: Because of the large time interval between stopping micafungin (day 5) and death (day 45), this death was not likely related to micafungin.*

**Patient 11645009** was a 29 year-old mestizo male from Peru with a CD4 count of 29 cell/mm<sup>3</sup>. Baseline conditions in this patient included night sweats, weight loss, cough, diarrhea, PCP pneumonia, chronic gastritis and duodenitis, cachexia, and increased alkaline phosphatase. The patient received micafungin 150 mg/day for 5 days for EC. Concomitant medications included clindamycin, primaquine, rifampin, isoniazid, etambutol, pyrazinamide, ceftazidime, and dopamine. The patient developed a headache and tuberculous meningitis on study day 2, pulmonary tuberculosis (day 9), sepsis (day 6) and septic shock (day 26). The patient died on day 34 due to tuberculous meningitis and multifactorial shock. No autopsy was performed and the death was not considered related

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to micafungin. Only baseline laboratories were available for this patient. Abnormalities at baseline included anemia (hemoglobin 8.5 g/dL), elevated alkaline phosphatase (1066 U/L), elevated AST (98 U/L), ALT (67 U/L), and LDH (449 U/L).

*Medical Officer Comments: I would agree that death in this case was not related to micafungin, given the concurrent opportunistic infections (PCP and tuberculosis), and the time lag between last micafungin administration (day 5) and death (day 34).*

**Patient 11655005** was a 41 year-old black South African female with HIV. The CD4 count was not measured and the patient was not receiving antiretroviral therapy. Baseline conditions included cough, vomiting, tachycardia, fever, abnormal pulmonary examination, nausea, and painful legs. She received micafungin 150 mg/day for 14 days for EC. Concomitant medications included vitamin B complex, vitamin C, and cotrimoxazole. Phlebitis was reported as an adverse event (day 6) which resolved day 10. The patient died on study day 35. Cause of death was reported as worsening of HIV disease. No autopsy was performed, and the death was not attributed to micafungin. Laboratory evaluations for this patient are shown in the table below.

### Laboratory Values\* for Patient 11655005

Study Day	WBC x 10 <sup>9</sup>	Hemoglobin g/dL	Platelets x 10 <sup>9</sup>	BUN mg/dL	Creatinine mg/dL	Sodium mmol/L	Potassium mmol/L
Baseline	8.6	7.1	248	6	0.8	136	3.7
Day 7	9.5	6.1	216	4	0.7	134	4.2
Day 14	11.7	5.9	216	6	0.8	131	4.6
Day 29	17.2	6.5	253	12	0.7	135	5.0
	AST U/L	ALT U/L	Total bilirubin mg/dL	Alkaline phosphatase U/L	LDH U/L	Albumin g/dL	Calcium mg/dL
Baseline	74	27	0.5	110	1147	2.3	10.2
Day 7	117	51	1.0	208	1144	2.0	10.0
Day 14	110	33	1.0	155	1513	2.0	10.5
Day 29	149	28	1.6	169	1713	2.3	10.8

\*normal laboratory values are shown in Appendix 10.

*Medical Officer Comments: The cause of death in this patient is not clear. Significant laboratory findings in this patient include mild elevation of bilirubin (day 29), increasing LDH throughout the study period, and increasing calcium, as well as rising WBC, and a slight worsening of baseline anemia. Given the time lag between last dose of micafungin (day 14) and death (day 35) it is not likely that the death was related to micafungin.*

**Patient 11655009** was a 43 year-old black male from South Africa with HIV and a CD4 count of 57 cells/mm<sup>3</sup>. Baseline conditions included cough and abnormal lung

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examination (rales). The patient received micafungin 150 mg/day for 10 days for EC. Concomitant medications included only cotrimoxazole. The patient developed shortness of breath and suspected pneumonia on day 10, and micafungin was discontinued. The patient died on day 13. The cause of death was reported as pneumonia, with HIV as a contributing factor. No autopsy was performed and the death was not considered related to micafungin. The only significant laboratory abnormalities included mild hyponatremia (sodium 134 mmol/L at baseline and day 7), mild elevation of AST (58 U/L at baseline and 43 U/L day 7), elevated calcium (10.9 mg/dL at baseline, 10.5 mg/dL on day 7), and elevated LDH (484 U/L baseline)

*Medical Officer Comments: This patient was probably developing pneumonia at baseline. I agree that the death was not likely related to micafungin.*

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**Serious Adverse Events**

A total of 35/260 (13.5%) patients in the micafungin group and 24/258 (9.3%) patients in the fluconazole group experienced at least one serious adverse event in this study. Table shows all serious adverse events classified by COSTART term for both treatment arms. Some patients had more than 1 serious adverse event.

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Table .35 All Serious Adverse Events (SAEs) in Study 005 (adapted from Applicant's Table 13.5.3)

SAE (COSTART Term)	Micafungin N=260 n (%)	Fluconazole N=258 n (%)
Any SAE	35 (13.5)	24 (9.3)
Pneumonia	6 (2.3)	4 (1.6)
AIDS	5 (1.9)	2 (0.8)
Delirium	3 (1.2)	1 (0.4)
Pulmonary tuberculosis, reactivated	3 (1.2)	0 (0)
Respiratory failure	3 (1.2)	0 (0)
Kidney failure	3 (1.2)	3 (1.2)
Infection	2 (0.8)	0 (0)
Sepsis	2 (0.8)	2 (0.8)
Tuberculosis, reactivated	2 (0.8)	1 (0.4)
Anemia	2 (0.8)	2 (0.8)
Acute kidney failure	2 (0.8)	1 (0.4)
Shock	1 (0.4)	2 (0.8)
Sarcoma	1 (0.4)	0 (0)
Arrhythmia	1 (0.4)	0 (0)
Congestive heart failure	1 (0.4)	1 (0.4)
Heart failure	1 (0.4)	1 (0.4)
Dysphagia	1 (0.4)	0 (0)
Gastrointestinal hemorrhage	1 (0.4)	0 (0)
Hepatic failure	1 (0.4)	1 (0.4)
Vomiting	1 (0.4)	1 (0.4)
Leukopenia	1 (0.4)	0 (0)
Electrolyte abnormality	1 (0.4)	0 (0)
Healing, abnormal	1 (0.4)	0 (0)
Hemiplegia	1 (0.4)	0 (0)
Apnea	1 (0.4)	0 (0)
Dyspnea	1 (0.4)	0 (0)
Respiratory distress syndrome	1 (0.4)	0 (0)
Retinitis	1 (0.4)	0 (0)
Cardiomyopathy	0 (0)	1 (0.4)
Gastroenteritis	0 (0)	1 (0.4)
Gastrointestinal carcinoma	0 (0)	1 (0.4)
Diarrhea	0 (0)	2 (0.8)
Asthenia	0 (0)	1 (0.4)
Melena	0 (0)	1 (0.4)
Hypokalemia	0 (0)	1 (0.4)
Hypomagnesemia	0 (0)	1 (0.4)
Hyponatremia	0 (0)	1 (0.4)

Hypoproteinemia	0 (0)	1 (0.4)
Peripheral edema	0 (0)	1 (0.4)
Cerebrovascular accident	0 (0)	1 (0.4)
Meningitis	0 (0)	1 (0.4)
Bronchitis	0 (0)	1 (0.4)

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Pyelonephritis	0 (0)	1 (0.4)
Total SAEs	50	38

**Medical Officer Comments:** *The incidence of serious adverse events was higher in the micafungin- than in the fluconazole treatment group; and there were more total serious adverse events in the micafungin group (50) in comparison to the fluconazole group (38). In patients treated with micafungin the frequency of serious adverse events including tuberculosis, pneumonia, AIDS, respiratory failure, renal failure, infection, and delirium was higher than in fluconazole-treated patients. Hepatic failure was observed as a serious adverse event in 1 micafungin-treated patient, and in 1 fluconazole-treated patient.*

Serious adverse events for those who received micafungin are summarized by patient in the table below. Notably 52/260 (20.0%) patients micafungin-treated patients were found in the database who had at least one serious adverse event rather than 35/260 (13.5%) as noted above.

**Medical Officer Comment:** *This difference in the number of patients with at least one serious adverse event may be due to differences in accounting of patients who died and also had serious adverse events. All patients with serious adverse events in the database are summarized in the table below.*

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Table 136. Summary of Micafungin-Treated Patients with Serious Adverse Events

#	Patient Number	SAE	Onset SAE (study day)	Micafungin discontinuation (study day)	Outcome	Relationship to micafungin*
1	02545002	Anemia (1); Confusional state (2)	14 (1) 24 (2)	14	Recovered (1,2)	Definitely not
2	02545016	Vomiting (1); renal insufficiency (2); pulmonary tuberculosis (3)	19 (1,2)	19	Death (1,2,3)	Definitely not
3	02545018	Apnea	6	3	Death	Definitely not
4	03235005	Cytomegalovirus retinitis	7	5	Recovered	Definitely not
5	03235015	Septic shock	11	10	Death	Definitely not
6	03235021	Interstitial lung disease		14	Death	Definitely not
7	03245007	Myelopathy			Not recovered	Definitely not
8	03245019	Leukopenia (1); neutropenia (2)	7 (1,2)	14	Recovered (1,20)	Definitely not (1,2)
9	10305003	Respiratory failure	2	20	Recovered	Definitely not
10	10385001	Fever (1); diarrhea (2)	24 (1,2)	13	Recovered (1,2)	Definitely not
11	10445008	Disseminated tuberculosis (1); coma (2)	19 (1) 26 (2)	14	Death	Definitely not
12	10445013	Pneumonia (1); respiratory distress (2)	8 (1) 13 (2)	14	Recovered (1,2)	Definitely not (1,2)
13	10545001	Dysphagia (1); postoperative wound complication (2)	13 (1) 25 (2)	22	Recovered (1,2)	Unlikely (1,2)

\*investigator's assessment of drug-relatedness

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Table 136. (continued) Summary of All Serious Adverse Events in Micafungin-Treated Patients

