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

### Respiratory Adverse Events

A total of 50/260 (19.2%) patients in the micafungin treatment group and 43/258 (16.7%) patients in the fluconazole treatment group experienced at least one adverse event involving the respiratory system. Respiratory adverse events are listed in the table below. There were 3 cases of respiratory failure, 1 case of respiratory distress syndrome, and one patient who experience apnea in the micafungin group; while no patients in the fluconazole group had adverse events reported as such. All of these adverse events were considered serious, but none was considered drug-related by the investigator. Narrative summaries for serious respiratory adverse events were provided in the section under Serious Adverse Events.

Table 155. Incidence of Respiratory Adverse Events in Study 005 (adapted from applicant's table 13.5.1)

Adverse Event (COSTART Term)	Micafungin N=260	Fluconazole N=258
	n (%)	n (%)
Any AE	50 (19.2)	43 (16.7)
Pneumonia	25 (9.6)	13 (5.0)
Bronchitis	6 (2.3)	7 (2.7)
Cough increased	5 (1.9)	7 (2.7)
Pharyngitis	4 (1.5)	5 (1.9)
Pulmonary tuberculosis, reactivated	4 (1.5)	1 (0.4)
Respiratory failure	3 (1.2)	0 (0)
Asthma	2 (0.8)	0 (0)
Dyspnea	2 (0.8)	3 (1.2)
Apnea	1 (0.4)	0 (0)
Epistaxis	1 (0.4)	1 (0.4)
Hiccup	1 (0.4)	1 (0.4)
Lung disorder	1 (0.4)	0 (0)
Pleural disorder	1 (0.4)	4 (1.6)
Respiratory distress syndrome	1 (0.4)	0 (0)
Rhinitis	1 (0.4)	3 (1.2)
Respiratory disorder	0 (0)	1 (0.4)
Sinusitis	0 (0)	2 (0.8)
Total respiratory AEs*	58	47

\*Individual patient could have more than one AE

**Medical Officer Comments:** *The incidence of respiratory system adverse events was higher in the micafungin group than in the fluconazole group. Most respiratory adverse events in both treatment groups were infections (pneumonia, bronchitis, pharyngitis, tuberculosis, etc.). However, the micafungin group had more patients who experienced pneumonia and pulmonary tuberculosis than in the fluconazole group. The clinical significance of this finding is not clear, as there is no obvious plausible biological explanation for this observation.*

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### **Cardiovascular Adverse Events**

A total of 60/260 (23.1%) micafungin-treated patients and 28/258 (10.9%) fluconazole-treated patients experienced an adverse event classified under cardiovascular system. Most of these events were actually phlebitis and thrombophlebitis, as shown in the following table. The incidence of phlebitis, including thrombophlebitis, and deep thrombophlebitis was higher in the micafungin than in the fluconazole treatment group, with 51/260 (19.6%), and 13/258 (5.0%) patients, respectively, suggesting a relationship to micafungin. No difference was seen in the incidence of heart failure (including congestive heart failure), which was reported in 2 patients in each group. Hypotension (including postural hypotension) was more frequent in the micafungin group, with 5 reported cases in micafungin-treated patients and 2 in fluconazole-treated patients. One patient in the micafungin treatment group had an arrhythmia (ventricular fibrillation); while no cases of arrhythmia were reported in the fluconazole group. No apparent relationship of the arrhythmia to micafungin was reported.

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Table 156. Cardiovascular Adverse Events in Study 005 (adapted from applicant's Table 13.5.1)

Adverse Event (COSTART Term)	Micafungin N=260	Fluconazole N=258
	n (%)	n (%)
Any cardiovascular AE	60 (23.1)	28 (10.9)
Phlebitis	40 (15.4)	12 (4.7)
Thrombophlebitis	10 (3.8)	1 (0.4)
Hypotension	4 (1.5)	2 (0.8)
Arrhythmia	1 (0.4)	0 (0)
Arterial anomaly	1 (0.4)	0 (0)
Congestive heart failure	1 (0.4)	1 (0.4)
Deep thrombophlebitis	1 (0.4)	0 (0)
Heart failure	1 (0.4)	1 (0.4)
Postural hypotension	1 (0.4)	0 (0)
Shock	1 (0.4)	2 (0.8)
Syncope	1 (0.4)	0 (0)
Valvular heart disease	1 (0.4)	0 (0)
Cardiomyopathy	0 (0)	1 (0.4)
Chest pain	0 (0)	3 (1.2)
Hemorrhage	0 (0)	1 (0.4)
Hypertension	0 (0)	1 (0.4)
Palpitation	0 (0)	1 (0.4)
Peripheral vascular disease	0 (0)	2 (0.8)
Tachycardia	0 (0)	1 (0.4)
Total Cardiovascular AEs*	63	29

\*Individual patient could have more than one AE

*Medical Officer Comments: Although the overall incidence of cardiovascular events was higher in the micafungin treatment group than in the fluconazole group, most of these events were local vascular events, including phlebitis and thrombophlebitis. Whether these events could be prevented by use of a central venous catheter or peripherally-inserted central catheter (PICC) catheter was not studied. There were no reported myocardial infarctions or ischemic events in either treatment group in this study. Hypertension was not reported as an adverse event in this study, although it was considered a notable adverse event in the most recent Japanese label.*

### Gastrointestinal Adverse Events

A total of 85/260 (32.7%) micafungin-treated patients, and 91/258 (35.3%) fluconazole-treated patients experienced a gastrointestinal adverse event. Most of these gastrointestinal events (76% in the micafungin group, and 77% in the fluconazole group) were nausea, vomiting and diarrhea, with a similar incidence in each treatment group. Hepatic adverse events were reviewed above. No other gastrointestinal adverse events had a significantly higher incidence in the micafungin group.

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### Allergic- and Histamine Release-Type Reactions

The incidence of adverse events which could be due to allergy or histamine-release reactions was higher in the micafungin than the fluconazole group, as shown in Table below. Rash, (including maculopapular rash and urticaria) occurred in 24/260 (9.2%) micafungin-treated patients, and in 8/258 (3.1%) fluconazole-treated patients, accounting for most of the difference between groups. No serious adverse events were reported in this category. Micafungin was discontinued in 5 patients receiving micafungin. These cases are summarized in the table below.

Table 157. Incidence of Allergic-Type or Histamine Release Reactions in Study 005 (adapted from Table 13.5.7.4.1)

Adverse Reaction (COSTART Term)	Micafungin N=260 n (%)	Fluconazole N=258 n (%)
Any Allergic-type reaction	39 (15.0)	25 (9.7)
Allergic Reaction	3 (1.2)	2 (0.8)
Eosinophilia	5 (1.9)	7 (2.7)
Maculopapular rash	4 (1.4)	1 (0.4)
Pruritis	9 (3.5)	10 (3.9)
Rash	17 (6.5)	7 (2.7)
Urticaria	3 (1.2)	0 (0)
Total allergic-type events*	41	27

\*Individual patients could have more than 1 event listed.

*Medical Officer Comments: These data suggest an association of rash or urticaria with micafungin. Notably, no cases of anaphylaxis or anaphylactoid reactions were observed in this study in comparison to study FG463-21-09, in which several micafungin-treated patients experienced such events. Additionally, no cases of Stevens-Johnson syndrome or other severe rashes were reported in micafungin-treated patients in this study, however, rash was a common reason for micafungin discontinuation as discussed above.*

### Infusion-Related Adverse Events

Infusion-related reactions, (which occurred within 1 hour of study drug infusion) were identified prospectively by the investigator. A total of 12/260 (4.6%) micafungin-treated patients, and 8 of 258 (3.1%) fluconazole-treated patients experienced an infusion-related adverse event. "Chills" accounted for most of the infusion-related events in the micafungin group; while somnolence occurred more frequently in the fluconazole group. One patient experienced hypoglycemia in the micafungin group; however, this event was not considered drug-related by the investigator. These events are summarized in the table below.

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Table 158. Infusion-Related Adverse Events in Study 005 (adapted from applicant's Table 13.5.7.5.1)

Adverse Event (COSTART Term)	Micafungin N=260	Fluconazole N=258
	n (%)	n (%)
Any infusion-related AE	12 (4.6)	8 (3.1)
Chills	5 (1.9)	0 (0)
Procedural complication	2 (0.8)	0 (0)
Rash	2 (0.8)	1 (0.4)
Fever	1 (0.4)	1 (0.4)
Hypoglycemia	1 (0.4)	0 (0)
Emotional lability	1 (0.4)	0 (0)
Somnolence	1 (0.4)	4 (1.6)
Phlebitis	0 (0)	1 (0.4)
Sweating	0 (0)	1 (0.4)
Total infusion-related AEs*	13	8

\*Individual Patients could have more than one adverse event listed.

*Medical Officer Comments: infusion-related chills were more frequent in patients who received micafungin than in those who received fluconazole.*

#### Musculoskeletal System Adverse Events

In the micafungin treatment group, 14/260 (5.4%) patients experienced a musculoskeletal adverse event in comparison to 8/258 (3.1%) patients in the fluconazole group. In micafungin-treated patients, most of these events were due to myalgia (8 patients) and arthralgia (5 patients); while myalgia and arthralgia occurred in 3 and 1 fluconazole-treated patients, respectively.

*Medical Officer Comments: These data could signal a potential association of myalgia and arthralgia with micafungin.*

#### Nervous System

Fifty four of 260 (20.8%) micafungin-treated patients, and 57/258 (22.1%) fluconazole-treated patients experienced an adverse event classified under "nervous system". Headache was the most common adverse event in this category, occurring in 22 patients in the micafungin group, and in 21 patients in the fluconazole group. Events which occurred in more than one patient more frequently in the micafungin than in the fluconazole group included anxiety (5 vs. 3 patients), dizziness (8 vs. 6 patients) delirium (5 vs 3 patients), "convulsion" (2 vs 0 patients), and paresthesia (2 vs. 1 patient) for micafungin vs. fluconazole groups.

*Medical Officer Comments: Delirium was considered serious adverse event in 3 micafungin-treated and 1 fluconazole-treated patient. Discontinuation of micafungin in 2 patients with delirium resulted in resolution of this adverse event in both cases, suggesting a potential relationship to micafungin.*

#### Metabolic and Nutritional Adverse Events

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A total of 35/260 (13.5%) patients treated with micafungin, and 35/258 (13.6%) patients treated with fluconazole had an adverse event classified as a metabolic and nutritional disorder. The most common events in this category were increased lactic dehydrogenase (3.1%), increased alkaline phosphatase (2.3%), and dehydration (2.7%) in patients who received micafungin, and hypoproteinemia (3.1%), hypokalemia, (3.1%), and dehydration (3.1%) in fluconazole-treated patients. Adverse events in this category are shown in the table below.

Table.159. Metabolic and Nutritional Adverse Events (adapted from Applicant’s Table 13.5.1)

Adverse Event * (COSTART Term)	Micafungin N=260	Fluconazole N=258
Any AE (Metabolic and Nutritional Disorder)	35 (13.5)	35 (13.6)
Lactic dehydrogenase increased	8 (3.1)	6 (2.3)
Dehydration	7 (2.7)	8 (3.1)
Alkaline phosphatase increased	6 (2.3)	5 (1.9)
Hypokalemia	5 (1.9)	8 (3.1)
Hypoproteinemia	5 (1.9)	8 (3.1)
Hyponatremia	2 (0.8)	5 (1.9)
AST increased	2 (0.8)	5 (1.9)
Edema	1 (0.4)	3 (1.2)
Electrolyte abnormality	1 (0.4)	0
Healing abnormal	1 (0.4)	0
Hypocalcemia	1 (0.4)	1 (0.4)
Hypomagnesemia	1 (0.4)	4 (1.6)
Hypoglycemia	1 (0.4)	0
Peripheral edema	1 (0.4)	2 (0.8)
ALT increased	1 (0.4)	6 (2.3)
Hyperglycemia	0	1 (0.4)
Hyperphosphatemia	0	1 (0.4)
Ketosis	0	1 (0.4)

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

**Medical Officer Comments:** Overall the number of patients with adverse events in this category is similar between treatment groups. Adverse events which occurred more frequently in micafungin-treated patients were increased LDH, electrolyte abnormality, abnormal healing, and hypoglycemia. In review of cases with serious adverse events, it was notable that many laboratory abnormalities which occurred during treatment were not considered clinically significant, and were not reported as adverse events.

Metabolic and nutritional adverse events were considered drug-related in 10/260 (3.8%) micafungin-treated, and in 9/258 (3.5%) fluconazole-treated patients. The most common drug-related adverse events in this category were increased alkaline phosphatase in 4/260 (1.5%) patients who received

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micafungin, and in 3/258 (1.2%) patients who received fluconazole. Serious adverse events in this category occurred in 2/260 (0.8%) micafungin-treated and in 3/258 (1.2%) fluconazole-treated patients, as shown in the following table.

Table 160. Serious Metabolic and Nutritional Adverse Events (adapted from Applicant's Table 13.5.3)

Adverse Event* (COSTART Term)	Micafungin N=260	Fluconazole N=258
Any AE (Metabolic and Nutritional Disorders)	2 (1.8)	3 (1.2)
Electrolyte abnormality	1 (0.4)	0
Healing abnormal	1 (0.4)	0
Hypokalemia	0	1 (0.4)
Hypomagnesemia	0	1 (0.4)
Hyponatremia	0	1 (0.4)
Hypoproteinemia	0	1 (0.4)
Peripheral edema	0	1 (0.1)

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

***Medical Officer Comment:** The overall incidence of serious adverse events in this category was similar for the two treatment groups. The two serious adverse events in micafungin-treated patients were reviewed above. (See narrative summaries for patients with serious adverse events).*

### Conclusions Regarding Safety of Micafungin in Study 03-7-005

1. The incidence of adverse events, serious adverse events, and discontinuation of study drug due to adverse events was somewhat higher in the micafungin than the fluconazole treatment group.
2. A similar proportion of patients died in each treatment arm. One death in the micafungin treatment group was attributed to micafungin by the investigator (HIV progression). The most common cause of death in both treatment groups was infection, tuberculosis, pneumonia, or AIDS.
3. The most common adverse events in patients who received micafungin were phlebitis (15%), fever (13%), diarrhea (10%), pneumonia (9.6%), and headache (8.5%).
4. The most common adverse events attributed to micafungin were phlebitis (3.8%), rash (4.2%), leukopenia (3.8%), headache (2.7%), chills (2.3%), and abdominal pain (2.3%).
5. Tuberculosis, pneumonia, AIDS, respiratory failure, renal failure, infection, and delirium were reported as serious adverse events more frequently in the micafungin than in the fluconazole treatment group.
6. Serious adverse events attributed to micafungin included delirium (2 patients), and HIV progression (1 patient).

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7. The most common adverse event leading to discontinuation of micafungin was rash. Adverse events attributed to micafungin which led to discontinuation were rash (4 patients) and delirium (1 patient).
8. Hepatic adverse events were observed at similar frequencies in micafungin- and fluconazole-treated patients. One serious hepatic adverse event occurred in the micafungin treatment group. This event was reported as hepatic failure, but appeared to be only isolated bilirubinemia in the absence of other signs/symptoms of liver failure.
9. Elevations of AST, ALT, alkaline phosphatase, and total bilirubin during treatment were generally modest, and of similar magnitude to that observed in fluconazole-treated patients.
10. No patient had conjoint elevation of bilirubin and AST or ALT to  $\geq 3x$  the upper limit of normal (ULN) in either treatment group.
11. The incidence of renal adverse events was similar in both treatment groups. Renal failure was reported as a serious adverse event in a number of micafungin-treated patients; however, none of these events appeared to be related to micafungin.
12. Leukopenia was reported as an adverse event more frequently in micafungin than in fluconazole-treated patients. In patients who received micafungin, leukopenia was considered drug-related in 10/16 cases.
13. Anemia was reported as an adverse event more frequently in fluconazole-treated patients. One patient who received micafungin had hemolysis which was mild and not considered serious.
14. The reported incidence of thrombocytopenia was similar in each treatment group.
15. Respiratory adverse events occurred more frequently in micafungin- than fluconazole treated patients, due largely to a higher incidence of tuberculosis and pneumonia reported in the micafungin treatment group.
16. The incidence of cardiovascular adverse events was higher in the micafungin than in the fluconazole treatment group, due mainly to a higher incidence of phlebitis, and thrombophlebitis reported in micafungin-treated patients. One case of deep venous thrombosis was reported in a patient who received micofungin. However, there were no reports of more serious vascular events such as myocardial ischemia or infarction, pulmonary embolism or stroke in either treatment group.
17. The overall incidence of gastrointestinal adverse events was similar in each treatment group.
18. Allergic and histamine-type reactions were more frequent in micafungin treated patients, particularly rash and urticaria. However, there were reported cases of severe rash (such as Stevens Johnson syndrome), anaphylaxis, or anaphylactoid reaction in this study.
19. Infusion-related reactions were somewhat more common in the micafungin treatment group, particularly chills, rash, and procedural complications.