#	Patient Number	SAE	Onset SAE (study day)	Micafungin stop day	Outcome	Relationship to micafungin
14	10575008	Delirium (1); pulmonary tuberculosis (2)	11	10	Recovered (1); not recovered (2)	possible (1); unlikely (2)
15	10575015	Pulmonary tuberculosis	28	14	Death	Definitely not
16	10575026	Cardiac failure	23	14	Death	Unlikely
17	10575041	Pulmonary tuberculosis(1); HIV progression (2)	20 (1) 21 (2)	14	Death	Definitely not
18	10575045	Pulmonary tuberculosis (1); HIV progression (2)	3 (1,2)	2	Death	Unlikely
19	10575046	Multi-organ failure (Heart, renal, respiratory failure)	17	14	Death	Unlikely
20	10575050	Delirium	6	6	Recovered	Possible
21	10625002	Severe electrolyte disturbance (1); ventricular fibrillation (2); HIV progression (3)	1 (1,2)	1	Death	
22	10655006	Progression of HIV	13	12	Death	Possible
23	10655007	Diarrhea			Recovered	Definitely not
24	10655010	Bacteremia	14	14	Recovered	Definitely not
25	10655003	Pulmonary tuberculosis	29	14	Death	Definitely not
26	10665007	Delirium	4	14	Recovered	Definitely not
27	10665017	Bronchopneumonia	26	14	Death	Definitely not
28	10665018	Progression of HIV	17	14	Death	Definitely not
29	10665036	Pulmonary tuberculosis	31	14	Death	Definitely not

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Table 136. (continued) Summary of All Serious Adverse Events in Micafungin-Treated Patients

#	Patient Number	SAE	Onset SAE (study day)	Micafungin stop day	Outcome	Relationship to micafungin
30	10665037	Progression of HIV (1); renal insufficiency (2); pulmonary tuberculosis (3); cardiac failure (4)		16	Death	Definitely not
31	10685011	Pneumonia (1); pulmonary tuberculosis (2)	13 (1) 10 (2)	14	Recovered	Definitely not
32	10695018	septic ascites	17	14	Recovered	Definitely not
33	10705001	Acute renal failure	9	14	Recovered	Definitely not
34	10705004	<i>Pneumocystis carinii</i> pneumonia	19	14	Death	Definitely not
35	10705010	<i>Pneumocystis carinii</i> pneumonia (1); tuberculosis (2)		14	Recovered (1); death (2)	Definitely not
36	10705024	Anemia (1); acute renal failure (2)		14	Not recovered (1); death (2)	Unlikely
37	10705047	<i>Pneumocystis carinii</i> pneumonia		13	Death	Definitely not
38	10745011	Atypical lower respiratory tract infection			Recovered	Definitely not
39	10745013	Facial nerve paralysis (1); hemiplegia (2)	11 (1,2)	15	Not recovered (1,2)	Definitely not
40	10745031	Acute renal failure	7	9	Death	Definitely not

\*investigator's assessment of drug-relatedness

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Table 136. (continued) Summary of All Serious Adverse Events in Micafungin-Treated Patients

#	Patient Number	SAE	Onset SAE (study day)	Micafungin stop day	Outcome	Relationship to micafungin
41	10745035	Hepatic failure (1); pulmonary tuberculosis (2)	4 (1) 6 (2)	5	Not recovered (1); death (2)	Unlikely (1); definitely not (2)
42	10745048	Respiratory tract infection (atypical)	12	14	Recovered	Definitely not
43	10755007	Pulmonary tuberculosis (1); respiratory failure (2)	8 (1,2)	7	Death	Definitely not
44	10755009	Progression of HIV	27	21	Death	Definitely not
45	10755011	Anemia (1); renal insufficiency (2)			Not recovered (1); death (2)	Definitely not (1, 2)
46	11635004	Pulmonary tuberculosis (1); sepsis (2)	2 (1) 29 (2)	14	Death (1,2)	Definitely not (1,2)
47	11645004	Acute respiratory distress syndrome (1, 2); disseminated Kaposi's sarcoma (3)	6 (1,2,3)	5	Recovered (1); death (2)	Definitely not (2)
48	11645006	Sensory disturbance (1); cryptococcal meningitis (2)			Recovered (1,2)	Definitely not (1,2)
49	11645009	Tuberculous meningitis (1); septic shock (2); pulmonary tuberculosis (3); hypovolemic shock (4); sepsis (5)	2 (1) 9 (3) 6 (5) 26 (2)	5	Death (1, 2,4)	Definitely not (1-5)
50	11655001	Melena	4	14	Not recovered	Definitely not
51	11655005	Progressive HIV	35	14	Death	Definitely not
52	11655009	Pneumonia	10	10	Death	Definitely not

\*investigator's assessment of drug-relatedness

**Narrative summaries for Patients with Serious Adverse Events**

Narrative summaries for patients who died and had serious adverse event(s) are provided above in section "Deaths".

**Patient 02545002**, a 31 year-old black male from South Africa with HIV and a CD4 count of 89 cells/mm<sup>3</sup> received micafungin 150 mg/day for 14 days for EC. At baseline, the patient had cough, and cachexia. Adverse events reported during micafungin treatment included fever, sweating, pneumonia, reactivated tuberculosis, phlebitis, pain, abnormal WBCs, hypoproteinemia, and increased LDH, in addition to anemia and confusion, which were reported as serious adverse events on study days 14, and 24, respectively. None of the adverse events were considered related to micafungin. Concomitant medications included painamol, cotrimoxazole (bactrim), immunity one (nutritional supplement), diazepam (day 12) for disorientation, and lorazepam (day 24) for confusion. The patient received a blood transfusion on day 25. The confusion initially resolved on day 14, but recurred day 26. Anemia and confusion were ongoing at the time of follow-up (day 45). Pertinent laboratory data for this patient is shown in the table below. Renal and hepatic laboratory values were normal throughout the study.

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Laboratory Values\* for Patient 0254002

Study day	WBC x 10 <sup>9</sup>	Hemoglobin g/dL	Platelets x 10 <sup>9</sup>	LDH U/L	Total bilirubin mg/dL	Sodium mmol/L
Baseline	4.5	8.0	322	625	0.4	131
Day 7	8.0	7.5	319	809	0.4	121
Day 14	7.2	6.0	258	670	0.8	127
Day 31	11.5	5.9	165	1455	0.5	131

\*normal laboratory values are shown in Appendix 10.

**Medical Officer Comments:** *This patient had progressive anemia despite discontinuation of micafungin on day 14. Other hematopoietic cell lines were not affected significantly. Although the LDH increased, there was no concomitant rise in bilirubin suggestive of hemolysis. The patient developed pneumonia and/or tuberculosis during treatment with micafungin, and received bactrim for presumed PCP, but did not receive antituberculous therapy. If his anemia were due to chronic infection, it would not be expect to progress as rapidly as in this case. Because the anemia cannot be attributed to other factors, it was possibly related to micafungin in my opinion.*

**Patient 3235005** was a 26 year-old mestizo female with HIV. A narrative summary was not available for this patient. Baseline conditions included diarrhea, retinitis, reactivate tuberculosis, anemia, bronchitis, leukopenia, and “abnormal WBC”. She received 5 days of micafungin 150 mg/day for EC. Concomitant medications included cotrimoxazole, rifampin, isoniazid, ethambutol, pyrazinamide, ketoconazole (prior to study entry), vitamin B, chlorpheniramine, ganciclovir (started prior to study entry), alprazolam, ciprofloxacin, midazolam, and fluconazole (post-treatment with micafungin). Adverse events reported during treatment included insomnia, “tooth disorder”, and cytomegalovirus (CMV) retinitis (day 7), reported as a serious adverse event. The patient recovered from this latter event (with residual effects). Except for leucopenia and anemia which were present at baseline, no significant laboratory abnormalities were observed during the study.

**Medical Officer Comment:** *This patient had CMV retinitis at baseline, and apparently had worsening of the infection during micafungin treatment. I would agree that any relationship of this event to micafungin would be unlikely.*

**Patient 3245007:** No narrative summary or patient profile was available for review.

**Patient 3245019** was a 36 year-old mestizo male with HIV and a CD4 count of 17 cells/mm<sup>3</sup>. The patient was receiving antiretroviral therapy. Conditions at baseline included PCP, thrombocytopenia, leucopenia, lymphopenia, anemia, hypocalcemia, and depression. The patient received micafungin 150 mg/day for 14 days for EC. Concomitant medications included stavudine, lamivudine, nevirapine, alprazolam, moclobemide, prednisone, cotrimoxazole, dimenhydrinate, xylocaine (topical anesthetic for endoscopy). After micafungin was discontinued, the antiretroviral regimen was changed to zidovudine, didanosine, and efavirenz. Worsening leukopenia was reported as a serious adverse event on study day 7, which resolved (day 14) with “residual effects”. The leukopenia was considered

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unlikely related to micafungin. Nausea and eosinophilia were also reported as adverse events. Pertinent laboratory data for this patient are shown in the table below.

### Laboratory Values\* for Patient 03245019

Study day	WBC (x 10 <sup>9</sup> )	ANC (cells/mm <sup>3</sup> )	Hemoglobin g/dL	Platelets (x 10 <sup>9</sup> )
Baseline	2.7	2050	10.5	142
Day 7	1.4	630	10.5	120
Day 11	1.6	848	10.4	131
Day 14	2.4	1536	10.1	121
Day 28	3.4	2006	11.2	164

\*normal values are shown in Appendix 10.

**Medical Officer Comments:** *This patient was also receiving bactrim for PCP, and bactrim can cause leukopenia. Bactrim was stopped on study day 7 and restarted for PCP prophylaxis on day 15. Because the leukopenia and neutropenia improved before micafungin was stopped (day 14), I would agree that any relationship to micafungin is unlikely.*

**Patient 10305003** was a 35 year-old mixed race female from South America with acute myeloid leukemia, for which she received chemotherapy approximately 2 prior to study entry. Other baseline conditions included fever, anemia, gastritis, thrombocytopenia, and dehydration. She received micafungin 150 mg/day for 20 days for EC. Concomitant medications included dipirona, ranitidine, ceftazidime, amikacin, hydrocortisone, vancomycin, meropenem, potassium chloride, saline solution, ovelicin, pavulon, fentanyl, midazolam (the latter 4 drugs for intubation/mechanical ventilation), berotec (inhaled), atrovent (inhaled), plasit, paracetamol, and hidantal for seizures. Respiratory failure was reported as a serious adverse event on day 2, and resolved without residual effects on day 6. The respiratory failure was considered unrelated to micafungin. Other adverse events which occurred in this patient included fever, "lung disorder (pulmonary infiltrate on CRF), hypokalemia, peripheral edema, convulsion, and vomiting. None of the latter events were considered serious, and none of the adverse events were considered related to micafungin. Review of laboratory data revealed mild hypocalcemia at baseline which improved by day 15, persistent hypomagnesemia, elevated alkaline phosphatase and LDH, anemia, leukopenia, neutropenia, and thrombocytopenia which resolved during treatment.

**Medical Officer Consult:** *The etiology of respiratory failure in this patient is not obvious from the narrative summary. Presumably the patient had pneumonia because a pulmonary infiltrate was noted as an adverse event on the CRF. The case report form also noted that respiratory failure was due to adult respiratory distress syndrome. Because respiratory failure resolved while the patient continued receiving micafungin, I would agree it was probably not related to micafungin.*

**Patient 10385001** is summarized in the section below on Discontinuation of Micafungin due to Adverse Event.

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**Patient 10445013** was a 35 year-old Caucasian male with HIV and a CD4 count of 31 cells/mm<sup>3</sup>. Baseline conditions included dyspnea and stomach ulcer. The patient received micafungin 150 mg/day for 14 days for EC. Concomitant medications included ranitidine, zidovudine, lamivudine, and efavirenz (the latter antiretroviral medications started on study day 1), dipirone, metoclopramide, diazepam, furosemide, prednisone, ceftriaxone, trimethoprim-sulfamethoxazole, ipratropium, fenoterol (inhaled), omeprazole, propofol, midazolam, heparin, cefepime, morphine, vancomycin, rifampin, isoniazid, and pyrazinamide. Pneumonia was reported as a serious adverse event on study day 8, and respiratory distress, requiring intubation, and severe pneumonia on day 13. These adverse events resolved and were considered unrelated to micafungin. Additional adverse events reported in this patient during micafungin treatment included dizziness and penile condyloma. No significant laboratory abnormalities were observed in this patient on review of the database.

*Medical Officer Comments: I would agree with the investigator that these events were not likely related to micafungin.*

**Patient 10545001** was a 58 year-old Caucasian female with esophageal cancer who received micafungin 150 mg/day for 22 days for EC. A narrative summary was not available for this patient. Other baseline conditions were hypertension, duodenitis, and cachexia. Concomitant medications included amiodarone, hydrochlorothiazide, captopril, ranitidine, potassium and sodium chloride, dipirone, cephalothin, bupivacaine (epidural), tramadol, dimethicone, hyoscine, xylocaine (topical), meperidine, midazolam, tenoxicam, fentanyl citrate, codeine, and ceftriaxone. Dysphagia was reported as a serious adverse event on study day 13, and a postoperative wound complication (surgical dehiscence of wound) on day 25. Other, non-serious adverse events during treatment were dehydration, and esophagitis. Calcium was low at baseline (8.6 mg/dL), and decreased to 7.0 mg/dL (day 8), 7.6 mg/dL (day 15), 6.8 mg/dL (day 22) and returned to baseline level on day 37. Creatinine remained normal; while BUN was modestly elevated throughout the study.

*Medical Officer Comments: This case is confounded by esophageal cancer which by itself can cause dysphagia. The patient had surgery on day 9 presumably for esophagectomy. I would agree that the dysphagia and surgical wound dehiscence are most likely not related to micafungin.*

**Patient 10575008** is summarized below in the section, “Drug-Related Serious Adverse Events”.

**Patient 10575050** is summarized below in the section, “Drug-Related Serious Adverse Events”.

**Patient 10655007:** Narrative summary or patient profile was not available.

**Patient 10655010** was a 31 year-old black male with HIV and underlying tuberculosis, abdominal pain, rectal disorder, constipation, diarrhea, insomnia, fever, and vomiting. A narrative summary was not available for this patient. He received micafungin 150 mg/day for 14 days for EC. Concomitant medications included rifampin (isoniazid, rifampin, pyrazinamide, and ethambutol), augmentin, cotrimoxazole (bactrim), propoxyphene, zolpidem, metoclopramide, paracetamol, levofloxacin, and fluconazole (after micafungin treatment was completed). Sepsis (bacteremia) was reported as a serious adverse event on study day 14. The patient recovered from this adverse event, which was not

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considered related to micafungin. Other adverse events reported in this patient included dizziness, nausea, vomiting, increased cough, and epistaxis, none of which were considered serious. No significant laboratory abnormalities were noted in this patient except for an elevated LDH, which was high at baseline (559 U/L) and increased to 691 U/L by study day 28. Notably, the patient became leukopenic during treatment (WBC  $5.2 \times 10^9$  at baseline,  $2.6 \times 10^9$  on day 7,  $2.8 \times 10^9$  on day 14, and  $2.6 \times 10^9$  on day 14). Absolute neutrophil counts were also low, but not below 1000 cells/mm<sup>3</sup>. Platelet counts and hemoglobin levels remained normal throughout the study.

*Medical Officer Comments: I would agree with the investigator that bacteremia in this patient was most likely not related to micafungin.*

**Patient 10655007** was a 34 year-old black female with HIV disease. A narrative summary was not available for this patient. Baseline conditions included anemia and back pain. For EC, the patient received micafungin 150 mg/day for 14 days total, interrupted after the fifth dose because of delirium, which was listed as a serious adverse event on days 4 through 9. Delirium resolved without any residual effects, and it was considered unrelated to micafungin. Micafungin was restarted on day 7 and continued to complete 14 days of treatment. Additional adverse events reported for this patient included nausea, vomiting, fever, myalgia, extrapyramidal syndrome and pneumonia. Concomitant medications included valoid, cozole (bactrim), voltaren, etomien, inza, panado, valium, ativan, rociject, akineton, and serenace. No abnormal laboratory values were noted that would contribute to mental status changes.

*Medical Officer Comments: A relationship between micafungin and delirium is unlikely because the delirium resolved after restarting micafungin.*

**Patient 10685011** was a 46 year-old black female with HIV and a CD4 count of 126 cells/mm<sup>3</sup>. She was not receiving antiretroviral therapy. Baseline conditions included pneumonia, lymphadenopathy, weight loss, anemia, and increased LDH. The patient received micafungin 150 mg/day for 14 days. Concomitant medications included vitamin B complex, ampicillin, cotrimoxazole (bactrim), paracetamol, pregamal, lasix, rapifen, dornicum (midazolam), pyridoxine, rifafour (isoniazid, rifampin, pyrazinamide, and ethambutol), cefazolin, and fluconazole (started after micafungin treatment). Tuberculosis was reported as a serious adverse event on day 10, and was persistent at the end of the study. Pneumonia was listed as a serious adverse event on day 13, with recovery noted on day 20. Additional adverse events noted for this patient included hypokalemia, kidney failure, leukocytosis, and thrombocytopenia. The latter events were considered possibly related to micafungin. Laboratory values of interest for this patient are shown in the table below.

Laboratory Values\* for Patient 10685011

Study day	WBC (x 10 <sup>9</sup> )	Hemoglobin g/dL	Platelets (x 10 <sup>9</sup> )	Sodium mmol/dL	K mmol/dL	Mg mg/dL	BUN mg/dL	Creatinine mg/dL
Baseline	2.8	9.9	96	136	4.6	1.6	30	1.4
Day 7	2.0	8.6	205	127	4.1	1.5	22	1.1
Day 14	5.9	6.9	65	130	2.7	2.0	56	1.6
Day 24	5.4	5.2	55	133	4.0	1.7	20	1.1

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	AST U/L	ALT U/L	Total bilirubin mg/dL	Alkaline phosphatase U/L	LDH U/L	Albumin gdL		
Baseline	156	88	0.2	354	1914	1.7		
Day 7	42	36	0.5	285	1115	1.7		
Day 14	54	29	2.1	318	1181	1.5		
Day 24	25	9	0.9	267	527	1.2		

\*normal values are shown in Appendix 10.

**Medical Officer Comments:** *In addition to the adverse events listed above, this patient developed progressive anemia, hyponatremia, and transient bilirubinemia during receipt of micafungin. I would concur with the investigator that the tuberculosis and pneumonia were not related to micafungin, but would consider the latter events possibly related.*

**Patient 10695018** was a 22 year old black female with HIV and a CD4 count of 18 cells/mm<sup>3</sup>, who received 14 days of micafungin 150 mg/day for EC. A narrative summary was not available for this patient. Baseline conditions included weight loss, pulmonary tuberculosis, anemia and maculopapular rash. Concomitant medications were rifabour (isoniazid, rifampin, pyrazinamide, and ethambutol), pyridoxine, and flagyl. On study day 17, infection (septic ascites) was listed as a serious adverse event from which the patient recovered. No other adverse events were reported and the event was not considered related to micafungin. Significant laboratory abnormalities included severe anemia (hemoglobin 6.2 g/dL at baseline) with worsening throughout the study (7.3 g/dL day 7, 4.6 g/dL day 14, and 3.8 g/dL day 31), thrombocytosis at baseline, which improved, increasing LDH throughout the study (668 U/L at baseline and 1487 U/L on day 31), hypoalbuminemia, mild hypercalcemia (at baseline, and intermittently throughout study), and hyponatremia at baseline and throughout study.

**Medical Officer Comments:** *On review of the case report form, neither of these events was listed as an adverse event. I would agree that the infection, referred to as "septic ascites" was not related to micafungin. However, micafungin may have contributed to worsening anemia.*

**Patient 10705001** was a 44 year-old black male with HIV. He was not receiving antiretroviral therapy and a CD4 count was not measured. Significant baseline conditions included neuropathy, lymphadenopathy, *Pneumocystis jiroveci* (formerly *carinii*) pneumonia, and anemia. The patient received micafungin 150 mg/day for 14 days for EC. Concomitant medications included multivitamins, ranceph (), painamol (), clear cough (cough medication), xylocaine, dormicum (midazolam), articulen (), saline, septran DS (bactrim), voltaren, panado (), dextrose, dulcolax, toradol, myprodol (), stilnox (), and etomine (). Acute renal failure was reported as a serious adverse event on study day 9. This event resolved with intravenous hydration, and was not considered related to micafungin. Other adverse events during micafungin treatment included myalgia, anemia, fever, constipation, and delirium. The patient received a blood transfusion on study day 13 for anemia. None of these events were considered related to micafungin.

Pertinent laboratory values for this patient are shown in the table below.