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20. Musculoskeletal adverse events, specifically, myalgias and arthralgias were more frequent in micafungin-treated patients.

21. The overall incidence of nervous system adverse events was similar in both treatment groups. Delirium was considered a serious adverse event in 3 patients who received micafungin, and resulted in micafungin discontinuation in 2 cases.

22. The overall incidence of metabolic and nutritional adverse events was similar in both treatment groups.

23. Overall, safety signals associated with micafungin treatment include phlebitis, thrombophlebitis, rash, delirium, infection (tuberculosis, pneumonia and AIDS), leucopenia, and increased alkaline phosphatase.

24. The association between infection and micafungin is not clear. A review of the literature does not suggest any direct immunosuppressant activity associated with micafungin or other echinocandins.

10.1.2 Clinical Trial # 2: Study FG463-21-09:

### **A Multicenter, Double Blind, Four Parallel Group, Randomized Study to Investigate the Dose Response of Micafungin (FK463) Compared with Fluconazole Administered to HIV Positive Patients with Confirmed Esophageal Candidiasis**

**Study Objectives:** To investigate the dose response of micafungin using 3 different doses (50 mg/day, 100 mg/day and 150 mg/day) compared with fluconazole (200 mg/day) in HIV positive patients with confirmed esophageal candidiasis (EC).

**Rationale:** In a previous study, 97-7-003, a dose-response relationship was shown for micafungin treatment of EC, with most (> 85 %) patients achieving endoscopic cure at doses  $\geq$  50 mg/day. This study was performed to determine the optimal dose of micafungin for treatment of esophageal candidiasis in HIV patients in comparison to fluconazole, an approved product for this indication.

**Study Design:** This was a phase 2, multicenter, randomized, active drug-controlled, double-blind, parallel-group study designed to evaluate 3 different doses of micafungin in comparison with fluconazole for treatment of esophageal candidiasis in patients with HIV infection. A total of 251 patients were enrolled at 24 investigative sites, with 10 sites in Brazil, 2 in Peru, and 12 in South Africa.

### **Protocol Overview**

### **Primary Efficacy Endpoint**

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The primary study endpoint was the endoscopic response rate, defined as the proportion of patients with resolution of endoscopic lesions (grade 0) at end-of-therapy (EOT). Endoscopic grades were defined as follows:

Grade 0: no evidence of esophageal candidiasis-associated plaques

Grade 1: individual raised plaques of < 2 mm in size

Grade 2: multiple raised plaques of > 2 mm in size

Grade 3: confluent plaques combined with ulceration

## Secondary Efficacy Endpoints

The following secondary endpoints were evaluated in this study:

- Proportion of patients with endoscopic grade 0 on day 14 of treatment
- Mycological response, defined as the proportion of patients with either fungal eradication or residual colonization at day 14 and EOT. Grading for mycological response was as follows:
  - Eradication: histology, cytology, and fungal cultures were negative
  - Persistence (colonization): histology and cytology were negative, but fungal culture was positive
  - Persistence (invasive): histology and cytology were positive, and fungal culture could be positive or negative.
- Clinical response at EOT, as determined by the investigator and defined as follows:
  - Cleared: resolution of signs and symptoms (grade 0)
  - Improved: reduction in clinical signs and symptoms by 2 or more grades
  - Unchanged/worse: no change or progression of clinical signs and symptoms
- Changes in the quantitative endoscopic assessment of esophageal candidiasis compared to baseline
- Changes in the quantitative clinical assessment of esophageal candidiasis compared to baseline. For quantification, each symptom (dysphagia, odynophagia, and retrosternal pain) was assigned a grade of either 0 (no symptom), 1, 2, or 3.
- Changes in the quantitative clinical assessment of oropharyngeal candidiasis compared to baseline. For quantification, each sign or symptom (fissures, mouth pain, inflammation and plaques) was assigned a grade of either 0 (no symptom), 1, 2, or 3.
- Incidence of disease progression at EOT based on both clinical and endoscopic assessment compared to baseline.
- Incidence of relapse of esophageal candidiasis by clinical assessment at 2 weeks post-treatment. Relapse was defined as follows: For patients who had positive clinical response (cleared or improved) at EOT, relapse was considered an increase in 2 or more grades, or grade 3 in the clinical assessment, or the patient required antifungal treatment (non-prophylactic) during the 2 week follow-up period.
- Overall therapeutic success, defined as resolution or improvement in both clinical signs and endoscopic grades from baseline to EOT.

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*Medical Officer Comments: This study evaluated early relapse (2 weeks post-treatment) only, in comparison with protocol 03-7-005, which evaluated EC relapse at 2 weeks and 4 weeks post-therapy.*

## Randomization and Blinding

Randomization was 1:1:1:1 (micafungin 50 mg/day: micafungin 100 mg/day: micafungin 150 mg/day: fluconazole 200 mg/day, stratified by center. Investigators, who administered the infusion and performed the assessments, and the study monitors who monitored the patient case report form (CRF), were blinded with regard to treatment allocation. An unblinded staff member of the study center prepared the study drug in accordance with patient treatment allocation. All infusion bottles containing study medication were covered with foil. An unblinded study monitor was assigned to monitor drug accountability.

## Treatment

Eligible, randomized patients received 50, 100 or 150 mg/day of intravenous micafungin, or 200 mg/day of intravenous fluconazole. The planned treatment period was 14 days, but could be extended to 21 days for patients who did not achieve endoscopic clearance by day 14.

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**Assessments and Procedures**

Assessments were performed at baseline, on days 1, 3, 7, and 14 of treatment, at the end of therapy (EOT), and at the end of study (EOS) at 2 weeks following the last treatment. A schedule of assessments is shown in Table 1.

**Table 1. Schedule of Assessments (adapted from applicant’s Table 1; and Appendix 14.1.1)**

Variable	Specific assessments performed	Time of assessment
Demographics and baseline patient characteristics	Age, sex, ethnic group, height, weight, antifungal medication history, medical history and secondary diagnoses, HIV/AIDS status, total CD4 count, physical exam	Baseline. CD4 count within 6 weeks of starting study drug
Treatment compliance	Drug accountability	Recorded throughout study
	Record of study drug administration on CRF	Recorded throughout study
Efficacy	Endoscopy with biopsy, brushings and fungal culture	Baseline (within 48 hours of study drug administration); Day 14 of treatment and EOT (biopsy performed only if lesions persisted)
	Mycological response	Day 14 and EOT
	Clinical response	EOT
	Clinical signs and symptoms	Baseline (within 48 hours of study drug administration), days 3, 7, and 14 of treatment, EOT, and 2 weeks post-treatment
Safety	Adverse events	Recorded throughout study
	Laboratory assessments†	Baseline, days 7 and 14 of treatment, EOT, and 2 weeks post-treatment
	Vital signs	Baseline (within 48 hours of study drug administration), days 3, 7, and 14 of treatment, EOT, and 2 weeks post-treatment
Pharmacokinetics*	Pharmacokinetic profile	Day 1 and EOT
	Micafungin trough level	Days 3, 7, and 14
Susceptibility testing	Testing of positive fungal cultures for micafungin sensitivity at central laboratory	Baseline and EOT

EOT = end of therapy

\* The pharmacokinetic sampling was not performed at all investigative sites.

† Laboratory tests are outlined in the text

**Inclusion Criteria**

Patients were required to meet the following inclusion criteria for study participation:

- Patient (male or female) > 18 years of age with diagnosis of HIV infection or AIDS
- Esophageal candidiasis (with or without oropharyngeal involvement) documented by clinical signs and symptoms and confirmed by esophageal endoscopy. Histological/cytological confirmation from esophageal brushings was required, but the patient could be enrolled while results were pending.
- Patient capable of understanding purposes and risks of the study and gave informed consent

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- Patients of childbearing potential agreed to maintain adequate birth control practice during the study
- Patient had sufficient venous access to permit administration of study medication and monitoring of safety variables.

## Exclusion Criteria

The following criteria excluded patient participation in the study protocol:

- Patient who was pregnant or breast-feeding
- Evidence of liver disease (aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 5 times the upper limit of normal (ULN); or total bilirubin > 2.5 times the ULN; or alkaline phosphatase > 2.5 times the ULN)
- Significant renal impairment (serum creatinine > 2.0 mg/dL or equivalent)
- Concomitant medication which could interfere with study medication as determined by the investigator
- Patient with concomitant *Herpes simplex* virus esophagitis or *Cytomegalovirus* esophagitis, which could interfere with evaluation of the clinical signs and symptoms of esophageal candidiasis, identified by endoscopic exam.
- Patient with acute or chronic hepatitis or cirrhosis
- Patient with known hypersensitivity or history of anaphylaxis attributed to azole compounds, to the echinocandin class of antifungal drugs, or to structurally-related compounds
- Receipt of an oral topical (non-absorbable) antifungal agent within 48 hours or a systemic antifungal agent within 72 hours of the first dose of study drug
- Patients who required treatment with oral topical or systemic antifungal drugs for conditions other than esophageal candidiasis

*Medical Officer Comments: Essentially all systemic and non-systemic antifungal agents were prohibited for treatment of conditions other than esophageal candidiasis, including amphotericin B, and lipid formulations of amphotericin, systemic azoles, topical nystatin and clotrimazole, and all investigational agents.*

- Patients with abnormalities which would preclude esophageal endoscopy before or during the study
- Concomitant conditions that could pose an additional risk to the patient as determined by the investigator or medical monitor
- Known substance abuse or psychiatric disorder which could interfere with communication with the investigator
- Participation in an investigational drug study currently or within 28 days of planned study entry
- Patient with life expectancy of less than 2 months
- Patient with esophageal candidiasis caused by a known fluconazole-resistant strain of *Candida*
- Patient with more than 3 episodes of esophageal candidiasis requiring systemic antifungal therapy

*Medical Officer Comments: Inclusion and exclusion criteria were appropriate for this study.*

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### Criteria for Study Withdrawal

The patient were free to withdraw from the study at any time, but were encouraged to complete the appropriate examinations. Investigators could withdraw a patient from the study if warranted by the patient's clinical condition. Discontinued patients were followed for adverse events for 28 days.

Reasons for study withdrawal included the following:

- Death
- Unconfirmed diagnosis of esophageal candidiasis
- Withdrawal of consent
- Patient non-compliance
- Pregnancy
- Emergency de-coding
- Loss to follow-up
- Use of prohibited medications
- Intolerable adverse event
- Lack of efficacy (i.e. progression of infection or requirement for additional antifungal therapy)

*Medical Officer Comments: Ideally all patients withdrawn from the study would be counted as failures. In this study, similar proportions of patients were withdrawn from all study arms, and would not significantly alter conclusions regarding efficacy.*

### Safety Evaluation

Safety assessments included monitoring for adverse events, laboratory assessments, and vital sign monitoring as shown in the schedule of assessments (Table 1 above).

### Adverse Events

An adverse event was defined as any untoward medical occurrence, including abnormal laboratory findings, symptoms, or disease, regardless of a suspected relationship to study medication. Severity (mild, moderate or severe), and relationship to study medication (highly probable, probable, possible, unlikely, definitely not, or not assessable) were assigned by the investigator. A serious adverse event was defined as any adverse event that resulted in death, was life-threatening, resulted in a persistent or significant disability or congenital anomaly/birth defect, required inpatient hospitalization, prolonged existing hospitalization, or required intervention to prevent any of the above.

Adverse events were classified using a modified Coding Symbols for Thesaurus of Adverse Reaction Terms (COSTART), and by MedDRA (version 5.1). A treatment-emergent adverse event was defined as any adverse event or worsening of pre-existing condition that occurred during the treatment period (time from the first dose until 72 hours after the last dose of study medication).

### Laboratory Evaluations

The following laboratory parameters were assessed at baseline, days 7 and 14 of treatment, end of therapy (EOT), and 2 weeks post-treatment: serum chemistry, including sodium, potassium, calcium, chloride, magnesium, aspartate aminotransferase (AST), (ALT), albumin, glucose, alkaline

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phosphatase (AP), blood urea nitrogen (BUN), serum creatinine, total bilirubin, lactate dehydrogenase (LDH); hematology, including hemoglobin, hematocrit, red blood cell count, platelet count, reticulocyte count, white blood cell count (WBC), and differential WBC. Any clinically significant laboratory data measured at a non-scheduled visit was recorded in the "Unscheduled laboratory" section of the case report form (CRF).

## Data and Safety Monitoring Board (DSMB)

The DSMB was responsible for making recommendations to the applicant regarding trial modifications or termination based on interim reviews of blinded safety data. DSMB members were listed in the study report.

## Statistical Considerations

Please see Ms. Laree Tracey's Statistical Review for full details regarding statistical analysis in this study. The targeted enrollment for the study was 200 patients, 50 patients in each treatment group. The following assumptions were made for the sample size calculation: response at EOT (primary endpoint) would be 40% for patients in the 50 mg/day micafungin group, 70% in the 100 mg/day group, and 75% in the 150 mg/day group. Additionally, it was assumed that approximately 10% of patients would be excluded at baseline because of negative histology/cytology, and 10% patients would be non-evaluable in the Per Protocol set (PPS). To reject the null hypothesis that the proportion of patients with a positive response was equivalent for each of the micafungin doses with an  $\alpha = 0.05\%$ , and a 95% confidence interval width of 30%, 200 patients had to be enrolled to yield approximately 40 patients in the PPS for each treatment group.

For the primary efficacy endpoint, the first step used a two-sided Cochran-Mantel-Haenszel test adjusted for the variable pooled center to compare the 3 micafungin dose groups at a significance level of  $\alpha = 0.05$ . Using a stepwise procedure, the 3 micafungin dose groups were tested further using pairwise comparisons with a two-sided Cochran-Mantel-Haenszel test adjusted for the variable pooled center, if a significance difference was observed in the first step at an  $\alpha = 0.05$ . Logistic regression analysis was also used to assess the robustness of the conclusions for the primary efficacy endpoint, using important baseline parameters as predictors. Statistical comparisons between the fluconazole group and the three micafungin group were performed in a similar manner, but were considered descriptive.

For safety analysis, incidence of adverse events and serious adverse events was compared between treatment groups using a two-sided Fisher's exact test.

*Medical Officer Comments: This study was not designed to demonstrate non-inferiority of micafungin to fluconazole.*

## Statistical Analysis Populations:

**Full Analysis Set (FAS):** This set included all randomized patients who received at least one dose of study medication. (This set is analogous to an ITT population). The FAS was used for primary efficacy and safety analysis.

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**Per Protocol Set (PPS):** For inclusion in the PPS, patients had to have confirmed esophageal candidiasis at baseline, had received at least 10 doses of study medication, had an endoscopic evaluation at baseline and EOT, and did not receive a prohibited concomitant antifungal medication.

A third data set included all patients with confirmed esophageal candidiasis (defined as endoscopic grade > 0 and positive histology/cytology at baseline), who received at least one dose of study drug. This set, called the confirmed EC set in the applicant's final study report, will be referred to as the **Modified Full Analysis Set (MFAS)**. This set, which could be considered an MITT population, was also used for primary efficacy endpoint analysis.

*Medical Officer Comments: The FAS (ITT) population was appropriately designated for safety analysis.*

## Study Results

### Patient Disposition

A total of 251 patients were enrolled in this study. Six randomized patients (1 patient randomized to micafungin 50 mg/day, 2 to micafungin 100 mg/day, 1 to micafungin 150 mg/day and 2 to fluconazole) did not receive study medication and were not included in the FAS. The reasons for not receiving study drug after randomization included the following: death in 2 patients prior to receiving study treatment, a negative test for HIV in 1 patient, renal failure in 1 patient, esophageal candidiasis not confirmed in 1 patient, and withdrawal of consent by 1 patient. The MFAS set included 223 patients, and the PPS, 199 patients. A summary of overall patient disposition by analysis population is shown in Table 2 below.

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Table 2. Overall Patient Disposition by Analysis Population (adapted from applicant’s summary Table 2, page 28; source Table 13.1.1.1)

Population	Micafungin 50 mg/day	Micafungin 100 mg/day	Micafungin 150 mg/day	Fluconazole 200 mg/day	Total
	N	N	N	N	N (%)
Randomized	65	64	60	62	251 (100)
FAS	64	62	59	60	245 (97.6)
MFAS	56	59	56	52	223 (88.8)
PPS	52	48	51	48	199 (79.2)

N= number of patients in specified population; %= percentage of randomized patients  
 FAS= Full Analysis set (all patients who received at least one dose of study medication)  
 MFAS = Modified Full Analysis set (all patients with confirmed EC who received at least one dose of study medication)  
 PPS= Per Protocol set (all patients with confirmed EC who received at least 10 days of study drug, had an endoscopic assessment at baseline and EOT, and did not receive prohibited antifungal drug prior to EOT)

*Medical Officer Comments: For each analysis population, the number of patients was similar between treatment groups.*

**Reasons for Non-Evaluability**

Reasons for non-evaluability in the PPS are shown in the following table.