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### Laboratory Values\* for Patient 10705001

Study day	WBC (x 10 <sup>9</sup> )	Hemoglobin (g/dL)	Platelets (x 10 <sup>9</sup> )	BUN (mg/dL)	Creatinine (mg/dL)	Bilirubin (mg/dL)	LDH U/L
Baseline	8.2	7.0	284	16.3	1.2	0.8	1511
Day 7	11.6	5.7	171	44.8	1.9	1.5	1079
Day 14	8.9	7.0	160	10.1	1.1	1.2	1484
Day 31	2.9	7.5	255	5.3	0.7	0.5	501

\*normal values are shown in Appendix 10.

**Medical Officer Comments:** *This patient received a number of other medications which can cause renal insufficiency, namely voltaren and bactrim (particularly with the high doses used to treat PCP). I would agree that renal insufficiency was probably not related to micafungin. This patient developed worsening anemia requiring a blood transfusion, which was possibly related to micafungin. There was no strong evidence for hemolysis, however.*

**Patient 10745011:** Narrative summary and patient profile were not available.

**Patient 10745013** was a 24 year-old black female with HIV (CD4?), who received 15 days of micafungin 150 mg/day for EC. No narrative summary was available for this patient. Other baseline conditions included gastroenteritis, lymphadenopathy, "ear disorder", and headache. Hemiplegia and left facial nerve palsy were noted as serious adverse events on study day 11. These events were not considered related to micafungin, and persisted at the end of the study. Other adverse events reported included hypotension, myalgia, and normocytic anemia. Concomitant medications included allergex, scopex, clopamon, immodium, potassium chloride, normal saline, medigel, tramal, ciprofloxacin, stilpain, effortil, decadron and bactrim (for Toxoplasmosis), voltaren, nystatin and fluconazole (after completion of micafungin therapy). No pertinent laboratory abnormalities were noted on review of the database.

**Medical Officer Comments:** *This patient apparently developed cerebral Toxoplasmosis resulted in left hemiparesis and a left facial nerve palsy during treatment with micafungin. I would agree that these adverse events were not likely related to micafungin.*

**Patient 10745048** was a 26 year-old black female with HIV (CD4?) who received 14 days of micafungin (150 mg/day) for EC. Other baseline conditions included pulmonary tuberculosis, hemorrhoids, lower respiratory tract infection, normocytic anemia, thrombocytopenia, hypoproteinemia, and vulvovaginitis. Concomitant medications included rifafour (isoniazid, rifampin, pyrazinamide, and ethambutol), bactrim, ibuprofen, cough syrup, amethocaine cream, anusol suppositories and liquid paraffin for hemorrhoids, canasore, vaginal cream, tramahexal, vitamin B complex, zinacef, alcophyllex, zinnat, and nystatin oral suspension (after micafungin treatment completed). Atypical lower respiratory tract infection was reported as a serious adverse event on study day 12 and was persistent at the end of the study. Headache was also reported as an adverse event. Neither event was considered related to micafungin. Laboratories were remarkable only for progressive thrombocytopenia throughout the study period. Baseline platelet count was  $97 \times 10^9$ , which decreased to  $57 \times 10^9$  on day 7, to  $37 \times 10^9$  on day 14, and increased to  $75 \times 10^9/L$  on day 29.

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*Medical Officer Comments: I would agree that the atypical pneumonia was not related to micafungin; however, the progressive thrombocytopenia which improved after micafungin was discontinued is suggestive of a drug-related adverse event.*

**Patient 11645006:** Narrative summary and patient profile were not available.

**Patient 11655001** was an 80 year-old Caucasian male with bullous pemphigoid who received 14 days of micafungin (150 mg/day) for EC. A narrative summary was not available for this patient. Other baseline conditions included gastrointestinal hemorrhage, constipation, peripheral edema, tachycardia, and heart failure. Concomitant medications included cimetidine, pantoloc, ulsanic, lasix, tarka, celestone soluspan, solucortef, spiractin, duphalac, pantoloc, kloref (potassium supplement), pulmison, tranquipam, vitothion, amoxicillin and clacef. Gastrointestinal hemorrhage (melena) was reported as a serious adverse event on study day 4, and the patient required a blood transfusion. The patient recovered and this event was not considered related to micafungin. Additional adverse events reported for this patient included phlebitis, infection, and hypokalemia. Pertinent laboratory data for this patient is shown in the table below.

Laboratory Values\* for Patient 11645006

Study day	WBC x 10 <sup>9</sup>	Hemoglobin g/dL	Platelets x 10 <sup>9</sup>	Sodium mmol/L	Potassium mmol/L	BUN mg/dL	Creatinine mg/dL
Baseline	15.6	12.5	220	135	3.5	27	0.9
Day 7	9.3	15.9	128	133	2.4	13	1.2
Day 14	14.0	14.0	274	132	3.7	12	1.1
Day 29	20.2	13.2	407	131	4.3	15	1.1

\*normal values are shown in Appendix 10.

*Medical Officer Comments: This patient had gastrointestinal hemorrhage listed as a baseline condition, so I would agree that this adverse event was not related to micafungin. During micafungin treatment, the patient developed mild hyponatremia, and hypokalemia, which could possibly be attributed to lasix, and transient thrombocytopenia, which remains unexplained and could be related to micafungin.*

**Drug-Related Serious Adverse Events**

Serious adverse events considered by the investigator to be related to the study drug occurred in 3 patients treated with micafungin, and 1 patient treated with fluconazole. These events are summarized in the following table.

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Table 137. Serious Drug-Related Adverse Events in Study 005 (adapted from applicant's table 23)

Patient Number	Study drug/cumulative dose	Discontinued due to SAE	Duration of study drug	SAE COSTART Term	Day of SAE Onset	Patient Outcome
10575008	Micafungin 1500 mg	yes	10 days	Delirium	11	SAE resolved day 12, patient recovered
10575050	Micafungin 900 mg	yes	6	Delirium	6	SAE resolved day 10; patient recovered
10655006	Micafungin 1800 mg	yes	12	Progression of HIV disease	13	Death day 13
10575051	Fluconazole	yes	6	Asthenia; Delirium	6	SAE persistent at time of death day 8

*Medical Officer Comments: It is difficult to attribute causality to study drug in these patients with advanced HIV disease, multiple baseline conditions, and multiple concomitant medications. Accordingly, more emphasis is placed in this review on serious adverse events regardless of causality. In the two cases of delirium in micafungin-treated patients, a clearer case for attribution to drug can be made because the delirium resolved after micafungin discontinuation. Narrative summaries for patients who received micafungin and subsequently developed delirium are provided in the section on adverse events leading to treatment discontinuation below.*

**Narrative Summaries for Serious Drug-Related Adverse Events**

**Patient 10575008** was a 34 year old black male from South Africa with HIV and a CD4 count of 98. He was not receiving antiretroviral therapy. At baseline, the patient had weight loss, anemia, and abnormal pulmonary examination (“creps”). The patient received no concomitant medications except for normal saline infusion. For EC, the patient received micafungin 150 mg/day for 10 days, at which time, micafungin was stopped due to delirium. This was considered a serious adverse event, possibly related to micafungin. Delirium reportedly resolved on day 12; however, the patient was hospitalized on study day 28 due to delirium. Other adverse events reported for this patient included dizziness (day 2), diarrhea (day 4), rash (day 11), all of which were considered possibly related to micafungin. Reactivated pulmonary tuberculosis was also reported as a serious adverse event on study day 28. Laboratory data was reviewed and low sodium was noted at baseline (134 mmol/L) and during

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micafungin treatment (133 mmol/L on day 7, 127 mmol/L on day 11). Calcium, magnesium, and renal laboratory values were normal, and no other significant laboratory abnormalities were noted.

*Medical Officer Comments: Patients with AIDS and low CD4 counts are at risk for HIV encephalopathy (dementia), opportunistic infections affecting the CNS (such as cerebral toxoplasmosis or cryptococcal meningitis), or CNS malignancy. This patient was apparently lost to follow up because he was hospitalized for delirium and any procedures performed to determine its etiology was not obtainable by the applicant. In the absence of this information, I would agree that the delirium was possibly related to micafungin because it resolved (at least temporarily) within 2 days after stopping the drug.*

**Patient 10575050** was a 40 year-old black male from South Africa with HIV and a CD4 count of 55 cells/mm<sup>3</sup>. Significant baseline conditions included cachexia, weakness, abnormal lung examination (“creps”), dehydration and anemia. Concomitant medications included loperamide, vitamin B complex, normal saline, bactrim, and paracetamol. He received micafungin 150 mg/day for 6 days for EC. Micafungin was discontinued due to delirium which required hospitalization and was reported as a serious adverse event on study day 6. The delirium resolved on study day 10. Other adverse events reported during micafungin treatment included diarrhea (day 2 and day 6), headache (day 3), fecal and urinary incontinence (day 6). Review of laboratory values for this patients revealed baseline hyponatremia (sodium 128 mmol/L at baseline and until day 28 of study), normal BUN and creatinine at baseline and day 6 (BUN and creatinine were mildly elevated day 28 at 19 mg/dL and 1.4 mg/dL, respectively), normal calcium at baseline and day 6, but slightly elevated day 28 (10.3 mg/dL), normal potassium at baseline and day 6, but slightly decreased day 29 (3.3mmol/L). Except for possibly the hyponatremia, the laboratory abnormalities noted on study day 28 would probably not have resulted in delirium noted on days 6-10.

*Medical Officer Comments: As mentioned above, patients with AIDS and low CD4 counts are at risk for HIV encephalopathy or dementia, as well as opportunistic infections or malignancies involving the CNS. Hyponatremia can also cause confusion, however, this patient was hyponatremic at baseline and the hyponatremia was stable during micafungin treatment. Because delirium resolved in this patient, with no report of recurrence at follow-up, I would agree with the investigator that this adverse event was possibly related to micafungin.*

### Adverse Events Leading to Discontinuation of Study Drug

Sixteen of 260 (6.2%) patients treated with micafungin and 10/258 (3.9%) patients treated with fluconazole experienced an adverse event leading to study drug discontinuation. A summary of these events is shown in the following table. The number of adverse events leading to study drug discontinuation was higher in the micafungin group (21 events) in comparison with the fluconazole group (12 events).

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Table 138. Adverse Events Leading to Study Drug Discontinuation (adapted from applicant's table 13.5.5.)