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Table 3. Reasons for Non-Evaluability in Per Protocol Set (PPS) (adapted from Table 13.1.1.1, and Appendix 14.4.1.3)

Reason	Micafungin 50 mg/day N=64	Micafungin 100 mg/day N=62	Micafungin 150 mg/day N= 59	Fluconazole 200 mg/day N=60
Did not receive study medication	1	2	1	2
EC not confirmed at baseline	8	3	3	8
Patient received < 10 days study drug (only)	0	1	0	0
Endoscopy not performed at EOT (only)	2	2	2	2
< 10 days study drug and endoscopy not performed at EOT	2	8	3	2
Prohibited antifungal drug	0	0	0	0
Total Non-evaluable for PPS	13 (20.3%)	16 (25.8%)	9 (15.3)	14 (23.3)

N= number of patients in FAS

**Medical Officer Comments:** *The total numbers of patients considered non-evaluable for the PPS were generally similar across treatment groups, with a somewhat lower number of non-evaluable patients in the 150 mg/day micafungin treatment arm than in the other arms of the study. Additionally, more patients in the 100 mg/day micafungin treatment arm were non-evaluable because they received < 10 days study drug and did not have endoscopy performed at the EOT; and more patients in the 50 mg/day micafungin group did not have EC confirmed at baseline than in the other groups. However, none of the differences noted between treatment groups were statistically significant as determined by the exact test (p-value = 0.63 for total number of non-evaluable patients; and p-value=0.124 for patients who received < 10 days study drug and did not have endoscopy performed at the EOT).*

### Treatment Discontinuation

Treatment was discontinued in 36 patients (14.7% patients in FAS). Reasons for discontinuation are shown in Table 4 below. The highest rate of treatment discontinuation was observed among patients treated with micafungin 100 mg/day group. The most common reason for treatment discontinuation was occurrence of an adverse event for all treatment groups, but was highest in the 100 mg/day micafungin group. This difference was not statistically significant however (p-value= 0.325 by the exact test).

Table 4. Reasons for Treatment Discontinuation (FAS)(adapted from applicant's summary Table 3, study report, source Tables 13.1.1.2, 13.1.3.1, Appendix 14.4.1.2)

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Reason for Discontinuation	Micafungin 50 mg/day N=64	Micafungin 100 mg/day N=62	Micafungin 150 mg/day N=59	Fluconazole 200 mg/day N=60
	n (%)	n (%)	n (%)	n (%)
Adverse event	3 (4.7)	8 (12.9)	3 (5.1)	4 (6.7)
Withdrawal of consent	1 (1.6)	1 (1.6)	1 (1.7)	1 (1.7)
Non-compliance	1 (1.6)	0 (0)	0 (0)	2 (3.3)
Lost to follow-up	0 (0)	1 (1.6)	1 (1.7)	0 (0)
Death	0 (0)	0 (0)	1 (1.7)	0 (0)
Lack of efficacy	1 (1.6)	0 (0)	0 (0)	0 (0)
Prohibited medication	0 (0)	0 (0)	0 (0)	1 (1.7)
Other reason*	2 (3.1)	3 (4.8)	1 (1.7)	0 (0)
Total discontinued treatment	8 (12.5)	13 (21.0)	7 (11.9)	8 (13.3)

N= number of patients (FAS)

\*Other reasons included withdrawal of consent due to adverse event; insufficient venous access; social problems; misunderstanding of investigator; condition of patient did not allow endoscopy

**Medical Officer Comments:** Further discussion of adverse events resulting in treatment discontinuation is found in the safety section for this study review. The pattern of adverse events that resulted in discontinuation of micafungin appeared somewhat different in the 100 mg/day micafungin group. In that treatment group, micafungin was discontinued in at least 4 patients due to an allergic-type or infusion-related reaction, in comparison to 1 patient in each the 50 and 150 mg/day group. At least 3 of these 4 reactions in the 100 mg/day micafungin group occurred at the same investigational site. Otherwise, there is no apparent reason for the larger number of treatment discontinuations in that group (will need to look at summaries). No statistically significant differences were noted in baseline CD4 counts between the treatment groups to explain the higher number of withdrawals due to adverse events in the 100 mg/day micafungin group. However, the mean CD4 count was somewhat higher in that group than the others, which may be clinically significant. For example, patients with higher CD4 counts have higher levels of antibodies in general, than patients with lower CD4 counts, and may be more susceptible to allergic reactions. Additionally, 2 patients in the 100 mg/day micafungin group withdrew consent due to adverse events, increasing the total number of patients to 10 in whom treatment was discontinued due to an adverse event in the 100 mg/day micafungin group.

**Study Completion**

A total of 208/245 (84.9%) patients in the FAS completed the study (including treatment and 2-week follow-up periods). Table 5 shows the reasons for patients not completing the study. Ten patients died

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during the post-treatment follow-up period; but none died during treatment. The applicant also reported 4 additional deaths which occurred after study completion (3 in the 50 mg/day micafungin group, and 1 in the 150 mg/day micafungin group). Further descriptions of the deaths that occurred in this study are found in the safety section of this review.

Table 5. Study Completion (FAS) (adapted from applicant's Table 5, page 30, Table 13.1.4.1, Appendix 14.4.6.6)

Patient status at end of study	Micafungin 50 mg/day N=64	Micafungin 100 mg/day N=62	Micafungin 150 mg/day N=59	Fluconazole 200 mg/day N=60	Total N= 245
Completed study	54 (84.4%)	50 (80.6%)	51 (86.4%)	53 (88.3%)	208 (84.9%)
Died during treatment	0	0	0	0	0
Died during follow-up period	3	3	3	1	10
Lost to follow-up	7	6	4	4	21
Other*	0	3	1	2	6
Total number not completing study	10 (15.6%)	12 (19.4%)	8 (13.6%)	7 (11.7%)	37 (17.8%)

N= number of patients (FAS)

\*Other reasons for not completing study included no confirmed diagnosis of EC, patient withdrew consent, consent drawn due to adverse event, "patient gave up", and patient had a negative HIV test result (obtained directly from database).

*Medical Officer Comments: A somewhat higher proportion of patients in the the 100 mg/day micafungin group did not complete the study in comparison with the other treatment groups.*

### Patient Demographics

Baseline characteristics of patients with regard to age, race/ethnic background, and gender are summarized in Table 6 below. The treatment groups were similar with respect to age, gender, and racial/ethnic origin. Overall, 52% patients were female, and 48% of patients were male in this study. Proportionately more females than males were enrolled in each treatment group except for the micafungin 150 mg/day.

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Table 6. Baseline Patient Demographics (FAS) (adapted from applicant's Table 6, page 32)

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

\*note that Hispanic patients were counted as Caucasian

\*\* Other includes Mulatto (15 patients), native Brazilian (2 patients), Cape colored (2 patients), Colored (1 patient), Mestizo (1 patient).

SD= standard deviation

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

**Medical Officer Comment:** *The small differences in gender and race noted between treatment groups is probably not clinically significant. Patients that were Hispanic, Caucasian, or Mestizo were described as Caucasian for demographic purposes in this study. Most likely, a large proportion of "Caucasian" patients were Hispanic or Mestizo, particularly for investigative sites in South America.*

*In 2003, in the U.S., approximately 28 % of patients with AIDS were white, non-Hispanics, 50% were non-Hispanic blacks, 20% were Hispanics, and approximately 2% were Asian/Pacific Islanders, and American Indian or Alaska native in origin (CDC, Division of HIV/AIDS Prevention, [www.cdc.gov](http://www.cdc.gov)). In this study, 51% of patients were black, and 40% were Caucasian or Mestizo. Significant pathophysiological differences in esophageal candidiasis are not expected between HIV patients of different racial origin. Thus, the results from this study should be broadly applicable to patients in the U.S. with AIDS and EC.*

Baseline HIV status, and CD<sub>4</sub> counts for patients in the FAS are shown in Table 7. No statistically significant differences were noted between treatment groups for mean baseline CD<sub>4</sub> counts (one-way

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ANOVA, p-value = 0.39) However, it is notable that the median CD<sub>4</sub> count was lowest in the fluconazole-treatment group, and although not statistically significant (p-value= 0.066), this difference could be clinically significant, indicating a more highly immunocompromised patient population in the fluconazole treatment group.

Table 7. Baseline HIV Status and CD4 Count (FAS) (adapted from applicant's Table 6, page 32)

Characteristic	Micafungin 50 mg/day N=64	Micafungin 100 mg/day N=62	Micafungin 150 mg/day N=59	Fluconazole 200 mg/day N=60	Total N=245
	n (%)	n (%)	n (%)	n (%)	n (%)
HIV confirmed*	42 (65.6)	37 (59.7)	37 (62.7)	34 (56.7)	150 (61.2)
CD <sub>4</sub> cell count obtained	N=63	N=62	N=58	N=60	N= 243
Mean CD <sub>4</sub> cells/mm <sup>3</sup> ± SD	60 ± 74.1	87.6 ± 142.2	69.5 ± 119.5	53.8 ± 114.6	67.8 ± 115.1
Median CD <sub>4</sub> cells/mm <sup>3</sup>	38	30	30	17	29
Range CD <sub>4</sub> cell/mm <sup>3</sup>	0-431	0-900	1-806	0-689	0-900
CD <sub>4</sub> count not measured	1	0	1	0	2

N= number of patients

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

**Medical Officer Comments:** The overall mean CD<sub>4</sub> count (across treatment groups) was 68 cells/mm<sup>3</sup>, and the median was 29 cells/mm<sup>3</sup>, indicating a severely immunocompromised patient population. Although HIV infection was not confirmed serologically in approximately 39% of patients, we can assume that virtually all enrolled patients were HIV-positive in the absence of other risk factors for EC (e.g. chronic corticosteroid use, other conditions resulting in loss of T-cell immunity).

Baseline disease (EC) severity as assessed by endoscopic grade and clinical symptoms was similar between micafungin treatment groups, but baseline endoscopic grade was somewhat higher in the fluconazole group as shown in Table 8. The average baseline endoscopic grade was 2, but between 17 and 30% patients had a baseline endoscopic grade of 3. The overall mean and median clinical symptom grade was approximately 4.0. Overall, the esophageal biopsy histology was positive in 78.3% patients, and cytology was positive in 88.9%. Fungal cultures were positive in 96.3% of patients in the FAS group, and 99.6% of fungal isolates were *Candida albicans*. Other *Candida* isolates included *C. glabrata* (10 isolates), *C. krusei* (1 isolate), and *C. tropicalis* (4 isolates).

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Table 8. Baseline Clinical and Endoscopic Grade (FAS) (adapted from applicant's Tables 7 and 8)

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

N= total number of patients in FAS

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

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

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

**Medical Officer Comments:** Overall, the baseline disease (EC) severity was similar between treatment groups. However the higher baseline endoscopic grade observed in the fluconazole group (30% patients were grade 3 at baseline) could potentially result in a lower rate of endoscopic cure (primary endpoint) in that group if cure rate was inversely proportional to baseline severity. As noted above, the median CD<sub>4</sub> count for patients in the fluconazole treatment group was somewhat lower than that for patients in any of the micafungin treatment groups. Although this difference was not statistically significant, it may have been clinically significant, and may have been reflected in the higher number of patients with endoscopic grade 3 EC at baseline in the fluconazole group.

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### Prior Antifungal Therapy

Systemic antifungal therapy was not permitted within 72 hours of receipt of first dose of study drug. Topical, or oral, non-absorbable antifungal agents were not permitted within 48 hours of the first dose of study medication. Additionally, concomitant antifungal agents were prohibited during the treatment phase. Table 9 shows antifungal therapy (systemic and non-systemic) therapy received within 14 days of first dose of study medication. Approximately 11% of micafungin-treated patients and 13% of fluconazole-treated patients in the full analysis set received either systemic or non-systemic antifungal therapy in the 2 weeks prior to study entry.

Table 9. Prior Antifungal therapy (FAS) (derived directly from database for study FG463-21-09)

Antifungal therapy	Micafungin 50 mg/day N=64	Micafungin 100 mg/day N=62	Micafungin 150 mg/day N=59	Micafungin Total N= 185	Fluconazole 200 mg/day N=60
	n (%)	n (%)	n(%)	n (%)	n (%)
Systemic	5	5	1	11	2
Non-systemic*	2	7	0	9	6
Total patients who received prior antifungal therapy	7 (10.9)	12 (19.4)	1 (1.7)	20 (10.8)**	8 (13.3)**

\* includes oral, non-absorbable antifungal agents, topical (dermatological or intravaginal)

\*\*Overall p-value = 0.010 by the exact test

N= number of patients in FAS

n= number of patients who received antifungal therapy within 14 days of study entry

% = percentage patients in all treatment groups who received prior antifungal therapy within 14 days

*Medical Officer Comment: Although differences were observed between the treatment groups in this analysis, because patients were excluded from the study if they received an antifungal agent within 72 hours of receiving study drug, it is unlikely that the efficacy results would be affected. Most of the indications for receipt of antifungal agents in the 2 weeks prior to enrollment were oropharyngeal (OPC) or esophageal candidiasis.*

### Concomitant Antifungal Therapy

Antifungal therapy received during the treatment period, after treatment or after study completion is shown in Table 10 below. Concomitant antifungal agents were prohibited during the treatment phase. Antifungal use was highest in the period after treatment with study medication, and was higher for each micafungin dose group than for the fluconazole group. The most common indication for use of other antifungal agents in the micafungin treatment groups was oropharyngeal candidiasis, followed by esophageal candidiasis or both.

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Table 10.) Concomitant Antifungal (Systemic or Topical) Therapy at any Time (FAS)(Reviewer's Analysis from Appendix 14.4.3.3)

Antifungal therapy	Micafungin 50 mg/day N=64	Micafungin 100 mg/day N=62	Micafungin 150 mg/day N=59	Fluconazole 200 mg/day N=60
	n (%)	n (%)	n (%)	n (%)
During Any Time Period	30 (46.9)	17 (27.4)	13 (22.0)	9 (15%)
Indications:				
EC	9	4	2	0
OPC	13	8	9	3
EC plus OPC	5	3	1	2
Other*	3	2	1	4

N= number of patients in FAS

n= number of patients (in this table, a patient may have received antifungal therapy in more than one time period.

EC= esophageal candidiasis

OPC= oropharyngeal candidiasis

\*Other indications included adverse events such as adverse event, or other fungal infection

The use of antifungal agents during the treatment phase is shown in the following table.

Table 11. Concomitant Antifungal (Systemic or Topical) Therapy During the Treatment Period (FAS)(Reviewer's Analysis from Appendix 14.4.3.3)

Antifungal therapy	Micafungin 50 mg/day N=64	Micafungin 100 mg/day N=62	Micafungin 150 mg/day N=59	Fluconazole 200 mg/day N=60
	n (%)	n (%)	n (%)	n (%)
During Treatment period:	3 (4.7)	1 (1.6)	1 (1.7)	1 (1.7)
Indications:				
EC	1	0	1	0
OPC	2	0	0	0
EC plus OPC	0	0	0	1
*Other	0	1	0	0

N= number of patients in FAS

n= number of patients who received antifungal therapy during treatment period

EC= esophageal candidiasis; OPC= oropharyngeal candidiasis

\*Other indications included adverse events such as adverse event, or other fungal infection

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**Medical Officer Comment:** Patients who required treatment for EC with another antifungal agent during the treatment period were counted as treatment failures, and were excluded from the Per Protocol analysis.

The use of antifungal agents during the post-treatment period is shown in the table below.

Table 12. Concomitant Antifungal (Systemic or Topical) Therapy during Post-Treatment Period (FAS)(Reviewer’s Analysis from Appendix 14.4.3.3)

Antifungal therapy	Micafungin 50 mg/day N=64	Micafungin 100 mg/day N=62	Micafungin 150 mg/day N=59	Fluconazole 200 mg/day N=60
	n (%)	n (%)	n (%)	n (%)
After Treatment Period	30 (46.9)	20 (32.2)	12 (20.3)	11 (18.3)
Indications:				
EC	9	3	2	5
OPC	13	8	8	0
EC plus OPC	5	4	1	2
Prophylaxis	2	3	1	0
Other*	1	2	0	4

N= number of patients in FAS

n= number of patients who received antifungal therapy during post-treatment period

EC= esophageal candidiasis; OPC= oropharyngeal candidiasis

\*Other indications included adverse events such as adverse event, or other fungal infection

**Medical Officer Comments:** Similar proportion of patients in the fluconazole and 150 mg/day micafungin treatment group received antifungal therapy after the study treatment (and prior to relapse evaluation); however, a higher proportion of patients who received antifungal in this time period was observed with the two lower doses of micafungin (50 mg/day and 100 mg/day). A number of patients in each of the treatment groups received systemic antifungal therapy for reasons other than EC relapse or primary treatment failure (e.g. OPC or prophylaxis for EC) and were assessed as not having an EC relapse at two weeks. The applicant’s analysis of relapse is thus confounded by concomitant antifungal therapy. Further analysis was performed by the medical officer to evaluate relapse rates including patients who received systemic (but not topical) antifungal therapy during this period for OPC or prophylaxis having EC relapse (see section below on relapse).