Adverse Event* COSTART Term	Micafungin N=260	Fluconazole N=258
	n (%)	n (%)
Any adverse event resulting in discontinuation	16 (6.2)	10 (3.9)
Rash	4 (1.5)	1 (0.4)
Pneumonia	3 (1.2)	2 (0.8)
AIDS	2 (0.8)	0 (0)
Delirium	2 (0.8)	1 (0.4)
Pulmonary tuberculosis, reactivated	2 (0.8)	0 (0)
Sarcoma	1 (0.4)	0 (0)
Tuberculosis, reactivated	1 (0.4)	0 (0)
Arrhythmia	1 (0.4)	0 (0)
Heart failure	1 (0.4)	0 (0)
Shock	1 (0.4)	2 (0.8)
Hepatic failure	1 (0.4)	0 (0)
Respiratory distress syndrome	1 (0.4)	0 (0)
Kidney failure	1 (0.4)	2 (0.8)
Asthenia	0 (0)	1 (0.4)
Sepsis	0 (0)	1 (0.4)
Hypokalemia	0 (0)	1 (0.4)
Cerebrovascular accident	0 (0)	1 (0.4)
Total Events	21	12

\*Patient could have more than one adverse event within a body system

Drug-related adverse events leading to study drug discontinuation occurred in 6 micafungin-treated patients (2.3%) and 2 fluconazole-treated patients (0.8%). Drug-related events in this category included rash (4 events), delirium (2 events) and AIDS (1 event) in the micafungin treatment group, and rash, delirium, and asthenia (1 event each) in the fluconazole group. Serious drug-related adverse events that resulted in micafungin discontinuation were shown in Table 137 above. Drug-related adverse events resulting in micafungin discontinuation are summarized in the table below.

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Table 139. Drug-Related Adverse Events Resulting in Drug Discontinuation (adapted from applicant's table 25)

Patient number	Study Drug/ cumulative dose	Day of Drug Discontinuation	Adverse Event	Severity	Onset of Adverse Event (day)	Outcome
10365002	Micafungin 1200 mg	11	Rash	Severe	2	Resolved day 13
10365007	Micafungin 1500 mg	14	Rash	Moderate	10	Resolved day 14
10385001	Micafungin 1500 mg	13	Rash	Severe	8	Resolved day 15
10575008	Micafungin 1500 mg	10	Delirium/rash*	Moderate	10	Delirium resolved day 12, and rash day 13

\* In narrative summary, micafungin was stopped because of delirium

*Medical Officer Comments: The adverse events of rash and delirium in micafungin-treated patients resolved after drug discontinuation, supporting drug relatedness to these events.*

**Narrative Summaries for Patients who Discontinued Micafungin for Drug-Related Adverse Events**

**Patient 10575008** was reviewed in the section above on serious drug-related adverse events.

**Patient 10385001** was a 26 year-old mestizo male from Brazil with HIV and a CD4 count of 46 cells/mm<sup>3</sup>, and was receiving antiretroviral therapy. He received 13 days of micafungin, 150 mg/day for EC. Other baseline conditions included diarrhea and fever. Concomitant medications included zidovudine, lamivudine, and Lopinavir/ritonavir, dapson, hydroxyzine, prednisone, Tylenol, loperamide, dipirone, vitamin B complex and ranitidine. Rash was reported as an adverse event on day 8 and the patient was treated with hydroxyzine and prednisone. Micafungin was interrupted on day 9, restarted on day 13, but stopped again due to skin rash. No eosinophilia was noted on review of the laboratory data. The rash resolved on day 15, and was considered probably related to micafungin. On day 24, fever and diarrhea were reported as serious adverse events, considered unrelated to micafungin.

*Medical Officer Comments: Clearly, the rash was related to micafungin, resolving on de-challenge, and recurring on re-challenge. I agree with the investigator that the diarrhea and fever were probably not related to micafungin, given that these were listed as baseline conditions, and apparently worsening about 10 days after micafungin was stopped.*

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**Patient 10365007** was a 23 year-old Cuacasian female from Brazil with HIV and a CD4 count of 68 cells/mm<sup>3</sup>. She was receiving zidovudine, lamivudine and nelfinavir as antiretroviral therapy. Significant baseline conditions included hyponatremia, hypokalemia, leg pain, esophageal ulcer and genital HSV. The patient received micafungin 150 mg/day for 14 days for EC. Concomitant medications included antiretroviral therapy as noted above, amitryptaline, midazolam, meperidine, ranitidine, valacyclovir, bacrim, and pyramethamine. Pruritis and skin rash were noted as adverse events on study day 10, and micafungin was discontinued on that day due to leukopenia. The pruritis and skin rash were treated with dexchlorpheniramine and promethazine, and micafungin was restarted on day 11, and discontinued again on day 14 due to the skin rash (persistent or recurrent). After micafungin discontinuation, the skin rash and pruritis resolved, but the leucopenia persisted. Other adverse events in this patient included nausea, fever, headache, low visual acuity and vomiting. Pertinent laboratory data for this patient are shown in the table below. AST and ALT were normal at baseline and became only slightly elevated, with values of 67 U/L for AST and 41 U/L for ALT by day 7 of micafungin treatment. No eosinophilia was observed.

### Laboratory Values\* for Patient 10365007

Study Day	WBC x 10 <sup>9</sup>	ANC cells/mm <sup>3</sup>	Hemoglobin g/dL	Platelets x 10 <sup>9</sup>
Baseline	3.9	2935	10.4	268
Day 6	0.9	432	10.9	149
Day 14	1.1	344	10.2	169

\*normal values are shown in Appendix 10.

***Medical Officer Comments:** The skin rash and pruritis in this patient were most likely related to micafungin because of the positive de-challenge and re-challenge. The leucopenia could have been related to concomitant medications, particularly zidovudine, bacrim, or pyramethamine, so the leukopenia cannot be clearly attributed to micafungin.*

**Patient 10365002** was a 39 year-old Caucasian male from Brazil with HIV and a CD4 count of 80 cells/mm<sup>3</sup>. Significant baseline conditions included fever, anemia, and lymphopenia. The patient was not receiving antiretroviral therapy. He received micafungin 150 mg/day for 11 days for EC. Concomitant medications included bacrim, which had been started many months before, and acetaminophen. Micafungin was interrupted on day 8 because of a skin rash which had initially started on study day 2 and treated with dexchlorpheniramine. Micafungin was restarted on day 11, but promptly discontinued again the same day due to the rash. Other adverse events included fever which started on day 2, and loss of consciousness (check) day 14. The rash was treated until day 13 when it apparently resolved. On review of laboratory data, this patient was noted to have mild eosinophilia, and mild elevation of AST during micafungin treatment as shown in the table below.

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Laboratory Values\* for Patient 10365002

Study day	WBC (x 10 <sup>9</sup> )	Eosinophils (%)	Absolute eosinophil count cells/mm <sup>3</sup>	AST U/L	ALT U/L
Baseline	5.6	2	112	39	19
Day 8	4.7	10	470	47	26
Day 27	2.4	12	288	41	19

\*normal values are shown in Appendix 10.

*Medical Officer Comments: I would agree that the skin rash was probably related to micafungin given the positive de-challenge and re-challenge.*

Other Significant Adverse Events

Hepatic Adverse Events

The incidence of hepatic adverse events was similar in the micafungin and fluconazole treatment arms in this study. Hepatic adverse events occurred in 17/260 (6.5%) patients treated with micafungin and 13/258 (5.0%) patients treated with fluconazole. The most common hepatic adverse events in the micafungin group were increased alkaline phosphatase and abnormal liver function tests; while increased AST, ALT, and alkaline phosphatase were the most common in the fluconazole group. Hepatic adverse events that occurred in this study are summarized in the following table.

Table 140. Hepatic Adverse Events in Study 005 (adapted from applicant's Tables 26 and 13.5.7.1)

Adverse Event COSTART Body System and Term	Micafungin N=260 n (%)	Fluconazole N=258 n (%)
Patients with any hepatic AE	17 (6.5)	13 (5.0)
Digestive System:		
Hepatic failure	1 (0.4)	1 (0.4)
Hepatitis, nonspecific	1 (0.4)	1 (0.4)
Jaundice	2 (0.8)	1 (0.4)
Liver damage	0 (0)	1 (0.4)
Abnormal liver function tests	5 (1.9)	2 (0.8)
Metabolic and Nutritional Disorders:		
Alkaline phosphatase increased	6 (2.3)	5 (1.9)
Bilirubinemia	0 (0)	1 (0.4)
AST increased	2 (0.8)	5 (1.9)
ALT increased	1 (0.4)	6 (2.3)
Total number of hepatic AEs*	18	23

N= number of patients in FAS

n (%)= number and percentage of patients with adverse event

\*Note that an individual patient may have experienced more than one AE within a body system.

*Medical Officer Comments: Overall the number of patients who had at least one hepatic adverse event was similar in the micafungin and fluconazole treatment groups; while the*

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*overall number of adverse events was higher in the fluconazole group. One serious hepatic adverse event in a micafungin-treated patient occurred in this study, hepatic failure, which was described above in the narrative summary for patient #10745035. In that case, hepatic failure was considered a contributing factor in the patient's death, which was attributed to multi-drug resistant tuberculosis. This case was reviewed in the section above on Patient Deaths.*

### Hepatic Adverse Events Related to Study Drug

Hepatic adverse events considered drug-related occurred in 10/260 (3.8%) micafungin-treated patients, and 8/258 (3.1%) fluconazole-treated patients. These are listed in the following table.

Table 141. Drug-Related Hepatic Adverse Events in Study 005 (adapted from applicant's Table 13.5.7.1.2)

Adverse Event COSTART Term	Micafungin N=260 n (%)	Fluconazole N=258 n(%)
Any hepatic AE (drug-related)	10 (3.8)	8 (3.1)
Digestive System:		
Hepatitis, non-specific	1 (0.4)	1 (0.4)
Jaundice	0 (0)	1 (0.4)
Abnormal liver function tests	3 (1.2)	1 (0.4)
Metabolic and Nutritional Disorders:		
Alkaline phosphatase increased	4 (1.5)	3 (1.2)
AST increased	2 (0.8)	4 (1.6)
ALT increased	1 (0.4)	5 (1.9)
Total drug-related hepatic AEs*	11	15

*Medical Officer Comments: Overall, the incidence of hepatic adverse events attributed to study drug was similar for the micafungin and fluconazole treatment groups.*

### Hepatic Laboratory Abnormalities

Mean and median laboratory values for alkaline phosphatase, AST, ALT and total bilirubin were compared at weekly intervals, end-of therapy, and 2- and 4-weeks post-treatment. Baseline, 2 weeks during treatment, end-of-therapy, and 2-week post-therapy laboratory values are shown in Tables 142 through 145 below.

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Table 142. Alkaline phosphatase (AP) values during study (adapted from applicant's Tables 31 and 13.6.2)

Treatment / Sampling Time	N	AP (U/L) Mean ± Std. Deviation	AP (U/L) Median (range)
Micafungin/baseline	260	133.3 ± 142.3	84 (10-1066)
Micafungin/2 weeks treatment	235	158.5 ± 192.1	98 (27-1670)
Micafungin/EOT	250	167.1 ± 200.3	101 (27-1670)
Micafungin/2 weeks post-treatment	213	150.0 ± 205.1	93 (36-2150)
Fluconazole/baseline	256	130.5 ± 182.2	85 (1-2623)
Fluconazole/2 weeks treatment	241	144.6 ± 223.6	94 (34-3235)
Fluconazole/EOT	252	148.6 ± 221.3	96 (69-3235)
Fluconazole/2 weeks post-treatment	218	143.4 ± 290.1	86 (26-4136)

N= number of patients in FAS with laboratory value obtained at specified time period  
 EOT= end-of-therapy

*Medical Officer Comments: In both treatment groups, the mean and median alkaline phosphatase values increased slightly over baseline at 2 weeks treatment and EOT, decreasing at 2 weeks post-treatment. However, the standard deviations of the means are large and the range of values is wide, suggesting that outliers may skew these data, limiting interpretation of these data.*

Table 143. AST Values during Study Period (adapted from applicant's Tables 31 and 13.6.2)

Treatment / Sampling Time	N	AST (U/L) Mean ± Std. Deviation	AST (U/L) Median (range)
Micafungin/baseline	260	51.1 ± 47.0	36 (14-400)
Micafungin/2 weeks treatment	236	51.5 ± 42.4	42 (15-417)
Micafungin/EOT	250	55.3 ± 61.7	42 (15-649)
Micafungin/2 weeks post-treatment	212	78.0 ± 396.6	35 (12-5670)
Fluconazole/baseline	258	49.0 ± 48.1	37 (10-418)
Fluconazole/2 weeks treatment	241	48.6 ± 43.1	38 (15-395)
Fluconazole/EOT	253	65.3 ± 252.1	39 (15-4002)
Fluconazole/2 weeks post-treatment	218	50.0 ± 72.5	33 (11-876)

N= number of patients in FAS with laboratory value obtained at specified time period  
 EOT= end-of-therapy

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**Medical Officer Comments:** AST values increased slightly over baseline in the micafungin group during treatment, with the highest mean value observed 2 weeks post-therapy. However, the median AST value decreased at this time point, indicating that the distribution was skewed. In the fluconazole treatment group, AST increased minimally except at the EOT time point, where the mean was significantly higher than other time points. However, the standard deviation of the mean at the EOT was high and the median value unchanged.

Table 144. ALT Values during Study Period (adapted from applicant’s Tables 31 and 13.6.2)

Treatment / Sampling Time	N	ALT (U/L) Mean ± Std. Deviation	ALT (U/L) Median (range)
Micafungin/baseline	260	34.9 ± 28.6	26 (8-215)
Micafungin/2 weeks treatment	236	37.3 ± 27.0	29 (8-187)
Micafungin/EOT	250	37.9 ± 31.5	29 (7-305)
Micafungin/2 weeks post-treatment	212	46.0 ± 135.9	25 (7-1760)
Fluconazole/baseline	258	37.2 ± 46.0	26 (4-576)
Fluconazole/2 weeks treatment	241	33.4 ± 21.7	27 (5-168)
Fluconazole/EOT	253	39.9 ± 81.4	28 (5-1274)
Fluconazole/2 weeks post-treatment	218	33.6 ± 38.1	26 (8-483)

N= number of patients in FAS with laboratory value obtained at specified time period

EOT= end-of-therapy

In both treatment groups, the mean and median total bilirubin changed little during the study.

**Medical Officer Comments:** Mean and median ALT values increased slightly over time (including the 2-week post-treatment period) in the micafungin group. However, the median value for ALT at that time point was lower, and the distribution was most likely skewed. For the fluconazole group, the median ALT value changed little during the study, while the mean increased somewhat at the EOT time point, most likely due to outliers.

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Table 145. Total Bilirubin Values during Study Period (adapted from applicant’s Tables 31 and 13.6.2)

Treatment / Sampling Time	N	Total bilirubin (mg/dL) Mean ± Std. Deviation	Total Bilirubin (mg/dL) Median (range)
Micafungin/baseline	260	0.61 ± 0.46	0.5 (0.1-4.6)
Micafungin/2 weeks treatment	235	0.67 ± 0.39	0.6 (0.4-3.9)
Micafungin/EOT	250	0.68 ± 0.45	0.6 (0.1-4.3)
Micafungin/2 weeks post-treatment	213	0.65 ± 0.48	0.5 (0.1-4.1)
Fluconazole/baseline	258	0.60 ± 0.29	0.5 (0.0-1.6)
Fluconazole/2 weeks treatment	240	0.57 ± 0.37	0.5 (0.1-3.6)
Fluconazole/EOT	252	0.61 ± 0.44	0.5 (0.0-3.7)
Fluconazole/2 weeks post-treatment	218	0.53 ± 0.26	0.5 (0.1-1.8)

N= number of patients in FAS with laboratory value obtained at specified time period  
 EOT= end-of-therapy

**Medical Officer Comments:** *The mean and median total bilirubin increased slightly over time in the micafungin group, but not in the fluconazole group.*

*Overall these data suggest that hepatic laboratory values changed minimally during the treatment period in both treatment groups. However, laboratory data evaluated by statistics describing central tendencies (mean and median) are limited because 1 or more patients having outlying values can skew the distribution significantly.*

Shifts in the hepatic laboratory values from baseline to the EOT were also evaluated by the applicant, as shown in Tables 146 through 149 below. In the micafungin group, 240/260 (92.3%) patients had a “normal” alkaline phosphatase (< 2.5 x upper limit of normal, ULN) value at baseline, and 221/260 (85%) patients had “normal” alkaline phosphatase at the EOT. Twenty patients had an alkaline phosphatase 2.5 x -< 5x ULN at the EOT, 10 of these patients had a normal alkaline phosphatase at baseline, and 10 had elevated alkaline phosphatase at baseline. At the EOT, 7 patients had an alkaline phosphatase 5x-<10x ULN, 3 of these patients had a normal alkaline phosphatase at baseline; while 4 had an elevated alkaline phosphatase at baseline. Two patients in the micafungin group had alkaline phosphatase ≥ 10x ULN at the EOT. Both of these patients had an AP elevation of 5x-<10x ULN at baseline.

In the fluconazole group, 241/258 (93.4%) patients had a “normal” alkaline phosphatase at baseline; and 232/258 (89.9%) patients had a “normal” alkaline phosphatase at EOT. Seventeen patients had an alkaline phosphatase 2.5x- <5xULN at the EOT. Seven of these patients had a normal and 10 had an elevated alkaline phosphatase value at baseline. Two patients, both of whom had a normal value at baseline, had an alkalkine phosphatase 5x- <10x ULN at EOT. One patient had an alkaline phosphatase value> 10x ULN at baseline and EOT in the fluconazole group.

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Table 146. Shift in Alkaline phosphatase values from baseline to end-of therapy (adapted from applicant's Appendix 14.3.7.4.1)

Baseline	EOT Normal	EOT AP 2.5x - < 5x ULN	EOT AP 5x - <10x ULN	EOT AP ≥ 10x ULN	No data	Total Patients
	n	n	n	n	n	n
<b>Micafungin:</b>						
Normal	218	10	3	0	9	240
AP 2.5x-<5x ULN	3	8	3	0	0	14
AP 5x-<10x ULN	0	2	1	2	1	6
AP ≥ 10x ULN	0	0	0	0	0	0
No data	0	0	0	0	0	0
Total patients	218	20	7	2	10	260
<b>Fluconazole:</b>						
Normal	227	7	2	0	5	241
AP 2.5x-<5x ULN	4	10	0	0	0	14
AP 5x-<10x ULN	0	0	0	0	0	0
AP ≥ 10x ULN	0	0	0	1	0	1
No data	1	0	0	0	1	2
Total patients	232	17	2	1	6	258

EOT= end-of-therapy

ULN= upper limit of normal range for laboratory value

n= number of patients

*Medical Officer Comments: Eighteen of 260 (6.9%) micafungin-treated patients, and 9/258 (3.5%) fluconazole-treated patients had a higher alkaline phosphatase at the EOT than at baseline. Two patients in the micafungin group, and one in the fluconazole group developed alkaline phosphatase elevation to > 10 x ULN.*

In the micafungin group, 224/260 (86.2%) patients had a “normal” AST (< 2.5 x upper limit of normal, ULN) value at baseline, and 228/260 (87.7%) patients had “normal” AST at the EOT. Thirteen patients had an AST 2.5x -< 5x ULN at the EOT, 7 of these patients had a normal AST at baseline, and 6 had elevated AST at baseline. At the EOT, 6 patients had an AST 5x-<10x ULN, 1 of these patients had a normal AST at baseline; while 5 had an elevated AST at baseline. Three patients had an AST ≥

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10x ULN at the EOT in the micafungin group. One of these patients had a normal AST at baseline; while 2 had an AST elevation of 2.5x -< 5x ULN at baseline.

In the fluconazole group, 234/258 (90.7%) patients had a “normal” AST at baseline, and 229/258 (88.8%) patients had a “normal” AST at EOT. Nineteen patients (13 of whom had a “normal” AST at baseline) had an AST elevation of 2.5x-< 5x ULN at EOT. Two patients who had a baseline AST elevation of 2.5x-<5x ULN, developed AST elevation of 5x to <10x ULN at EOT; while 3 patients developed AST elevations >10x ULN at EOT. Only one of the latter patients had a “normal” AST at baseline.