After study completion, 5 patients who had received micafungin and 1 patient who had received fluconazole received antifungal therapy, as shown in the following table. .

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Table 13. Concomitant Antifungal (Systemic or Topical) Therapy after Study Completion (FAS)(Reviewer’s Analysis from Appendix 14.4.3.3)

Antifungal therapy	Micafungin 50 mg/day N=64	Micafungin 100 mg/day N=62	Micafungin 150 mg/day N=59	Fluconazole 200 mg/day N=60
After Study completion:	1 (1.6)	3 (4.8 )	1 (1.7)	1
Indications:				
EC	0	0	0	0
OPC	0	1	1	0
EC plus OPC	0	1	0	0
Other*	1	1	0	1

N= number of patients in FAS

n= number of patients who received antifungal therapy after study completion

EC= esophageal candidiasis; OPC= oropharyngeal candidiasis

\*Other indications included adverse events such as adverse event, or other fungal infection

***Medical Officer Comments:** Among those patients who received systemic (not topical) antifungal therapy after study completion, 1 patient in the 100 mg/day micafungin treatment group received antifungal therapy for EC plus OPC, and thus could be considered as having “late” relapse of EC. Other reasons for antifungal therapy in this time frame included prophylaxis for EC (1 patient in the 100 mg/day micafungin group), and fungal infections listed as adverse events in patient number 3120 micafungin 50 mg/day group, and in patient 2505 in fluconazole group.*

#### **Other Concomitant Medications**

The use of concomitant non-antifungal medications is shown in Table 14 below. Overall, 98.4% patients used at least one concomitant medication. Antiretroviral medications were used in approximately one-third of patients in the study. Proportionately more patients in the fluconazole group received antiretroviral therapy, but this difference was not significant (p-value = 0.251). Other antiviral medications, including acyclovir or ganciclovir were used in 11.8% patients overall, antituberculous medications in 30%, and bactrim (trimethoprim/sulfamethoxazole) in 73.1% patients in the study. No significant differences were observed between groups for patients who received bactrim, other antiviral medications, or antituberculous medications.

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Table 14. Selected Concomitant (non-antifungal) Medications (FAS)(adapted from applicant's Table 13.3.2.1)

Drug Category	Micafungin 50 mg/day N=64 n (%)	Micafungin 100 mg/day N=62 n (%)	Micafungin 150 mg/day N=59 n (%)	Fluconazole 200 mg/day N=60 n (%)	Total N=245 n (%)
Any non-antifungal medication	63 (98.4)	60 (96.8)	58 (98.3)	60 (100)	241 (98.4)
Antiretroviral medication	23 (35.9)	18 (29.0)	22 (37.3)	28 (46.7)	91 (37.1)
Other antiviral medication	8 (12.5)	10 (16.1)	5 (8.5)	6 (10.0)	29 (11.8)
Bactrim	49 (76.6)	42 (67.7)	47 (79.7)	41 (68.3)	179 (73.1)
Antituberculous medication	24 (37.5)	17 (27.4)	18 (30.5)	16 (26.7)	75 (30.1)

N= number of patients in FAS

n (%) = number and percentage of patients who received concomitant medication

**Medical Officer Comments:** *The use of highly active antiretroviral therapy (HAART), usually a combination of 3 antiretroviral medications, may be important for resolution and relapse of EC. Severely immunocompromised patients not receiving HAART may be less likely to clear EC, and may be more susceptible to EC relapse. Although more patients in the fluconazole treatment group received antiretroviral therapy than in the micafungin treatment groups, it is not known whether the therapy was actually effective in suppressing HIV replication or permitting CD4 count reconstitution. If more patients in the fluconazole treatment group were receiving an effective antiretroviral regimen, this could be a potential confounding factor, favoring higher rates of cure and lower relapse rates in the fluconazole group.*

*Efficacy of treatment for EC is probably not affected by the use of other antiviral medication, acyclovir or ganciclovir, given the strict diagnostic criteria for EC. Both Herpes simplex (HSV) and Cytomegalovirus (CMV) esophagitis have similar clinical presentations to EC, and can cause co-infection with EC; however, histologic and cytologic evaluation of endoscopic biopsy or brushings would detect these infections, and baseline CMV and HSV esophagitis were study exclusions.*

*The use of bactrim, presumably for Pneumocystis prophylaxis or treatment was similar between treatment arms. Bactrim use is not expected to affect the efficacy of EC treatment, but has known potential for renal and hepatic toxicity. Similarly, many of the antituberculous medications are associated with adverse events, including hepatotoxicity. Proportionately more patients in the 50 mg/day micafungin treatment arm received antituberculous therapy than in the other arms of the study, but this difference was not significant (p-value = 0.552)*

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**Efficacy**

**Primary Endpoint- Endoscopic Response at EOT**

Endoscopic cure rates (endoscopic grade 0) at the EOT are shown in Table 15 below for the Full Analysis Set (FAS), which included all patients who received at least one dose of micafungin. A clear dose-response was demonstrated with micafungin, with the highest rates of cure achieved with 150 mg/day micafungin, comparable to that seen with fluconazole.

Table 15. Endoscopic Response at End of Therapy (EOT) in Full Analysis Set (FAS) (from Applicant’s Table 13.5.1.1.1, study report)

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

\* 95% confidence interval

N= number of patients in FAS

n= number of patients with specified endoscopic response at EOT

The modified full analysis set (MFAS), which included patients who received at least one dose of micafungin, and who had histologically confirmed EC, was also analyzed for the primary endpoint results are shown in Table 16 below. Results in this analysis were similar to those observed in the FAS, shown above.

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Table 16. Primary Endpoint (Endoscopic Response) in MFAS (from applicant's Table 13.5.1.1.3))

MFAS	Endoscopy grade at EOT	Micafungin 50 mg/day N=56	Micafungin 100 mg/day N=59	Micafungin 150 mg/day N=56	Fluconazole 200 mg/day N=52
		n (%)	n (%)	n (%)	n (%)
Success	0	37 (66.1) [53.7, 78.5]	45 (76.3) [65.4, 87.1]	50 (89.3) [81.2, 97.4]	46 (88.5) [79.4, 97.1]
Failure	1	5 (8.9)	4 (6.8)	1 (1.8)	2 (3.8)
	2	9 (16.1)	1 (1.7)	0	1 (1.9)
	3	2 (3.6)	0	0	0
	Unknown	1 (1.8)	2 (3.4)	1 (1.8)	0
	Not recorded	2 (3.6)	7 (11.9)	4 (7.1)	3 (5.8)

\*95% confidence interval

N= number of patients in MFAS

n= number of patients with specified endoscopic response at EOT

Endoscopic cure rates in the Per Protocol Set (PPS) were higher, as expected, because patients who did not have an endoscopic evaluation at the end-of-therapy were excluded from the analysis. Although a dose-response for micafungin was still observed in the PPS, efficacy was similar for the 100 mg/day and 150 mg/day micafungin dose in this analysis, as shown in Table 17 below.

Table 17. Primary Endpoint (Endoscopic Response) in Per Protocol Set (PPS) (from applicant's Table 13.5.1.1.2)

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

\*95% confidence interval

N= number of patients in MFAS

n= number of patients with specified endoscopic response at EOT

**Medical Officer Comments:** In all three analysis populations, a clear dose response was seen with micafungin for the primary endpoint. Endoscopic cure rates were similar for micafungin 150 mg/day and fluconazole for the FAS, MFAS, and the PPS. Statistical analysis of these data revealed that the differences in endoscopic cure between the micafungin 100 mg/day and 150

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*mg/day dose groups were not significantly significant in the FAS or PPS. This study was not designed to show non-inferiority, and thus conclusions regarding non-inferiority to fluconazole cannot be made. Based on the statistical analysis of the FAS and PPS, either the 100 mg/day or 150 mg/day micafungin resulted in similar efficacy for the primary endpoint.*

*It would have been useful to look at endoscopic response off therapy (eg. 5-7 days post-treatment) so comparison could be made with the only echinocandin antifungal agent approved for this indication, Cancidas®.*

Further analyses of endoscopic cure by baseline endoscopic grade were performed by the statistical reviewer. For patients with more severe baseline EC (endoscopic grade 3), 6/11 (54.5%) patients in the FAS who received 50 mg/day micafungin were cured in comparison to 6/12 patients (50%) who received 100 mg/day, 11/11 patients (100%) who received 150 mg/day micafungin, and 14/18 patients (77.8%) who received fluconazole.

**Medical Officer Comments:** *This analysis suggests that the 150 mg/day dose of micafungin is more effective in treatment of severe EC; with the caveat that the number of patients with baseline endoscopic grade 3 was small in this study.*

## Secondary Efficacy Endpoints

### Endoscopic Response on Treatment Day 14

Endoscopic response was somewhat lower at treatment day 14 than that at EOT (primary endpoint) for all treatment groups; however none of the differences were statistically significant. Endoscopic response at 14 days is shown in Table 18 below for comparison with endoscopic response at EOT shown in Tables 15 and 17 above.

Table 18. Endoscopic Response\* at 14 days (adapted from applicant's Table 17).

Analysis Set	Micafungin 50 mg/day 14 days	Micafungin 100 mg/day 14 days	Micafungin 150 mg/day 14 days	Fluconazole 200 mg/day 14 days
	n/N (%)	n/N (%)	n/N (%)	n/N (%)
FAS	34/64 (53.1)	44/62 (71.0)	50/59 (84.7)	49/60 (81.7)
PPS	28/52 (53.8)	41/48 (85.4)	48/51 (94.1)	44/48 (91.7)

\*Endoscopic Response = resolution, grade 0

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

N= number of patients in analysis set

n= number of patients with endoscopic grade 0

**Medical Officer Comment:** *Because the mean duration of therapy was 14 days for each treatment group, similar efficacy for treatment at 14 days and EOT is not unexpected. Optimal duration of therapy can not be determined from these data.*

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**Clinical Response at End of Therapy**

A successful clinical response, defined as “cleared” or resolution of signs and symptoms (grade 0), was similar for micafungin, (100 mg/day and 150 mg/day) and fluconazole (200 mg/day); while clinical response for the lower dose of micafungin (50 mg/day) was lower in the FAS as shown in Table 19 below. When a successful clinical response was defined as “cleared or improved”, the cure rates were similar for all treatment groups, including the 50 mg/day micafungin group.

Table 19. Clinical Response at EOT in FAS(adapted from applicant’s Table 19)

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

FAS= full analysis set; MFAS= modified full analysis set; PPS= per Protocol set  
 N= number of patients in analysis set

n = number of patients with clinical response (resolution of EC signs and symptoms, grade=0) at EOT  
 Missing data: 50 mg/day micafungin group: 1 patient lost to follow-up on day 6; 1 missing value); 100 mg/day micafungin group: 4 patients lost to follow-up; 1 death on day 14, 1 patient withdrew consent day 16; 150 mg/day micafungin group: 2 patients lost to follow-up, 1 patient died on day 3, 1 patient withdrew consent on day 13; fluconazole group: 1 missing value, 1 death on day 11, 1 withdrew consent on day 1.

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

**Overall Therapeutic Response**

Overall therapeutic response was defined by the applicant as complete resolution or improvement in both clinical response and endoscopic grade from baseline to end of therapy. Improvement in clinical response required improvement of at least 2 grades in at least one clinical sign/symptom of EC; while improvement in endoscopic assessment required improvement of at least 1 grade. The following table shows the overall therapeutic response at end of therapy using the applicant’s definition. In this analysis, patients with missing values were counted as therapeutic failures. In the FAS, a similar response was seen with micafungin 150 mg/day and fluconazole; while in the PPS, similar responses were seen in the micafungin 100 mg/day and 150 mg/day and fluconazole groups.

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Table 20. Overall Therapeutic Response\* at EOT (adapted from Applicant's Table 23)

Analysis Set	Micafungin 50 mg/day	Micafungin 100 mg/day	Micafungin 150 mg/day	Fluconazole 200 mg/day
	n/N (%)	n/N (%)	n/N (%)	n/N (%)
FAS	51/64 (79.7)	52/62 (83.9)	54/59 (91.5)	55/60 (91.7)
PPS	42/52 (80.8)	47/48 (97.9)	51/51 (100)	48/48 (100)

FAS= full analysis set; CEC= confirmed esophageal candidiasis set; PPS= per Protocol set

\*Overall therapeutic response= complete resolution or improvement in clinical response and endoscopic grade from baseline

**Medical Officer Comments:** In the FAS, a clear dose-response for micafungin in overall therapeutic success was observed. In the PPS, except for the 50 mg/day micafungin group, success rates in all treatment groups were similar. A composite endpoint (overall therapeutic cure, combining clinical cure (defined as resolution of all clinical signs/symptom) plus endoscopic cure (defined as grade= 0 at EOT) would be a stricter measure of efficacy than overall therapeutic response as defined by the applicant, and may be more appropriate to use for evaluation of relapse. This data is shown in Table 21 below.

Table . Overall Therapeutic Cure\* at EOT, (adapted from Applicant's Table 13.5.4.1.1.)

Analysis Set	Micafungin 50 mg/day	Micafungin 100 mg/day	Micafungin 150 mg/day	Fluconazole 200 mg/day
	n/N (%)	n/N (%)	n/N (%)	n/N (%)
FAS	39/64 (60.9)	48/62 (77.4)	50/59 (84.7)	51/60 (85)
PPS	32/52 (61.5)	44/48 (91.6)	47/51 (92.1)	45/48 (93.8)

\* Overall therapeutic cure defined as clinically "cleared" and endoscopic resolution (grade 0) at EOT

n= number of patient with overall therapeutic cure

N=number of patients in analysis set

**Medical Officer Comments:** When overall therapeutic cure is measured this way, cure rates are lower across treatment groups in both the FAS and PPS. In the FAS, a clear dose-response is shown for micafungin, and overall cure rates in patients treated with 100 mg/day or 150 mg/day micafungin were not significantly different than seen in patients who received fluconazole (p-values were 0.36, and 1.0, respectively); while overall therapeutic cures in patients who received 50 mg/day micafungin were lower than in the other treatment groups (p-value 0.004 vs. fluconazole, 0.06 vs. micafungin 100 mg/day, and 0.004 vs. micafungin 150 mg/day). In the PPS analysis, overall therapeutic cure was similar for all groups except for the 50 mg/day micafungin group. Relapse is analyzed in patients having overall therapeutic cure defined in this manner in the section on relapse below.

### Relapse of EC at Two Weeks Post- Treatment

Relapse at 2 weeks post-treatment was assessed for those patients who had overall therapeutic cure, i.e., clinical cure (resolution) and endoscopic cure (grade 0) at the EOT. Relapse was determined by clinical assessment. Patient who had an EC clinical signs/symptoms score > 0 at the follow-up visit, or

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who received non-prophylactic antifungal medication during the follow-up phase were considered relapses. The following table shows relapse rates for patients who had overall therapeutic cure at EOT for each treatment group. No patients in the fluconazole treatment group had a recurrence of EC; while a total of 9 micafungin-treated patients in the full analysis set had an EC recurrence. No dose-response for EC relapse was noted. When patients who were not evaluated for EC relapse were counted as relapses, higher rates of relapse were noted in all treatment groups. When analyzed this way, a dose-response relationship is seen, with highest rate of EC relapse in the lowest micafungin dose group, and lowest with the highest micafungin dose group. Relapse rates were similar for fluconazole and 150 mg/day micafungin.

Table 22. Relapse of EC at 2-week Follow-up Visit in patients who had Overall Therapeutic Cure (clinical and endoscopic resolution) at EOT (FAS) (adapted from Table 13.5.4.1.1.1)

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

FAS= full analysis set

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

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

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

**Medical Officer Comments:** *In this analysis, EC relapse rates were similar for patients who received 150 mg/day micafungin or fluconazole. Higher rates of relapse were noted when lower doses of micafungin were used. However, no statistically significant differences were seen between treatment groups. In review of the database, it was noted that some patients who received systemic antifungal therapy in the post-treatment period were not counted as relapses. Relapse data was re-analyzed by the statistical reviewer, including these patients as relapses. These data are shown in the table below.*

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Table 23. Relapse of EC at 2-week Follow-up Visit (including patients who received post-treatment systemic antifungal therapy for any indication as relapses) (FAS) (Medical Officer and Statistical Reviewer's Analysis)

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

FAS= full analysis set

\*\*Missing data refers to patients with clinical and endoscopic resolution cure at EOT who were not evaluated for relapse, counted here as relapses

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

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

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

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

## Mycological Response

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

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the highest micafungin dose (150 mg/day) than for the 100 mg/day dose group. The lowest dose of micafungin (50 mg/day) resulted in lowest mycological response.