Table 147. Shifts in AST from baseline to EOT (adapted from applicant’s Appendix 14.3.7.4.1)

Baseline	EOT Normal	EOT AST 2.5X - < 5X ULN	EOT AST 5X - <10X ULN	EOT AST ≥ 10X ULN	No data	Total Patients
	n	n	n	n	n	n
<b>Micafungin:</b>						
Normal	209	7	1	1	6	224
AST 2.5X-<5X ULN	16	6	4	2	3	31
AST 5X-<10X ULN	2	0	0	0	1	3
AST ≥ 10X ULN	1	0	1	0	0	2
No data	0	0	0	0	0	0
Total patients	228	13	6	3	10	260
<b>Fluconazole:</b>						
Normal	216	13	0	1	4	234
AST 2.5X-<5X ULN	12	4	2	1	1	20
AST 5X-<10X ULN	0	1	0	0	0	1
AST ≥ 10X ULN	1	1	0	1	0	3
No data	0	0	0	0	0	0
Total patients	229	19	2	3	5	258

EOT= end-of-therapy

ULN= upper limit of normal range for laboratory value; n= number of patients

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*Medical Officer Comments: Fifteen of 260 (5.8%) micafungin-treated patients, and 16/258 (6.2%) fluconazole-treated patients had a higher AST at EOT than at baseline. Three patients in each group had AST elevations > 10 x ULN at EOT.*

In the micafungin group, 244/260 (93.8%) patients had a "normal" ALT (< 2.5 x upper limit of normal, ULN) value at baseline, and 236/260 (90.8%) patients had "normal" ALT at the EOT. Twelve patients had an ALT 2.5x -< 5x ULN at the EOT, 7 of these patients had a normal ALT at baseline, and 5 had elevated ALT at baseline. At the EOT, 2 patients had an ALT 5x-<10x ULN, 1 of these patients had a normal ALT at baseline; while 1 had an elevated ALT at baseline. No patients had an ALT  $\geq$  10x ULN at the EOT in the micafungin group.

In the fluconazole group, 242/258 (93.8%) patients had a "normal" ALT at baseline, and 243/258 (94.2%) patients had a "normal" ALT at EOT. Nine patients (7 of whom had a "normal" ALT at baseline) had an ALT elevation of 2.5x - < 5x ULN at EOT. No patients had an ALT of 5x to <10x ULN at EOT; while 1 patient, who had a normal ALT at baseline, had an ALT >10x ULN at EOT.

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Table 148. Shifts in ALT from baseline to EOT (adapted from applicant's Appendix 14.3.7.4.1)

Baseline	EOT Normal	EOT ALT 2.5x - < 5x ULN	EOT ALT 5x - <10x ULN	EOT ALT ≥ 10x ULN	No data	Total Patients
	n	n	n	n	n	n
<b>Micafungin:</b>						
Normal	209	7	1	1	6	224
ALT 2.5x-<5x ULN	16	6	4	2	3	31
ALT 5x-<10x ULN	2	0	0	0	1	3
ALT ≥ 10x ULN	1	0	1	0	0	2
No data	0	0	0	0	0	0
Total patients	228	13	6	3	10	260
<b>Fluconazole:</b>						
Normal	216	13	0	1	4	234
ALT 2.5-<5x ULN	12	4	2	1	1	20
ALT 5x-<10x ULN	0	1	0	0	0	1
ALT ≥ 10x ULN	1	1	0	1	0	3
No data	0	0	0	0	0	0
Total patients	229	19	2	3	5	258

EOT= end-of-therapy

ULN= upper limit of normal range for laboratory value

n= number of patients

**Medical Officer Comments:** Fifteen of 260 (5.8%) of patients who received micafungin, and 17/258 (6.6%) patients who received fluconazole had an increased ALT at EOT in comparison to baseline. Three patients in each group had ALT elevations > 10 x ULN.

Mean and median ALT values increased slightly over time (including the 2-week post-treatment period) in the micafungin group. However, the median value for ALT at that time point was lower, and the distribution was most likely skewed. For the fluconazole group, the median ALT value changed little during the study, while the mean increased somewhat at the EOT time point, most likely due to outliers.

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In the micafungin group, 244/260 (93.8%) patients had a “normal” bilirubin (< 2.5 x upper limit of normal, ULN) value at baseline, and 256/260 (98.5%) patients had “normal” bilirubin at the EOT. Two patients had a bilirubin 2.5x -< 5x ULN at the EOT, both of these patients had a normal bilirubin at baseline. No patients had a bilirubin ≥5x ULN at the EOT in the micafungin group.

In the fluconazole group, 258/258 (100%) patients had a “normal” bilirubin at baseline, and 249/258 (96.5 %) patients had a “normal” bilirubin at EOT. Three patients (all of whom had a “normal” bilirubin at baseline) had a bilirubin elevation of 2.5x - < 5x ULN at EOT. No patients had a bilirubin of ≥5 ULN at EOT.

Table 149. Shifts in Total Bilirubin from baseline to EOT (adapted from applicant’s Appendix 14.3.7.4.1)

Baseline	EOT Normal	EOT Total Bilirubin 2.5x - < 5x ULN	EOT Total Bilirubin 5x - <10x ULN	EOT Total Bilirubin ≥ 10x ULN	No data	Total Patients
	n	n	n	n	n	n
<b>Micafungin:</b>						
Normal	244	2	0	0	10	256
Total Bilirubin 2.5x-<5x ULN	4	0	0	0	0	4
Total Bilirubin 5x-<10x ULN	0	0	0	0	0	0
Total Bilirubin ≥ 10x ULN		0	0	0	0	0
No data	0	0	0	0	0	0
Total patients	248	2	0	0	10	260
<b>Fluconazole:</b>						
Normal	249	3	0	0	6	258
Total Bilirubin 2.5x-<5x ULN	0	0	0	0	0	0
Total Bilirubin 5x-<10x ULN	0	0	0	0	0	0
Total Bilirubin ≥ 10x ULN	0	0	0	0	0	0
No data	0	0	0	0	0	0
Total patients	240	3	0	0	6	258

EOT= end-of-therapy

ULN= upper limit of normal range for laboratory value;

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n= number of patients

**Medical Officer Comments:** Only 2 patients in the micafungin group and 3 in the fluconazole group had a increased bilirubin at EOT relative to baseline. No patients in either group developed bilirubin elevation > 10 x ULN.

These laboratory value “shift” tables were more useful than comparison of mean and median laboratory value changes during the study period. These data are limited by missing data at the EOT.

The following table summarizes the incidence of elevated hepatic laboratories at EOT and for the “worst value during treatment”. The incidence of AST and ALT elevation is higher for the “worst value during treatment” than at the EOT within both treatment groups. However, there does not appear to be any significant difference in the overall incidence of patients with any elevated hepatic laboratory value during treatment between the micafungin and fluconazole treatment groups.

Table 150. Overall Incidence of Abnormal (Elevated) Hepatic Laboratory Values at EOT and “Worst Value during Treatment”

Laboratory Test	Micafungin (EOT) N=260	Micafungin (worst value) N=260	Fluconazole (EOT) N=258	Fluconazole (worst value) N=258
	n (%)	n (%)	n (%)	n (%)
Alkaline phosphatase	29 (11.2)	31/260 (11.9)	20 (7.8%)	26 (10.1)
AST	22 (8.5%)	41/260 (15.8)	26 (10.1)	36 (14.0)
ALT	14 (5.4)	19/260 (7.3)	10 (3.9%)	18 (7.0)
Bilirubin	2 (0.8)	5/260 (1.9)	3 (1.2%)	4 (1.6)

N= number of patients in FAS

**Medical Officer Comments:** Looking only at laboratory values at the EOT would underestimate the incidence of hepatic laboratory elevations in both treatment groups, particularly for AST and ALT.

The concurrent elevation of bilirubin and transaminases (AST or ALT) may be an important predictor of hepatotoxicity. The applicant evaluated conjoint bilirubin and transaminase elevation for patients with normal bilirubin and transaminases at baseline each treatment group as shown in the table below. In the micafungin treatment group, a total of 10 patients had conjoint elevation of bilirubin and transaminases at some point during treatment. Seven patients experienced elevations in total bilirubin  $\leq$  3x ULN with concurrent transaminase elevations of the same magnitude; 2 patients experienced elevations in transaminases to > 3x ULN and bilirubin elevation to  $\leq$  3x ULN; and 1 patient had a transaminase elevation to  $\leq$  3x ULN with a bilirubin elevation > 3x ULN. In the fluconazole treatment group, 4 patients had concurrent bilirubin and transaminase elevation, all  $\leq$  3x ULN range. Fewer patients in both treatment groups had conjoint bilirubin and transaminase elevations when EOT laboratory values were analyzed.

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Table 151. Conjoint Elevation of Bilirubin\* and Transaminases\* at any time during the Study (adapted from applicant's Appendix 14.3.7.5.2)

Treatment	Worst Bilirubin	Worst AST or ALT ( $\leq$ ULN)	Worst AST or ALT ( $>$ ULN $\leq$ 3x ULN)	Worst AST or ALT ( $>$ 3x ULN)
	n	n	n	n
<b>Micafungin</b>	$\leq$ ULN	57	41	0
	$>$ ULN $\leq$ 3x ULN	6	7	2
	$>$ 3x ULN	0	1	0
<b>Fluconazole</b>	$\leq$ ULN	65	36	1
	$>$ ULN $\leq$ 3x ULN	2	4	0
	$>$ 3x ULN	0	0	0

\*Worst bilirubin and transaminase values during treatment

n= number of patients

ULN= upper limits of normal range

*Medical Officer Comments: No patients in either treatment group had conjoint bilirubin and transaminase elevation to  $>$  3x ULN; but several in each treatment group had moderate conjoint elevation ( $>$  ULN to  $\leq$  3 x ULN) These data suggest that the potential hepatotoxicity of micafungin is similar to that of fluconazole which carries a labeled warning for hepatotoxicity.*

**Renal Adverse Events**

A total of 8/260 (3.1%) patients in the micafungin treatment group, and 6/258 (2.3%) patients in the fluconazole treatment group experienced renal failure. One additional patient in the micafungin group experienced "abnormal kidney function". Only 1 micafungin –treated patient experienced a renal adverse event which was considered drug-related (patient number 10685011). In that case, the adverse event started on day 14 of treatment, continued a total of 11 days, was considered mild, and did not require discontinuation of micafungin. The event resolved with no residual effect. Five of these adverse events were reported as serious adverse events in the micafungin group, and 4 were considered serious adverse events in the fluconazole group. Four of the patients with a serious renal adverse event died, and in two cases renal failure was considered the primary cause of death. One patient had a serious renal adverse event which resolved (patient number 10705001). Serious renal adverse events are summarized in the table below. Narrative summaries for patients with serious renal adverse events are provided in section under Serious Adverse Events.