Table 24. Mycological Eradication at end-of therapy (adapted from Applicant's Tables 13.5.1.6.1 and 13.5.1.6.2)

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

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

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

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

n = number of patients with fungal eradication at EOT

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

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

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Table 25. Mycological Response at EOT (Eradication plus Colonization) (adapted from Applicant's Tables 13.5.1.6.1 and 13.5.1.6.2)

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

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

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

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

n = number of patients with fungal eradication at EOT

**Medical Officer Comments:** *Mycological response as measured as Candida eradication (Table 24) or eradication plus colonization (Table 25), was lower than either clinical or endoscopic response at the EOT for all treatment groups. Inability to eradicate the organism (a surrogate endpoint) may be related less to the antifungal agent than to the inability of the immune system (particularly T-cell related, cell-mediated immunity) to eliminate the pathogen, or to pharmacologic properties such as mucosal tissue levels. It is not clear why a lower mycological response was achieved with 150 mg/day than with 100 mg/day micafungin in this analysis.*

A total of five patients in this study had isolates that were fluconazole-resistant (or dose-dependent fluconazole-sensitive) *Candida albicans* at baseline. Mycological and clinical outcomes for these patients are shown in the table below.

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Table 26. Mycological and Clinical Outcomes in Patients who had Fluconazole-resistant (or fluconazole dose-dependent sensitive) *Candida* at baseline

Parameter	Patient 1504	Patient 1505	Patient 2605	Patient 2704	Patient 3012
Study Treatment and dose	50 mg/day micafungin	200 mg/day fluconazole	100 mg/day micafungin	200 mg/day fluconazole	200 mg/day fluconazole
Mycologic outcome	Eradication	Eradication	Persistent invasive	Eradication	Persistent (invasive)
Clinical response EOT	Cleared	Cleared	Cleared	Cleared	Improved
Endoscopic response	Grade 0	Grade 0	Grade 0	Grade 0	Grade 3
Relapse of EC	Not evaluated	No	No	No	yes

**Medical Officer Comments:** Patients with azole-resistant *Candida* were to be excluded from this study; however, 5 patients had fluconazole-resistant or dose-dependent sensitive organisms at baseline (presumably sensitivities were unknown on enrollment). Conclusions regarding efficacy of micafungin in treating azole-resistant *Candida* sp. cannot be drawn from this study. For *Candida* species, minimal inhibitory concentration (MIC) data has not been correlated with clinical outcomes, and clinically relevant breakpoints have not been established.

### Outcomes for patients with non-*Candida albicans* isolates

*Candida albicans* was isolated in 233/234 (99.6%) patients with a positive fungal culture at baseline. In addition to *C. albicans*, 15 patients had non-*C. albicans* isolates at baseline, including *C. glabrata*, *C. tropicalis*, and *C. krusei*. The clinical, mycologic, and endoscopic response at the end-of-therapy, and relapse of EC in these patients is shown in the following table. Endoscopic and clinical response (cure) was 100% in patients who received micafungin 100 mg/day or 150 mg/day, or fluconazole, but only 1 of 3 patients (33%) had an endoscopic grade 0 or clinical cure in the 50 mg/day micafungin group. Mycological response was 0% (0/3) in the 50 mg/day micafungin group, 80% (4/5) in the 100 mg/day micafungin group, 67% (2/3) in the 150 mg/day micafungin group, and 75% (3/4) in the fluconazole group. Relapse rates (missing values counted as failures) were 2/3 (67%) in micafungin 50/mg/day group, 2/5 (40%) in the micafungin 100 mg/day groups, 1/3 (33%) in the micafungin 150 mg/day, and 0/3 (0%) in the fluconazole group.

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Table 27. Outcomes in Patients who had non-*albicans Candida* isolated at baseline

Outcome measure	Micafungin 50 mg/day N=3	Micafungin 100 mg/day N=5	Micafungin 150 mg/day N=3	Fluconazole 200 mg/day N=4
	(number of patients)	(number of patients)	(number of patients)	(number of patients)
Baseline Organisms*	<i>C. glabrata</i> (2 patients); <i>C. tropicalis</i> (1 patient)	<i>C. glabrata</i> (4 patients); <i>C. tropicalis</i> (1 patient)	<i>C. glabrata</i> (1 patient); <i>C. krusei</i> (1 patient); <i>C. tropicalis</i> (1 patient)	<i>C. glabrata</i> (3 patients); <i>C. tropicalis</i> (1 patient)
Endoscopic response EOT	Cure (1)	Cure (5)	Cure (3)	Cure (4)
Clinical Response EOT	Cure (1)	Cure (5)	Cure (3)	Cure (4)
Mycological Response EOT	Persistent, invasive (3)	Eradication (4); persistent invasive (1)	Persistent invasive (2); not reported (1)	Eradication (3); Persistent colonization (1)
EC Relapse	Relapse (1) ( <i>C. tropicalis</i> ) No relapse (1) Not recorded (1)	Relapse (1) ( <i>C. tropicalis</i> ) No relapse (3); Not recorded (1)	Relapse (1) ( <i>C. tropicalis</i> ) No relapse (2)	Relapse (0) No relapse (3)

\*note than in each of these patients, *C. albicans* was a co-isolate  
 N= number of patients with non- *C. albicans* isolates

**Medical Officer Comments:** *Very few patients in this study had non-C. albicans isolates at baseline, so a statistical analysis of these data would not be appropriate. It is interesting to note that all three patients that relapsed after receiving micafungin had C. tropicalis at baseline; but no conclusions can be drawn about treatment of non-albicans Candida in this study due to small numbers of non-albicans isolates. However, These data suggest that micafungin at the higher doses may be useful in treating EC caused by non C.albicans isolates which are frequently resistant or have high fluconazole minimal inhibitory concentrations.*

**Clinical Assessment of Oropharyngeal Candidiasis (OPC)**

The majority 228/245 (93.1%) patients had signs/symptoms of OPC at baseline. The applicant did not assess clinical cure of OPC in this study; but rather, evaluated OPC by OPC symptom score during treatment. At baseline most patients in each treatment group had OPC scores of 3 or 4, which is relatively mild based on a 12 point score. Clinical improvement of OPC, as quantified by OPC signs/symptoms score was used to assess efficacy of micafungin for treatment of OPC. As shown in the table below, the OPC signs/symptom score was reduced from baseline by more than 50% for each treatment group by the third day of treatment, and by more than 85% in each group by the end of therapy. A dose-response was seen with micafungin when OPC was assessed at treatment day 3, but not at the EOT evaluation.

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Table 28. Clinical Assessment of OPC in FAS (adapted from Table 13.5.2.3.1)

Time of Assessment	Micafungin 50 mg/day N=64	Micafungin 100 mg/day N=62	Micafungin 150 mg/day N=59	Fluconazole 200 mg/day N=60
	Mean Overall Score* (% reduction)**	Mean Overall Score* (% reduction)**	Mean Overall Score* (% reduction)**	Mean Overall Score* (% reduction)**
Baseline	4.3	4.5	4.4	4.7
Treatment day 3	2.1 (51.1)	1.9 (57.8)	0.5 (88.6)	1.3 (72.3)
EOT	0.6 (86.0)	0.3 (93.3)	0.2 (95.5)	0.1 (97.9)

\* Mean overall score is average of the OPC signs/symptoms score, calculated as sum of plaques, inflammation, fissures, and mouth pain, each graded on scale of 0 to 3, with maximum score=12). The mean overall score includes only patients who were evaluated at each time point.

\*\* % reduction = mean overall score at specific time point/ mean overall score at baseline minus 1.0

*Medical Officer Comment: OPC in this patient population was not severe at baseline, given mean baseline signs/symptoms scores of between 4.3 and 4.7, with 12 points the maximum score. OPC is generally a superficial infection of the oral mucosa with minimal tissue invasion in contrast to EC which results from an invasive Candida infection. A more clinically relevant analysis of OPC in this study was performed by the statistical reviewer. In this analysis, patients with an OPC score of 0 (no signs or symptoms of OPC) and endoscopic grade 0 for EC, were scored as cured at EOT. Patients with both OPC and EC cure were then assessed for OPC relapse at the end-of-study. These data are shown in the table below.*

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Table 29. Oropharyngeal Candidiasis (OPC) at End-of-Therapy (EOT) and End-of-Study (EOS) in Patients who had OPC at baseline (Analysis by Medical Officer and Statistical Reviewer)

OPC Assessment	Micafungin 50 mg/day N=64	Micafungin 100 mg/day N=62	Micafungin 150 mg/day N=59	Fluconazole 200 mg/day N=60
	n (%)	n (%)	n (%)	n (%)
OPC at baseline	61/64 (95.3)	59/62 (95.2)	53/59 (89.8)	57/60 (95.0)
OPC and EC grade 0 at EOT	38 (59.4%)	45 (72.6%)	46 (78.0%)	50 (83.3%)
OPC status EOS:				
-No relapse	23	28	32	39
-Relapse	7	14	12	5
-Missing*	8	3	2	6
-Counted as no relapse but received systemic AFT PT	3	4	3	2
-Total OPC Relapse EOS	18/38 (47.4)	21/45 (46.7)	17/46 (40.0)	13/50 (26.0)

N= number of patients in FAS

n= number of patients with specified OPC assessment

\*Missing = death, lost to follow-up, or other

AFT= antifungal therapy

PT= post-treatment

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

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

A logistic regression analysis, performed by the statistical reviewer, demonstrated that CD<sub>4</sub> count was an independent predictor of EC cure by endoscopic evaluation; while race, age, and gender did not predict EC cure using the primary endpoint.

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**Subset Analyses of Efficacy**

**Baseline EC severity**

The applicant evaluated endoscopic response by baseline endoscopy grade. This analysis is limited by the small numbers of patients in each subset. Additionally, the majority of patients in each treatment group had a baseline endoscopic grade of 2. For the FAS, endoscopic response at EOT was similar regardless of baseline endoscopy grade for the highest dose of micafungin, 150 mg/day; while for fluconazole, and the 50 mg/day and 100 mg/day micafungin doses, a lower response rate was observed in patients with baseline endoscopic grade of 3. In the PPS, similar endoscopic responses were noted despite baseline endoscopic grade for micafungin 150 mg/day and fluconazole. For lower doses of micafungin, lower response rates were noted with higher baseline endoscopic grades. These data are shown in the following table.

Table 30. Endoscopic Response at EOT stratified by baseline Endoscopic grade (adapted from Applicant's Table 15)

Analysis Set	Baseline Endoscopic Grade	No.	Micafungin 50 mg/day N= 64	No.	Micafungin 100 mg/day N= 62	No.	Micafungin 150 mg/day N=59	No.	Fluconazole 200 mg/day N=60
			n (%)		n (%)		n (%)		n/No. (%)
FAS	0	0	--	0	--	0	--	1	0
	1	11	9 (81.8)	13	12 (92.3)	11	10 (90.9)	10	8 (80.0)
	2	42	29 (69.0)	37	30 (81.1)	37	32 (86.5)	31	30 (96.8)
	3	11	6 (54.5)	12	6 (50.0)	11	11 (100)	18	14 (77.8)
PPS	0	0	--	0	--	0	--	0	--
	1	9	7 (77.8)	10	9 (90.0)	8	8 (100)	5	5 (100)
	2	34	24 (70.6)	31	30 (96.8)	32	31 (96.9)	28	27 (96.4)
	3	9	6 (66.7)	7	5 (71.4)	11	11(100)	15	14 (93.3)

N= number of patients in analysis set  
 FAS = full analysis set; PPS= per protocol set  
 No.= number of patients with baseline endoscopic grade  
 n= number of patients with endoscopic response (grade 0)

*Medical Officer Comment: These data suggest that the 150 mg/day dose of micafungin is required for cure of the most severe cases of esophageal candidiasis.*

**Baseline CD<sub>4</sub> count**

An logistical regression analysis by the statistical reviewer, Ms. LaRee Tracy, adjusted for age, race, gender, baseline CD<sub>4</sub> count and treatment, showed that CD<sub>4</sub> count was an independent predictor of endoscopic cure, i.e., the higher the baseline CD<sub>4</sub> count, the higher the rate of endoscopic cure.

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*Medical Officer Comments: These results are not unexpected, as HIV patients with a higher CD<sub>4</sub> counts are more likely to clear opportunistic infections with treatment than patients with lower CD<sub>4</sub> counts and compromised cell-mediated immunity.*

## Efficacy Conclusions

1. For the primary endpoint, endoscopic response, a dose-response was seen for micafungin in the treatment of EC, with the highest endoscopic response observed at 150 mg/day.
2. For the primary endpoint, endoscopic response rates for micafungin at doses of 100 mg/day or 150 mg/day were similar to the response rate observed with fluconazole.
3. Secondary endpoints, including clinical response at the end-of therapy, overall response at EOT, and mycological response generally support the conclusions reached using the primary endpoint, endoscopic response.
4. The rate of EC relapse at 2 weeks post-treatment was similar for patients who received micafungin 150mg/day or fluconazole. No clear dose-response was observed for micafungin in EC relapse.
5. Although the rate of OPC cure was similar in patients who received micafungin 150 mg/day or fluconazole, relapse rates at two weeks post-treatment were somewhat higher for patients who received micafungin than those who received fluconazole. The difference however, was not statistically significant.
5. Study FG463-21-09 supports this NDA application for micafungin for treatment of esophageal candidiasis.

## Safety Analysis

### Drug Exposure

The median drug exposure was 14 days in each treatment group. As expected, total drug exposure, measured as cumulative dose in mg, increased across micafungin dosing groups from the lowest dose group, 50 mg/day to the highest, 150 mg/day. Drug exposure is shown in the table below.

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Table 31. Study Drug Exposure (Applicant's Table 11)

Table 11: Study Drug Administration

	Micafungin Dose			Fluconazole
	50 mg/day n=64	100 mg/day n=62	150 mg/day n=59	300 mg/day n=60
<b>Number of days on study drug per patient</b>				
Mean ± SD	16.3 ± 4.2	13.4 ± 4.5	14.0 ± 3.5	14.0 ± 3.3
Median	14.0	14.0	14.0	14.0
P25; P75	14.0; 21.0	14.0; 14.0	14.0; 14.0	14.0; 14.0
Min-max	3 to 22	1 to 21	2 to 21	1 to 21
<b>Number of infusions per patient</b>				
Mean ± SD	16.2 ± 4.2	13.4 ± 4.5	14.0 ± 3.5	14.0 ± 3.3
Median	14.0	14.0	14.0	14.0
P25; P75	14.0; 21.0	14.0; 14.0	14.0; 14.0	14.0; 14.0
Min-max	3 to 21	1 to 21	2 to 21	1 to 21
<b>Cumulative dose during the study per patient (mg)</b>				
Mean ± SD	810.9 ± 208.2	1338.7 ± 454.2	2102.5 ± 521.4	2803.3 ± 655.0
Median	700.0	1400.0	2100.0	2800.0
Min-max	150 to 1050	100 to 2100	300 to 3150	200 to 4200

Patient population (full analysis set): all patients who received at least one dose of study drug.

Source: Table 13.4.1.1

**Adverse Events**

A total of 165/185 (89.2%) micafungin-treated patients experienced at least one adverse event; while 56/60 (93.3%) fluconazole-treated patients had an adverse event. There was no significant difference in overall rate of adverse events between micafungin dose groups. The following table summarizes all adverse events, serious adverse events, and adverse events resulting in study drug discontinuation, including overall events regardless of relationship to study drug, and those considered related to the study drug.

Table 32. Summary of Adverse Events in Study FG463-21-09 (Applicant's Table 26)

Table 26: Overall Summary of Treatment-emergent Adverse Events – No. Patients (%)

	Micafungin Dose			Total	Fluconazole
	50 mg/day n=64	100 mg/day n=62	150 mg/day n=59	Micafungin n=185	200 mg/day n=60
<b>Adverse events</b>					
Overall	56 (87.5)	57 (91.9)	52 (88.1)	165 (89.2)	56 (93.3)
Related	32 (50.0)	34 (54.8)	26 (44.1)	92 (49.7)	26 (43.3)
<b>Serious adverse events</b>					
Overall	10 (15.6)	7 (11.3)	7 (11.9)	24 (13.0)	5 (8.3)
Related	1 (1.6)	4 (6.5)	2 (3.4)	7 (3.8)	2 (3.3)
<b>Adverse events leading to discontinuation †</b>					
Overall	3 (4.7)	10 (16.1)	3 (5.1)	16 (8.6)	4 (6.7)
Related	1 (1.6)	9 (14.5)	1 (1.7)	11 (5.9)	1 (1.7)

Patient population (full analysis set): all patients who received at least one dose of study drug.

Related: relation to study drug highly probable, probable, possible, not assessable or missing

† Adverse event was stated as the reason for withdrawal on the patient withdrawal CRF for a total of 18 patients and an additional 2 patients withdrew consent as a consequence of an adverse event.

Source: Tables 13.1.3.1 and 13.6.1.1 and Appendix 14.4.6.4

*Medical Officer Comments: The proportion of patients having any adverse event or any related adverse event was similar in the the micafungin and fluconazole treatment groups. The incidence of serious adverse events was somewhat higher in the pooled micafungin treatment*

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*group in comparison to the fluconazole group (13% vs. 8%); while the incidence of serious drug-related adverse events was similar for the two groups. Discontinuation of study drug occurred somewhat more frequently in the pooled micafungin treatment group; while drug-related adverse events were more common in the micafungin groups (approximately 6% vs. 2%). Among the micafungin dosing groups, more serious adverse events or events resulting in treatment discontinuation occurred in the 100 mg/day group than in the 50 mg/day or 150 mg/day groups.*

The most common adverse events, occurring in > 5% patients in any treatment group, are shown in the table below.

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Table 33. Most Common Adverse Events\* by COSTART Term (adapted from Applicant's Table 27)

COSTART Term	Micafungin 50 mg/day N=64	Micafungin 100 mg/day N=62	Micafungin 150 mg/day N=59	Micafungin (all doses) N=185	Fluconazole 200 mg/day N=60
	n (%)	n (%)	n (%)	n (%)	n (%)
<b>Body as a whole:</b>					
Fever	16 (25.0)	12 (19.4)	14 (23.7)	42 (22.7)	15 (25.0)
Abdominal pain	8 (12.5)	10 (16.1)	7 (11.9)	25 (13.5)	5 (8.3)
Infection	9 (14.1)	7 (11.3)	5 (8.5)	21 (11.4)	5 (8.3)
Tuberculosis (aggravated)	8 (12.5)	2 (3.2)	8 (13.6)	18 (9.7)	4 (6.7)
Back pain	1 (1.6)	2 (3.2)	2 (3.4)	5 (2.7)	3 (5.0)
Neck pain	1 (1.6)	1 (1.6)	0 (0)	2 (1.1)	3 (5.0)
<b>Cardiovascular system:</b>					
Chest pain	2 (3.1)	2 (3.2)	3 (5.1)	7 (3.8)	3 (5.0)
Phlebitis	2 (3.1)	4 (6.5)	2 (3.4)	8 (4.3)	0 (0)
Hypotension	4 (6.3)	1 (1.6)	2 (3.4)	7 (3.8)	2 (3.3)
<b>Digestive system:</b>					
Nausea	10 (15.6)	15 (24.2)	9 (15.3)	34 (18.4)	11 (18.3)
Vomiting	12 (18.8)	11 (17.7)	4 (6.8)	27 (14.6)	9 (15.0)
Diarrhea	12 (18.8)	11 (17.7)	8 (13.6)	31 (16.8)	5 (8.3)
Constipation	3 (4.7)	7 (11.3)	4 (6.8)	14 (7.6)	4 (6.7)
Dyspepsia	2 (3.1)	1 (1.6)	3 (5.1)	6 (3.2)	1 (1.7)
Flatulence	0 (0)	1 (1.6)	4 (6.8)	5 (2.7)	1 (1.7)
Gastritis	4 (6.3)	1 (1.6)	2 (3.4)	7 (3.8)	0 (0)
LFT abnormality	1 (1.6)	1 (1.6)	1 (1.7)	3 (1.6)	4 (6.7)
Esophageal ulcer	3 (4.7)	4 (6.5)	1 (1.7)	8 (4.3)	2 (3.3)
Ulcerative stomatitis	0 (0)	1 (1.6)	0 (0)	1 (0.5)	3 (5.0)
<b>Hematologic/Lymphatic system:</b>					
Leukopenia	10 (15.6)	7 (11.3)	8 (13.6)	25 (13.5)	8 (13.3)
Anemia	6 (9.4)	6 (9.7)	6 (10.2)	18 (9.7)	3 (5.0)
Thrombocytopenia	2 (3.1)	3 (4.8)	3 (5.1)	8 (4.3)	2 (3.3)

(Table is continued next page)

\* Adverse events which occurred in > 5% patients in any treatment group

LFT= liver function test

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Table 33. (continued) Most Common Adverse Events\* by COSTART Term (adapted from Applicant's Table 27)

COSTART Terms	Micafungin 50 mg/day N=64	Micafungin 100 mg/day N=62	Micafungin 150 mg/day N=59	Micafungin (all doses) N=185	Fluconazole 200 mg/day N=60
<b>Injection Site Reactions:</b>					
Injection site inflammation	7 (10.9)	4 (6.5)	6 (10.2)	17 (9.2)	10 (16.7)
<b>Metabolic and nutritional disorders:</b>					
Dehydration	2 (3.1)	3 (4.8)	4 (6.8)	9 (4.9)	2 (3.3)
AP increase	2 (4.7)	5 (8.1)	5 (8.5)	13 (7.0)	2 (5.0)
LDH increase	6 (9.4)	3 (4.8)	2 (3.4)	11 (5.9)	2 (3.3)
SGOT increase	3 (4.7)	3 (4.8)	5 (8.5)	11 (5.9)	1 (1.7)
Hyperkalemia	0 (0)	2 (3.2)	1 (1.7)	3 (1.6)	3 (5.0)
Hypokalemia	4 (6.3)	1 (1.6)	1 (1.7)	6 (3.2)	2 (3.3)
Hypoproteinemia	3 (4.7)	2 (3.2)	1 (1.7)	6 (3.2)	3 (5.0)
Hyponatremia	3 (4.7)	2 (3.2)	1 (1.7)	6 (3.2)	3 (5.0)
Peripheral edema	1 (1.6)	4 (6.5)	2 (3.4)	7 (3.8)	0 (0)
SGPT increase	1 (1.6)	3 (4.8)	4 (6.8)	8 (4.3)	0 (0)
BUN increase	1 (1.6)	1 (1.6)	3 (5.1)	5 (2.7)	0 (0)
<b>Musculoskeletal system:</b>					
Cramps	4 (6.3)	1 (1.6)	0 (0)	5 (2.7)	0 (0)
<b>Nervous system:</b>					
Headache	13 (20.3)	8 (12.9)	8 (13.6)	29 (15.7)	6 (10.0)
Somnolence	4 (6.3)	4 (6.5)	6 (10.2)	14 (7.6)	4 (6.7)
Dizziness	1 (1.6)	1 (1.6)	3 (5.1)	5 (2.7)	6 (10.0)
Insomnia	5 (7.8)	1 (1.6)	2 (3.4)	8 (4.3)	3 (5.0)
<b>Respiratory system:</b>					
Pneumonia	8 (12.5)	5 (8.1)	5 (8.5)	18 (9.7)	5 (8.3)
Cough increased	3 (4.7)	3 (4.8)	3 (5.1)	9 (4.9)	2 (3.3)
Pharyngitis	3 (4.7)	6 (9.7)	2 (3.4)	11 (5.9)	2 (3.3)
Bronchitis	4 (6.3)	3 (4.8)	2 (3.4)	9 (4.9)	2 (3.3)

(Table is continued next page)

\* Adverse events which occurred in > 5% patients in any treatment group

AP= alkaline phosphatase; LDH= lactate dehydrogenase; SGOT= serum glutamate pyruvate transaminase; SGPT= serum glutamate oxaloacetate transaminase; BUN= blood urea nitrogen

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Table 33. (continued) Most Common Adverse Events\* by COSTART Term (adapted from Applicant's Table 27)

	Micafungin 50 mg/day N=64	Micafungin 100 mg/day N=62	Micafungin 150 mg/day N=59	Micafungin (all doses) N=185	Fluconazole 200 mg/day N=60
<b>Skin and appendages:</b>					
Maculopapular rash	3 (4.7)	5 (8.1)	2 (3.4)	10 (5.4)	1 (1.7)
Herpes simplex	2 (3.1)	2 (3.2)	0 (0)	4 (2.2)	4 (6.7)
Pruritis	2 (3.1)	3 (4.8)	5 (8.5)	10 (5.4)	1 (1.7)
Rash	2 (3.1)	4 (6.5)	4 (6.8)	10 (5.4)	0 (0)
Skin ulcer	0 (0)	4 (6.5)	0 (0)	4 (2.2)	1 (1.7)
<b>Urogenital system:</b>					
Urinary tract infection	2 (3.1)	2 (3.2)	3 (5.1)	7 (3.8)	2 (3.3)

\* Adverse events which occurred in > 5% patients in any treatment group

The most common adverse events (reported by > 10% patients) for combined micafungin treatment groups were fever, abdominal pain, infection, nausea, vomiting, diarrhea, leukopenia, headache, and rash (combined COSTART terms, "maculopapular rash" and "rash"); while the most common adverse events for the fluconazole treatment group were fever, nausea, vomiting, leukopenia, injection site inflammation, headache, and dizziness.

*Medical Officer Comments: Common adverse events which were proportionately more frequent in the combined micafungin treatment group than in the fluconazole groups included abdominal pain, infection, tuberculosis, diarrhea, anemia, increased LDH, increased AST, peripheral edema, increased ALT, increased BUN, headache, rash, maculopapular rash, and pruritis, .*

**Drug-Related Adverse Events**

A total of 163 events considered to be drug-related (classified as highly probable, possible, not assessable, or missing relationship in database) occurred in the 185 micafungin-treated patients; while 42 events considered drug-related occurred in 60 fluconazole-treated patients. Drug-related adverse events that occurred in > 2 patients in any treatment group are listed in the following table. The most common adverse events attributed to micafungin (all dose groups combined) and to fluconazole were leukopenia and injection site inflammation. Events attributed to micafungin that did not occur in the fluconazole-treatment group included chills, allergic reaction, thrombophlebitis, SGOT, SGPT, and alkaline phosphatase increase, maculopapular rash, rash, and pruritis.

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Table 34. Drug-Related\* Adverse Events which occurred in > 2 patients in any treatment group (FAS)  
 (adapted from Applicant's Table 28)

COSTART Term	Micafungin 50 mg/day N=64	Micafungin 100 mg/day N=62	Micafungin 150 mg/day N=59	Micafungin (all doses) N=185	Fluconazole 200 mg/day N=60
<b>Body as a whole:</b>					
Abdominal pain	2 (3.1)	5 (8.1)	2 (3.4)	9 (4.9)	1 (1.7)
Fever	4 (6.3)	4 (6.4)	0 (0)	8 (4.3)	2 (3.3)
Chills	2 (3.1)	1 (1.6)	0 (0)	3 (1.6)	0 (0)
Allergic Reaction	0 (0)	2 (3.2)	0 (0)	2 (1.1)	0 (0)
<b>Cardiovascular:</b>					
Thrombophlebitis	2 (3.1)	0 (0)	0 (0)	2 (1.1)	0(0)
<b>Digestive System:</b>					
Nausea	4 (6.3)	3 (4.8)	5 (8.5)	12 (6.5)	4 (6.7)
Diarrhea	4 (6.3)	3 (4.8)	2 (3.4)	9 (4.9)	2 (3.3)
Vomiting	5 (7.8)	4 (6.5)	0 (0)	9 (4.9)	2 (3.3)
LFT abnormality	1 (1.6)	0 (0)	1 (1.7)	2 (1.1)	2 (3.3)
<b>Hematologic and lymphatic system:</b>					
Leukopenia	6 (9.4)	6 (9.7)	5 (8.5)	17 (9.2)	6 (10.0)
Anemia	2 (3.1)	3 (4.8)	2 (3.4)	7 (3.8)	2 (3.3)
Eosinophilia	0 (0)	0 (0)	0 (0)	0 (0)	2 (3.3)
<b>Injection site reaction:</b>					
Injection site inflammation	7 (10.9)	4 (6.5)	6 (10.2)	17 (9.2)	10 (16.7)
<b>Metabolic and nutritional disorders:</b>					
SGOT increased	3 (4.7)	3 (4.8)	5 (8.5)	11 (5.9)	0 (0)
AP increased	3 (4.7)	4 (6.5)	3 (5.1)	10 (5.4)	0 (0)
SGPT increased	1 (1.6)	3 (4.8)	4 (6.8)	8 (4.3)	0 (0)
LDH increased	1 (1.6)	3 (4.8)	0 (0)	4 (2.2)	1 (1.7)
Hypocalcemia	1 (1.6)	1 (1.6)	0 (0)	2 (1.1)	2 (3.3)
Hypoproteinemia	1 (1.6)	1 (1.6)	0 (0)	2 (1.1)	2 (3.3)

\* Drug-related as assessed by investigator was defined as a highly probable, probable, possible, not assessable or missing relationship to study drug.

LFT= liver function test; SGOT= serum glutamate oxaloacetic transaminase; SGPT= serum glutamate pyruvate transaminase; LDH= lactate dehydrogenase

Table continued on next page.

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Table 34. (continued) Drug-Related\* Adverse Events which occurred in > 2 patients in any treatment group (FAS) (adapted from Applicant's Table 28)

COSTART Term	Micafungin 50 mg/day N=64	Micafungin 100 mg/day N=62	Micafungin 150 mg/day N=59	Micafungin (all doses) N=185	Fluconazole 200 mg/day N=60
<b>Nervous system:</b>					
Somnolence	1 (1.6)	4 (6.5)	2 (3.4)	7 (3.8)	2 (3.3)
Headache	3 (4.7)	1 (1.6)	2 (3.4)	6 (3.2)	0 (0)
Dizziness	0 (0)	0 (0)	1 (1.7)	1 (0.5)	3 (5.0)
<b>Skin and appendages:</b>					
Maculopapular rash	2 (3.1)	2 (3.2)	2 (3.4)	6 (3.2)	0 (0)
Rash	1 (1.6)	1 (1.6)	2 (3.4)	4 (2.2)	0 (0)
Urticaria	2 (3.1)	0 (0)	1 (1.7)	3 (1.6)	1 (1.7)
Pruritis	0 (0)	1 (1.6)	2 (3.4)	3 (1.6)	0 (0)

\* Drug-related as assessed by investigator was defined as a highly probable, probable, possible, not assessable or missing relationship to study drug.

LFT= liver function test; SGOT= serum glutamate oxaloacetic transaminase; SGPT= serum glutamate pyruvate transaminase; LDH= lactate dehydrogenase

*Medical Officer Comments: Attribution of an adverse event is subjective and difficult by any measure. This review will focus more on all adverse events regardless of causality. Drug-related adverse events which were proportionately more common in patients treated with micafungin included fever, chills, allergic reaction, thrombophlebitis, diarrhea, vomiting, increased AST, alkaline phosphatase, ALT, and LDH, somnolence, headache, maculopapular rash, rash, and pruritis.*

**Deaths**

A total of 12 deaths occurred in this study, 2 of which occurred in patients who had not received a dose of study medication. No deaths occurred during treatment; but 10 occurred in the 2 week period post-treatment, 3 in each of the micafungin treatment arms, and 1 in the fluconazole treatment group. None of the deaths was considered related to study medication. Primary causes of death (as reported by the investigator) during the study period are listed in the following table. An additional 4 deaths were noted in the post-study period. These are outlined in Table 36 below. Narratives for patients who died in the post-treatment or post-study periods are detailed below.

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Table 35. Deaths during Study FG03-7-09 (adapted from Applicant's Table 29 and Appendix 14.4.6.6)

Patient Number	Baseline CD4 count (cells/mm <sup>3</sup> )	Treatment/Dose	Last day of Treatment	Day of Death	Primary Cause of Death (Investigator Term)	Autopsy proven Cause?
1019	7	Micafungin/50 mg/day	21	25	Pulmonary tuberculosis	no
2404	12	Micafungin/50 mg/day	14	16	Respiratory failure	no
2506	54	Micafungin/50 mg/day	13	23	Acute respiratory distress	yes
1702	6	Micafungin/100 mg/day	14	25	Septicemia and diarrhea	no
1904	0	Micafungin/100 mg/day	9	14	Cardiac arrest	no
3014	77	Micafungin/100 mg/day	21	33	Nosocomial pneumonia	no
1008*	290	Micafungin/150 mg/day	14	15	Pulmonary tuberculosis and liver failure	no
1908	260	Micafungin/150 mg/day	2	3	Cardiac arrest	no
3209	43	Micafungin/150 mg/day	15	17	Respiratory insufficiency	no
1608	0	Fluconazole 200 mg/day	9	11	AIDS dementia complex	no

\*Patient 1008 also had hepatic failure listed as a secondary cause of death.