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Table 152. Serious Renal Adverse Events in Micafungin-Treated Patients

Patient Number	Micafungin Cumulative Dose (mg)	Micafungin Duration (days)	Serious Adverse Event†	Day of Onset	Severity	Outcome	Drug-Related AE?
10705001	2100	14	Acute renal failure	9	severe	Resolved	no
10745031	1350	9	Acute kidney failure	7	severe	Death due to renal failure, day 17	no
10665037	2400	16	Renal failure	14	moderate	Death due to pneumonia, day 17	no
02545016	2850	19	Kidney failure	19	severe	Death due to kidney failure, day 19	no
10575046	2100	14	Kidney* failure	17	Severe	Death due to heart failure, day 17	unlikely
10705024	2100	14	Acute** renal failure	39		Death due to acute renal failure, day 39	Death not related to study drug

†Adverse event as described in narrative summary by investigator

\*Patient 1057046 had 2 renal adverse events listed, the first was impaired renal function which occurred days 7-17, not considered an SAE, followed by the SAE kidney failure listed above.

\*\*Patient 10705024 narrative summary obtained with those provided for patient deaths. The narrative states “the patient experienced no adverse events.” See MO comment below.

**Medical Officer Comment:** Query of the adverse events database revealed 10 micafungin-treated patients and 6 fluconazole-treated patients with renal adverse events (acute renal failure, aggravated renal failure, renal failure, or renal impairment by MedDRA preferred term). Additionally, 6 micafungin-treated patients with serious renal adverse events were identified rather than 5 as reported by the applicant.

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### Renal Laboratory Evaluation

The following table shows the mean and median laboratory values for renal function (BUN and creatinine) at baseline, end-of-therapy, 2 weeks treatment, and 2 weeks post-treatment in patients treated with micafungin or fluconazole. Only minimal changes from baseline were noted in mean and median BUN and creatinine for either treatment group; and there was no significant difference between treatment groups for these measures.

Table 153. Measures of Central Tendency for Renal Laboratory Values

Treatment / Time of Laboratory Evaluation	N	BUN* (mg/dL) Mean $\pm$ Std. Dev.	BUN* (mg/dL) Median (range)	N	Creatinine# (mg/dL) Mean $\pm$ Std. Dev.	Creatinine# (mg/dL) Median (range)
Micafungin/baseline	258	14.8 $\pm$ 13.6	11 (1-103)	260	0.94 $\pm$ 0.44	0.8 (0.4-3.6)
Micafungin/2 weeks treatment	233	14.0 $\pm$ 16.3	10 (2-205)	235	0.90 $\pm$ 0.52	0.8 (0.3-6.0)
Micafungin/EOT	248	14.7 $\pm$ 16.9	10 (2-205)	250	0.94 $\pm$ 0.67	0.8 (0.3-6.9)
Micafungin/2 weeks post-treatment	213	14.7 $\pm$ 14.3	10 (1-108)	214	0.93 $\pm$ 0.59	0.8 (0.2-5.9)
Fluconazole/baseline	255	14.1 $\pm$ 13.7	10 (3-97)	257	0.92 $\pm$ 0.64	0.8 (0.3-6.9)
Fluconazole/2 weeks treatment	239	12.9 $\pm$ 9.7	10 (1-85)	241	0.88 $\pm$ 0.41	0.8 (0.4-5.0)
Fluconazole/EOT	251	14.5 $\pm$ 17.6	10 (0-228)	253	0.94 $\pm$ 0.92	0.8 (0.4-13.5)
Fluconazole/2 weeks post-treatment	218	12.3 $\pm$ 9.4	10 (2-63)	218	0.84 $\pm$ 0.49	0.8 (0.4-6.8)

N= number of patients in FAS with laboratory test reported at specified time.

\*Normal range for BUN was 8.4-18.2 mg/dL (Appendix 14.1.6)

# Normal range for creatinine was 0.565-1.243 mg/dL (Appendix 14.1.6)

*Medical Officer Comments: Although means and median values for these laboratories were similar between treatment groups, and changed little from baseline within each group, the distribution of laboratory values was probably skewed for each time point because the median differs from the mean. Additionally, standard deviations were relatively and the ranges were wide, limiting the usefulness of this analysis.*

The applicant also performed analyses demonstrating the shift in creatinine from baseline. The table below shows the magnitude of shift in creatinine from baseline using the worst value during treatment. In the micafungin treatment group, 242/260 (93.1%) patients had a “normal” (< 2x ULN) creatinine at baseline; while 8/260 (3.1%) patients had an elevated creatinine level at some point during treatment. Five patients with creatinine level 2x-<3x ULN during treatment had “normal” creatinine at baseline;

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while one patient with a creatinine level 3x-<4x ULN had a “normal” creatinine at baseline. One patient with a baseline creatinine 2x-<3x ULN developed a creatinine ≥4x ULN during treatment. In the fluconazole treatment group 242 of 258 (93.8%) of patients had a “normal” (< 2x ULN) creatinine at baseline; while 8/258 (3.1%) patients had an elevated creatinine at some point during treatment. Seven of these patients had a “normal” creatinine at baseline; while 1 patient with a creatinine ≥4x ULN at baseline also had an abnormal creatinine level of the same magnitude during treatment.

When the shift in creatinine values from baseline to EOT were analyzed, 8/260 (3.1%) micafungin-treated patients (6 of whom had a normal creatinine at baseline) had an elevated creatinine at EOT (5 patients with creatinine 2x-< 3x ULN; and 1 patient with creatinine 3- < 4x ULN at EOT). In the fluconazole treatment group, 3/258 (1.2%) patients had an elevated creatinine at EOT.

Table 154. Shift in Creatinine from Baseline to Worst Value during Treatment (adapted from applicant’s Appendix 14.3.7.4.2)

Baseline	Normal (<2x ULN)	Worst Value Creatinine 2 - < 3x ULN	Worst Value Creatinine 3x - <4x ULN	Worst Value Creatinine ≥ 4x ULN	No data	Total Patients
	n	n	n	n	n	n
<b>Micafungin:</b>						
Normal (< 2x ULN)	242	5	1	0	9	257
Creatinine 2x-<3x ULN	0	0	0	2	1	3
Creatinine 3x-<4X ULN	0	0	0	0	0	0
Creatinine ≥ 4x ULN	0	0	0	0	0	0
No data	0	0	0	0	0	0
Total patients	242	5	1	2	10	260
<b>Fluconazole:</b>						
Normal (<2x ULN)	242	3	2	2	3	252
Creatinine 2x-<3x ULN	2	0	0	0	1	3
Creatinine 3x-<4x ULN	0	0	0	0	0	0
Creatinine ≥ 4x ULN	0	0	0	1	1	2
No data	1	0	0	0	0	1
Total patients	245	3	2	3	5	258

ULN= upper limit of normal

n= number of patients

*Medical Officer Comments: This analysis suggests that the overall incidence of abnormal (elevated) creatinine during treatment is similar with fluconazole and micafungin. The magnitude of creatinine elevation was also similar, with 2 micafungin-treated patients and 3*

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*fluconazole-treated patients experiencing creatinine elevations > 4x ULN at some point during therapy.*

### Hematological Adverse Events

Leukopenia was reported as an adverse event in 16/260 (6.2%) micafungin-treated patients, and in 12/258 (4.7%) fluconazole-treated patients. Leukopenia was considered a serious adverse event in 1 micafungin-treated patient and no fluconazole-treated patients. In 10 of the 16 micafungin-treated patients, and in 3 of the 12 fluconazole-treated patients who experienced leukopenia as an adverse event, leukopenia was considered study drug related. An additional 10 patients in the micafungin group, and 6 patients in the fluconazole had "WBC abnormal" reported as an adverse event; and pancytopenia was reported in one fluconazole-treated patient. The median WBC at baseline and EOT was similar for both treatment groups ( $4.7 \times 10^9$  cells/L baseline;  $4.4 \times 10^9$  cell/L EOT for micafungin group, and  $4.6 \times 10^9$  cells/L baseline;  $4.1 \times 10^9$  cells/L EOT for fluconazole group).

*Medical Officer Comments: The reported incidence of leukopenia was similar in both treatment groups, although drug-related cases occurred more frequently in the micafungin group.*

Anemia was reported as an adverse event in 12/260 (4.6%) micafungin-treated patients, and 21/258 (8.1%) patients in the fluconazole group, including 2 patients with anemia in each treatment group considered as a serious adverse event. In 4 patients in each group, anemia was considered drug-related. Additionally, one patient in the micafungin-treatment group (patient 10685012) experienced hemolysis (not reported under COSTART terminology, but coded under MedDRA as increased LDH). This adverse event was not considered serious by the investigator, and was reported as mild in intensity. Median hematocrit, hemoglobin, and RBC were similar at baseline and EOT for both treatment groups.

*Medical Officer Comments: The incidence of anemia was somewhat higher in the fluconazole treatment group. Laboratory data from micafungin-treated patient number 10685012 was reviewed to assess the extent of hemolysis. The hematocrit was 35.5% at baseline and at lowest reported value was 34.6%, hemoglobin, 11.7g/dL at baseline and 10.8 g/dL at lowest reported value; RBC,  $4.11 \times 10^9$ /L at baseline, and  $3.96 \times 10^9$ /L lowest value reported; LDH was 673 U/L at baseline and 775U/L at highest reported value; total bilirubin, 0.41 mg/dL at baseline and 0.99 mg/dl at highest reported value. The reported laboratory data suggest mild hemolysis, at best.*

Thrombocytopenia was reported as an adverse event in 9/260 (3.5%) micafungin-treated and 8/258 (3.1%) fluconazole-treated patients. Thrombocytopenia was considered drug-related in 3 micafungin- and 4 fluconazole-treated patients. None of these events was considered a serious adverse event. The median platelet count at baseline in the micafungin group was  $249 \times 10^9$ /L; and at EOT,  $245 \times 10^9$ /L; while in the fluconazole group, the baseline median platelet count was  $243 \times 10^9$ /L, and EOT,  $225 \times 10^9$ /L.

*Medical Officer Comments: The reported incidence of thrombocytopenia was similar in both treatment groups. Median WBC, hematocrit, hemoglobin, RBC, and platelet counts do not necessarily reflect significant changes in these parameters in individuals who may be outliers.*