**Medical Officer Comment:** None of these deaths were considered related to micafungin. Two additional patients died without receiving study medication, patient number 4005, who had been randomized to receive micafungin 100 mg/day, died of *Pneumocystis carinii* pneumonia, and patient number 1004 who had been randomized to receive fluconazole, died of worsening electrolyte imbalance and renal failure.

**Narrative Summaries for Patient Deaths during Study:**

**Patient 1019** was a 42 year old black male with AIDS, a CD4 count of 7 cells/mm<sup>3</sup>, and suspected *Pneumocystis carinii* pneumonia (PCP) at baseline. He was not on antiretroviral therapy. He received 21 days of micafungin, 50 mg/day, and was treated for PCP initially with trimethoprim/sulfamethoxazole without improvement. The patient subsequently developed adult respiratory distress syndrome (ARDS), and tuberculosis (pulmonary and pleural) was then diagnosed by polymerase chain reaction (PCR) of sputum and pleural fluid samples. The patient was started on antituberculous therapy on day 19, initially improved, but died on day 25 of the study. No autopsy was performed, and the cause of death was thought to be pulmonary tuberculosis. Other adverse events that

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occurred during the treatment period included hypoproteinemia, urinary retention, and worsening anemia.

**Patient 2404** was a 29 year old Caucasian male with AIDS, a CD4 count of 12 cells/mm<sup>3</sup>, fever, weight loss, and anemia at baseline. Antiretroviral therapy included zidovudine, lamivudine, and efavirenz. He received 14 days of micafungin 50 mg/day. He developed a cough on day 10, and chest X-ray (CXR) showed bilateral pulmonary infiltrates. Tuberculosis was diagnosed on day 13, and he was initially started on oral antituberculous medications, isoniazid, rifampin, and pyrazinamide. However, after 2 days, he presented with dyspnea and extreme fatigue, and was unable to take oral medications. Endoscopy at that time showed no evidence of EC, but deep ulcers were present, suggesting a possible tracheo-esophageal fistula. His condition progressively worsened with increasing dyspnea, hypotension, anemia and leukopenia. On day 16, he was started on pentamidine for presumed PCP, and was prescribed ciprofloxacin and streptomycin (ciprofloxacin was not received) for tuberculosis. Mechanical ventilation was initiated because of worsening hypoxemia. However, during intubation copious yellow secretions were noted, and were thought to be due to aspiration or a tracheo-esophageal fistula. The patient had a cardiac arrest, and died on day 16 of the study. No autopsy was performed, and the cause of death was thought to be respiratory failure due to tuberculosis. Other adverse events which were ongoing at the time of death included increased lactate dehydrogenase (LDH), leukopenia/neutropenia, and worsening anemia.

**Patient 2506** was a 47 year old Caucasian female with AIDS, a CD4 count of 54 cells/mm<sup>3</sup>, hypertension, urinary tract infection, ankle fracture, alcohol and tobacco addition, and cough at baseline. Antiretroviral therapy included zidovudine, lamivudine, amprenavir, and ritonavir. She received 13 days of micafungin 50 mg/day, and was subsequently switched to fluconazole due to persistent EC symptoms from day 14-22. She was diagnosed with PCP on day 4 of treatment, and was started on pentamidine from day 5-15. On day 23, the patient developed severe respiratory distress, and cardiac arrest, and died, presumably due to pulmonary embolism. An autopsy was performed, but results were not available at the time of CRF submission. Ongoing adverse events at the time of death included pneumonia, anal *Herpes simplex* infection, elevated LDH, and elevated BUN and creatinine. BUN rose from 6.33 mmol/L at baseline, (normal range 1.67-7.50 mmol/L) to 19 mmol/L on day 7, and to 32 mmol/L on day 13; while serum creatinine rose from 93 micromol/L at baseline (reference range was 53-88 micromol/L) to 206 micromol/L on day 7, and to 225 micromol/L on day 13 of micafungin. LDH rose from normal levels (240-480 U/L) on days 1 and 7, to 942 U/L on day 13 of treatment. The patient received a number of concomitant medications with known nephrotoxic potential, including pentamidine (day 5-15), and acyclovir, from day 13-22).

*Medical Officer Comments: Autopsy results would be useful in this case. The cause of renal impairment is not known, and could be related to study drug, or other concomitant nephrotoxic medications. Although the cause of death was listed as acute respiratory distress by the investigator, and the patient was at risk for pulmonary embolism due to inactivity related to her ankle fracture, no documentation of pulmonary embolism was provided.*

**Patient 1702** was a 29 year old black male with AIDS, a CD4 count of 6 cells/mm<sup>3</sup>, chronic, intermittent diarrhea (due to *Cryptosporidium*), vomiting, dehydration, and lymphadenopathy at baseline. He was not on antiretroviral therapy. He completed 14 days of treatment with micafungin

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100 mg/day. The patient had persistent diarrhea, but was discharged home on day 24 upon request. He developed fever and dehydration, and died on day 25. The cause of death was presumed sepsis. No other adverse events were noted on the day of death.

**Patient 1904** was a 33 year old black male with AIDS, a CD4 count of 0 cells/mm<sup>3</sup>, pulmonary tuberculosis, anemia of chronic disease, cachexia, and generalized lymphadenopathy. He received 9 days of micafungin 100 mg/day. He was hospitalized on day 10 with pulmonary edema thought to be secondary to volume overload. In addition, he was found to have bacteremia (*Acinetobacter baumannii*), and sepsis/systemic inflammatory response syndrome. Death, on day 14 of the study, was due to cardiac arrest. No autopsy was performed. Other adverse events that occurred during the study period included “lower respiratory tract infection”, diarrhea, hypotension, hyperglycemia, urethral stenosis, peripheral edema, decubitus ulcer, and multiple organ failure. Notably, total bilirubin, which was normal at baseline was significantly elevated on treatment day 7, with baseline level of 14 micromol/L (1-17 micromol/L reference range), and 51 micromol/L on day 7. AST was mildly elevated at baseline (53 U/L, reference range 7-41 U/L), and was somewhat higher on day 7 of treatment (70 U/L); while ALT was normal throughout. The increase in bilirubin was not reported as an adverse event, and was considered by the investigator to be related to antituberculous therapy (Kombipak II), which the patient had received at least 11 days prior to study entry.

*Medical Officer Comment: Although the increased total bilirubin (3 x ULN) could be related to antituberculous medications, to other concomitant medications, or to multi-system organ failure, a relationship between hyperbilirubinemia and micafungin cannot be excluded.*

**Patient 3014** was a 40 year old female with AIDS, a CD4 count of 77 cells/mm<sup>3</sup>, and secondary diagnoses of neurotoxoplasmosis, urinary tract infection, anemia, leukopenia, scabies, fever, hypoglycemia, anorexia, hypertension, gastritis/duodenitis, dehydration, elevated LDH, and vomiting. She received 21 days of micafungin 100 mg/day for EC. At that time, dysphagia was noted, and endoscopy revealed grade 2 lesions, although subsequent histology, cytology and fungal culture were negative. On the last day of study therapy, she developed fever, tachycardia, and tachypnea, and was diagnosed with nosocomial pneumonia, treated with vancomycin. At the same time, she was started on amphotericin B. Several days later, she had a cardio-respiratory arrest, and required mechanical ventilation. Subsequently (day 26), she was hypotensive, requiring vasopressors, and developed anuria, hematuria, and renal failure, requiring peritoneal dialysis. Death ensued on day 33, after the patient had another cardiac arrest. No autopsy was performed. The cause of death was listed as pneumonia and multiple system organ failure. Ongoing adverse events during the study included hepatomegaly, nephritis, pleural effusion, splenomegaly, Herpetic esophagitis, peripheral edema, myocarditis, relapse of urinary tract infection, nausea, vomiting, elevated BUN and creatinine, elevated alkaline phosphatase, hyponatremia, and hypokalemia. Other concurrent medications included sulfadiazine, pyramethamine, folic acid, norfloxacin, captopril, phenytoin, prednisone, acyclovir, zidovudine, lamivudine, stavudine, ceftriaxone, ceftazidime, and others. Creatinine was normal at baseline, but was elevated as early as day 7 of micafungin treatment (108 micromol/L, reference range 53-88 micromol/L), and on day 14 (168 micromol/L). Alkaline phosphatase was normal at baseline and day 7, but was elevated (534 U/L, reference range 50-250 U/L) at day 14 and 21 (887 U/L), of micafungin. AST and ALT were mildly elevated at baseline (3.3 x ULN, and 1.7 x ULN, respectively), and decreased to 2 x ULN, and 1.4 x ULN, respectively, at the end of therapy).

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**Medical Officer Comment:** *This patient developed renal failure requiring dialysis. The investigator suggested that the renal insufficiency was secondary to sulfa crystals, and in fact, sulfadiazine was started one week prior to study entry, however, no documentation was provided in support of that hypothesis. Creatinine began rising well at least 2 weeks prior to use of amphotericin B. A relationship between the renal impairment and micafungin cannot be disproved. Likewise, the elevation in alkaline phosphatase to more than 3X ULN, which occurred during micafungin treatment could potentially be related to micafungin.*

**Patient 1008** was a 48 year old male with HIV, a CD4 count of 290 cells/mm<sup>3</sup>, with a history of pneumonia, and ongoing diarrhea and cachexia. He was not on antiretroviral therapy. He was treated with micafungin 150 mg/day for 14 days for EC. On day 13, he developed confusion and disorientation. On the same day, endoscopy was performed with sedation, and the patient subsequently developed respiratory failure. A chest X-ray (CXR) revealed bilateral infiltrates with a small pleural effusion, and the attending physician made a presumptive diagnosis of tuberculosis. The patient had already been receiving bactrim for "bronchitis". The patient died on day 15, and cause of death was listed as pulmonary tuberculosis. Ongoing adverse events at the time of death included increased cough, confusion, hepatic failure, kidney failure, and respiratory failure. Laboratories performed on day 14 revealed elevated AST and ALT (both > 10 x ULN), a mild elevation of alkaline phosphatase (< 2x ULN), elevated BUN (9.9 mmol/L, reference range, 3.5-7.5 mmol/L), and elevated creatinine (158 micromol/L, reference 62-115 micromol/L). These laboratory tests were all normal at baseline, except for the mild elevation of alkaline phosphatase, which remained unchanged. Total bilirubin was normal throughout the study.

**Medical Officer Comments:** *The medical monitor suggested the following sequence of events that led to this patient's death: progressive deterioration of lung function causing the initial confusion and disorientation. The sedation given at the time of endoscopy (midazolam) caused the respiratory failure. "Liver and renal decompensation ensued, with possible progressive septicemia, resulting in multi-organ failure and death." The patient was hypotensive on day 14, with a blood pressure of 95/66 on day 14 of treatment, in comparison to 118/80 at baseline. Although this sequence of events is certainly feasible, we cannot rule out an association between the liver function tests or renal impairment and micafungin. Whether the patient actually had "hepatic failure" and "kidney failure" that contributed to his death, is not clear from the case report form.*

**Patient 1608** was a 33 year old black male with AIDS and a CD4 count of 0 cells/mm<sup>3</sup>, with baseline AIDS dementia complex, confusion, fever, peripheral neuropathy, "scaly" rash, anemia, leukopenia, thrombocytopenia, hypoalbuminemia, and mildly elevated AST (2 x ULN), ALT (1.7 x ULN), and alkaline phosphatase (2x ULN). He was not on antiretroviral therapy. He received 9 days of fluconazole, 200 mg/day for EC. He died suddenly on day 11 after having 2-3 days of increasing confusion. CT scan of the brain showed cerebral atrophy, and lumbar puncture showed no evidence of either cryptococcal or tuberculous meningitis. No autopsy was performed. Ongoing adverse events at the time of death included fever, hyponatremia, increased LDH, abnormal liver function tests, and achlorhydria. Laboratory tests performed on day 7 of treatment revealed a sodium of 126 mmol/L (reference 133-148 mmol/L) from 131 mmol/L at baseline; AST, 446 U/L (reference 7-41 U/L) from

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86 U/L at baseline; ALT 222 U/L (reference, 7-40 U/L) from 66 U/L at baseline; alkaline phosphatase 293 U/L (reference range 26-92 U/L) from 198 U/L at baseline; and LDH 1898 U/L (reference range 266-500) from 756 U/L at baseline. Total bilirubin, BUN and creatinine were normal on day 7.

*Medical Officer Comments: The cause of death in this patient was listed as worsening AIDS dementia complex. This would actually be an unusual cause of death even in patient with advanced AIDS. Certainly a post-mortem examination would have been helpful in this case. Liver function laboratories were elevated 3-5x ULN several days prior to death, and fluconazole has been associated hepatotoxicity, but whether this death was related to hepatic dysfunction is not known.*

**Patient 1908** was a 27 year old black female with AIDS, a CD4 count of 260 cells/mm<sup>3</sup>, cachexia, generalized lymphadenopathy, anemia, and “atypical lower respiratory tract infection” on study entry. She received 2 days of micafungin 150 mg/day for EC. She developed severe diarrhea on day 3 and intravenous rehydration was started. She subsequently developed respiratory distress considered to be secondary to pulmonary edema. The patient required mechanical ventilation, and death ensued the same day after an unsuccessful resuscitation effort. The cause of death was listed as cardiac arrest. In addition, ongoing events at the time of death included presumed cardiomyopathy, hypotension, and sepsis. A blood culture drawn on day 3 was positive for *Stenotrophomonas maltophilia*.

**Patient 3209** was a 50 year old Hispanic male with AIDS, a CD4 count of 43 cells/mm<sup>3</sup>, a history of syphilis, proctitis, as well as alcoholism and drug addiction. He had ongoing anemia, chronic diarrhea, nausea, cachexia, abdominal pain, back pain, and cough, as well as leukocytosis, mildly elevated alkaline phosphatase, LDH, mild hypocalcemia, moderate hyponatremia, and severe hypoalbuminemia. He received 15 days of micafungin 150 mg/day for EC. A diagnosis of pulmonary tuberculosis was made on day 2, and peritoneal tuberculosis on day 4. Antituberculous medications were administered starting on day 3, and ciprofloxacin and ceftriaxone were administered beginning on days 1, and 5, respectively. The patient developed progressive respiratory distress starting on day 13, and died on day 17, with respiratory failure due to disseminated tuberculosis listed as the cause of death. Other adverse events reported in this patient included fever, headache, abdominal distension, partial intestinal obstruction, hyponatremia, increased AST and ALT, pre-renal azotemia with increased BUN, generalized edema, thrombocytopenia, and leukocytosis. Laboratory abnormalities included mild AST elevation (36 U/L at baseline, reference range 10-35 U/L, to a maximum of 79 U/L at day 7 of micafungin), a mild ALT elevation (normal, 27 U/L at baseline, reference range 9-43 U/L, to a maximum of 56 U/L on day 14 of micafungin). Alkaline phosphatase was mildly elevated at baseline (170 U/L, reference range, 39-117 U/L) and increased to a maximum of 383 U/L on study day 14. BUN increased from normal at baseline (18 mg/dL, reference range 10-20 mg/dL) to 72 mg/dL on day 15; while creatinine level remained normal. The patient developed progressive anemia during the study, with a hematocrit of 27 % at baseline, and 21% by day 15. Additionally, his platelet count was elevated at baseline (542 x 10<sup>9</sup>/L, reference range, 142-424 x 10<sup>9</sup>/L), but decreased to 60 x 10<sup>9</sup>/L by day 15. Serum sodium was low at baseline (127 mmol/L, reference range 135-145 mmol/L), and remained at about the same level throughout the study.

*Medical Officer Comments: This patient had disseminated tuberculosis, and associated multiple complications and laboratory abnormalities. The cause of death was respiratory*

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*failure, presumably due to pulmonary/disseminated tuberculosis. Attribution of death or adverse events is difficult in this highly confounded case.*

The table below summarizes deaths which occurred after the study period.

Table. 36. Deaths that occurred after study period\* (source: Appendix 14.5)

Patient Number	CD <sub>4</sub> Count (cells/mm <sup>3</sup> )	Treatment/Dose	End of Treatment (study day)	Day of Death	Primary Cause of Death (Investigator Term)
3203	183	Micafungin 50 mg/day	21	45	Hypovolemic shock
3120	30	Micafungin 50 mg/day	3	41	Thrombocytopenia
1804	54	Micafugin 50 mg/day	13	30	Tuberculosis (meningitis)
1605	43	Micafungin 150 mg/day	14	43	Pulmonary tuberculosis (worsening)

\*after treatment period and 2-week follow-up period

**Medical Officer Comments:** *None of these deaths was temporally associated with micafungin, and none were considered related to micafungin. One additional patient, number 1202 (site ZA003), died after completing of the study, received micafungin 150 mg/day for 5 days, and developed Cryptococcal meningitis on day and micafungin was discontinued. The patient later died of Cryptococcal meningitis after transfer to another hospital, and the date of death was unknown. The serious adverse event (Cryptococcal meningitis) was not considered related to micafungin by the investigator. This patient is listed with study drug discontinuation.*

### Narrative summaries for deaths that occurred after the study period

**Patient 3203** was a 34 year old Hispanic female with AIDS, a CD4 count of 183 cells/mm<sup>3</sup>, a history of diarrhea attributed to *Cryptosporidium*, and *Cyclospora*, chronic anemia, wasting syndrome and hypoalbuminemia. She received micafungin 50 mg/day for EC for 21 days. On day 43 she developed severe diarrhea and vomiting. She was hospitalized on day 45 and died. The cause of death was listed as hypovolemic shock. Other adverse events reported for this patient included worsening hypoalbuminemia, gastritis, leucopenia, neutropenia, a respiratory infection (not further characterized, but coded as “bronchitis”), and pharyngeal pain .

**Patient 3120** was a 49 year old Hispanic male with AIDS, a CD4 count of 30 cells/mm<sup>3</sup>, with a history of chronic diarrhea, wasting syndrome, and baseline nausea, headache, dehydration, mild anemia, hypoalbuminemia, and increased LDH. He received 3 days of micafungin 50 mg/day for EC. He was diagnosed with cryptococcal meningitis (day 3), micafungin was discontinued, and he was started on amphotericin. He subsequently developed upper gastrointestinal bleeding (day 19), and was discharged from the hospital on day 25. He was re-hospitalized 1 week later with gastrointestinal bleeding, dehydration, and hemodynamic compromise. He died on day 41 of cardiac arrest according to the investigator. Thrombocytopenia was listed as the cause of death in the CRF. Other adverse events

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reported in this patient included intracranial hypertension, muscle weakness, suspected meningeal tuberculosis, vomiting, abdominal pain, depression, hypokalemia, impaired hearing, dysphagia, worsening anemia, hypocalcemia, leukopenia and weight loss. Significant laboratory abnormalities included decreased calcium, 8.4 mmol/L at baseline, (reference range 8.6-10.2 mmol/L), and 7.0 mmol/L on day 18; a normal platelet count of  $162 \times 10^9/L$  at baseline (reference range,  $142-424 \times 10^9/L$ ), which decreased to  $130 \times 10^9/L$  at day 3, and  $120 \times 10^9/L$  by day 18; and a hematocrit of 37% (reference range 43.5-53.7%), which dropped to 34% by day 3, and 27% by day 18. Laboratory data beyond day 18 was not provided on the CRF.

**Patient 1804** was 38 year old black female with AIDS, a CD4 count of 54 cells/mm<sup>3</sup>, with current diagnoses of military tuberculosis, pneumonia, *Cytomegalovirus* (CMV) retinitis, fever, intermittent confusion, dermatitis, and elevated LDH. She received 13 days of micafungin 50 g/day for EC. On day 10 of micafungin treatment, she developed fever, confusion, and neck stiffness. A lumbar puncture indicated tuberculous meningitis, diagnosed by elevated adenosine deaminase, and she was started on antituberculous therapy. A diagnosis of sepsis was made on day 22, and the patient died on day 30. Cause of death was listed as tuberculous meningitis. Other adverse events reported for this patient included headache, diarrhea, tachycardia, hyperventilation, hypotension, enlarged abdomen, deep thrombophlebitis, and peripheral edema. Laboratory abnormalities included

**Patient 1605** was a 40 year-old black male with AIDS, a CD4 count of 43 cells/mm<sup>3</sup>, with baseline gastritis, superficial *Tinea* infection, macrocytosis, pneumonia and pleural effusion. He received 14 days of micafungin 150 mg/day for EC. On day 6, he was diagnosed with pneumonia and with pulmonary tuberculosis on day 7. Antituberculous medications were started on day 15, and the patient died on day 43 with the diagnosis of worsening pulmonary tuberculosis. No additional adverse events were reported. The only significant laboratory abnormality was an elevated LDH, which was 743 U/L at baseline, and 912 U/L on day 14 (266-500 U/L, reference range).

### Serious Adverse Events

A total of 44 serious adverse events occurred in 26/185 (14.1%) micafungin-treated patients, and 6 serious adverse events in 5/60 (8.3%) fluconazole-treated patients. All serious adverse events that occurred in the study are listed in the following table. Note that patients could have more than one adverse event within a body system.

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Table 37. Incidence of serious adverse events (FAS) (adapted from Table 13.6.2.1)

Serious Adverse Event	Micafungin 50 mg/day N=64	Micafungin 100 mg/day N=62	Micafungin 150 mg/day N=59	Micafungin (all doses) N=185	Fluconazole 200 mg/day N=60
	n (%)	n (%)	n (%)	n (%)	n (%)
Total number of patients with SAE	17 (26.5)	10 (16.1)	14 (23.7)	41 (22.2)	5 (8.3)
Hypotension	2 (3.1)	1 (1.6)	1 (1.7)	4 (2.2)	0 (0)
Tuberculosis, aggravated	3 (4.7)	0 (0)	1 (1.7)	4 (2.2)	0 (0)
Leukopenia	1 (1.6)	0 (0)	1 (1.7)	2 (1.1)	1 (1.7)
Meningitis	1 (1.6)	0 (0)	1 (1.7)	2 (1.1)	1 (1.7)
Respiratory failure	1 (1.6)	0 (0)	2 (3.4)	3 (1.6)	0 (0)
Allergic reaction	0 (0)	2 (3.2)	0 (0)	2 (1.1)	0 (0)
Dementia	0 (0)	1 (1.6)	0 (0)	1 (0.5)	1 (1.7)
Lung edema	0 (0)	1 (1.6)	1 (1.7)	2 (1.1)	0 (0)
Pneumonia	1 (1.6)	1 (1.6)	0 (0)	2 (1.1)	0 (0)
Acidosis	1 (1.6)	0 (0)	0 (0)	1 (0.5)	0 (0)
Anaphylactoid reaction	0 (0)	1 (1.6)	0 (0)	1 (0.5)	0 (0)
Anemia	1 (1.6)	0 (0)	0 (0)	1 (0.5)	0 (0)
Cardiomyopathy	0 (0)	0 (0)	1 (1.7)	1 (0.5)	0 (0)
Chills	1 (1.6)	0 (0)	0 (0)	1 (0.5)	0 (0)
Dehydration	0 (0)	1 (1.6)	0 (0)	1 (0.5)	0 (0)
Gastrointestinal anomaly	0 (0)	0 (0)	0 (0)	0 (0)	1 (1.7)
Gastrointestinal disorder	1 (1.6)	0 (0)	0 (0)	1 (0.5)	0 (0)
Heart arrest	0 (0)	0 (0)	1 (1.7)	1 (0.5)	0 (0)
Hepatic failure	0 (0)	0 (0)	1 (1.7)	1 (0.5)	0 (0)
Hyperglycemia	0 (0)	1 (1.6)	0 (0)	1 (0.5)	0 (0)
Hypokalemia	1 (1.6)	0 (0)	0 (0)	1 (0.5)	0 (0)
Infection	0 (0)	0 (0)	1 (1.7)	1 (0.5)	0 (0)
Intestinal obstruction	0 (0)	0 (0)	1 (1.7)	1 (0.5)	0 (0)
Kidney failure	0 (0)	0 (0)	1 (1.7)	1 (0.5)	0 (0)
Liver damage	1 (1.6)	0 (0)	0 (0)	1 (0.5)	0 (0)
Psychosis	0 (0)	0 (0)	0 (0)	0 (0)	1 (1.7)
Rash	0 (0)	0 (0)	1 (1.7)	1 (0.5)	0 (0)
Respiratory distress syndrome	1 (1.6)	0 (0)	0 (0)	1 (0.5)	0 (0)
Sepsis	0 (0)	1 (1.6)	0 (0)	1 (0.5)	0 (0)
Vomiting	1 (1.6)	0 (0)	0 (0)	1 (0.5)	0 (0)

**Medical Officer Comments:** There are some discrepancies between applicant's the Table 13.6.2.1 and the adverse event database. In the database, in the micafungin 50 mg/day group, 17 events were reported in 10 patients; in the micafungin 100 mg/day, 16 adverse events were listed in 9 patients; in the micafungin 150 mg/day group, 11 events were listed in 7 patients;

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and total number of micafungin serious adverse events was 44. For the fluconazole group, 6 adverse events were reported in 5 patients.

Overall, a higher proportion of micafungin-treated patients had serious adverse events in comparison to those who received fluconazole. The most common serious adverse events among patients who received micafungin were hypotension and tuberculosis.

Serious adverse events considered to be related to study drug occurred in 7 micafungin-treated and 2 fluconazole-treated patients. The incidence of serious drug-related adverse events is shown in the table below. Summaries for these events are provided below.

Table 38. Incidence of Serious Drug-Related Adverse Events (adapted from Applicant's Table 13.6.2.2)

Serious Adverse Event	Micafungin 50 mg/day N=64	Micafungin 100 mg/day N=62	Micafungin 150 mg/day N=59	Micafungin Total N=185	Fluconazole 200 mg/day N=60
	n (%)	n (%)	n (%)	n (%)	n (%)
Allergic reaction	0	2 (3.2)	0	2 (1.1)	0
Leukopenia	0	0	1 (1.7)	1 (0.5)	1 (1.7)
Anaphylactoid reaction	0	1	0	1 (0.5)	0
Chills	1 (1.6)	0	0	1 (0.5)	0
Dementia	0	1	0	1 (0.5)	0
Gastrointestinal anomaly	0	0	0	0	1 (1.7)
Hypotension	1 (1.6)	0	0	1 (0.5)	0
Rash	0	0	1 (1.7)	1 (0.5)	0
Vomiting	1 (1.6)	0	0	1 (0.5)	0

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### Summary of Serious Drug-Related Adverse Events

Those events which were considered serious and drug-related are described by patient in Table 39 below.

Table 39. Serious Drug-Related\* Adverse Events (Applicant's Table 31, study summary)

Patient Number	COSTART term (Investigator term)	Onset/end day	Outcome
Micafungin 50 mg/day			
1105	Chills (rigor)	4 / 4	Recovered
	Hypotension (hypotension)	4 / 4	Recovered
	Vomiting (vomiting)	4 / 4	Recovered
Micafungin 100 mg/day			
1021	Dementia (HIV dementia complex)-worsening	3 / -	Ongoing
1606	Allergic reaction (allergic reaction to study drug [infusion-related rigor, body pain and chest pain])	1 / 5	Recovered
2902	Allergic reaction (infusion-related reaction [anaphylactic in pharmacovigilance case report])	1 / 1	Recovered
2909	Anaphylactoid reaction (study drug reaction [anaphylactic])	4 / 6	Recovered
Micafungin 150 mg/day			
3113	Leukopenia (worsening neutropenia)	14 / 28	Recovered with residual effect(s)
3124	Rash (rash)	14 / 19	Recovered
Fluconazole 200 mg/day			
1703	Gastrointestinal anomaly (recto-vaginal fistula) Flu syndrome (flu) † Vaginal haemorrhage (vaginal bleeding secondary to vaginitis and recto-vaginal fistula) † Vaginitis (vaginitis) †	8 / -29 / -29 / -29 / -	Ongoing Ongoing Ongoing Ongoing
3102	Leukopenia (neutropenia)	7 / 14	Recovered

Patient population (full analysis set): all patients who received at least one dose of study drug. Related: relation to study drug highly probable, probable, possible, not assessable or missing

† Event occurred after treatment discontinuation Source: Appendix 14.4.6.1

\*drug-related as assessed by the investigator

### Narrative Summaries for Drug-related Serious Adverse Events

**Patient 1105:** On day 4 of micafungin treatment, the patient developed rigors, nausea, vomiting, and tachycardia. The episode resolved after treatment with prochlorperazine (Stemetil®) and solucortef. This patient completed 21 days of therapy with micafungin.

**Patient 1021** developed severe confusion, unresponsiveness, and stupor on day 6 of micafungin treatment. "Dementia" was ongoing at the end of the study, and the investigator considered this reaction to be worsening of HIV dementia aggravated by micafungin. Notably, the patient had

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received concomitant codeine and morphine on days 4 and 6 of the study. These medications can also cause acute confusion, and would be considered confounding factors.

*Medical Officer Comment: Delirium rather than dementia seems more appropriate to describe this adverse event.*

**Patient 1606** received one dose of micafungin, and during the study drug infusion developed rigors, and severe generalized myalgias and chest pain, tachycardia. She was treated with hydrocortisone and panadol (acetaminophen) This reaction was also described in the narrative summary as angioedema of the lips, without cyanosis or dyspnea, and resolved after stopping micafungin.

**Patient 2902:** the narrative summary describes an acute reaction which occurred within 5-10 minutes of the first micafungin infusion, with facial redness, then cyanosis, and facial hypoesthesia, hypertension and tachycardia. These symptoms resolved spontaneously after micafungin infusion was stopped.

**Patient 2909:** the narrative summary describes cyanosis, and chills on days 4, 5, and 6 of micafungin treatment, and fever on day 5. These symptoms occurred either during micafungin infusion.

**Patient 3113** had neutropenia at baseline (ANC was 840 cells/mm<sup>3</sup>) which worsened during the study (ANC 320 cells/mm<sup>3</sup> on day 14), and had improved after stopping micafungin on day 14 (ANC 530 cells/mm<sup>3</sup>).

**Patient 3124** developed fever and rash on days 11 and 13, respectively. These resolved with prednisone and loratadine by 2 days after micafungin discontinuation.

**Patient 1703** was diagnosed with a recto-vaginal fistula on day 10 of fluconazole treatment. This was complicated by vaginal bleeding on day 31. These events were included as a drug-related event because they were not assessable.

**Patient 3102:** this patient had baseline leukopenia, with a total WBC of  $3.1 \times 10^9$  and ANC of 1860 cells/mm<sup>3</sup>. Fluconazole was discontinued on day 11 due to neutropenia, (WBC was  $2.1 \times 10^9$  and ANC was 966 cells/mm<sup>3</sup> on day 9 of treatment). Neutropenia resolved 3 days after stopping fluconazole, total WBC was 3400 cells/mm<sup>3</sup> and ANC 1740 cells/mm<sup>3</sup>.

*Medical Officer Comments: I would agree that all of the adverse events described above are at least possibly drug-related.*

### Study Discontinuation due to Adverse Events

A total of 16/185 (8.6%) patients experienced adverse events that led to discontinuation of micafungin and 4/16 (6.7%) patients receiving fluconazole required drug discontinuation. Micafungin was discontinued more frequently in the 100 mg/day dosed group, 15.6% (10/64) patients, than in the 50 mg/day, 4.8% (3/62) patients) or 150 mg/day group, 5.1% (3/59) patients). The reasons for study drug discontinuation are shown in the table below. Those events considered serious and drug-related were

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discussed above, and those events resulting in death were discussed under the section, "Deaths during Study".

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Table 40. Adverse Events Resulting in Treatment Discontinuation (adapted from Applicant's Tables 32 and 13.6.2.4)

Patient Number and Study Site	Study medication Dose (mg/day)	Adverse event (day on onset)	Day of Discontinuation	Outcome	Relationship to Study Drug/Serious?
2910 BR010	Micafungin 50 mg/day	Anaphylactoid reaction (day 11)	Day 11	Recovered day 11	Related/ Not serious
3120 PE001	Micafungin 50 mg/day	Cryptococcal meningitis (day 3)	Day 3	Ongoing at study end/ death after study end day 41	Not related/serious
4012 ZA011	Micafungin 50 mg/day	Pneumonia-tuberculosis (day 11)	Day 12	Recovered with TB treatment day 19	Not related/ Serious
1015 ZA001	Micafungin 100 mg/day	Asthenia (day 2)	Day 4	Ongoing at study end	Related/not serious
1021* ZA001	Micafungin 100 mg/day	HIV dementia complex (day 3)	Day 9	Ongoing at study end	Related/Serious
1301 ZA004	Micafungin 100 mg/day	Rigors (day 7)	Day 7	Recovered day 7	Related/not serious
1502* ZA006	Micafungin 100 mg/day	Nausea, vomiting, diarrhea (days 1, 2, 3)	Day 4	Ongoing at study end	Related (nausea and vomiting)/ not serious
1606 ZA007	Micafungin 100 mg/day	Allergic reaction (day 1)	Day 1	Recovered day 5	Related/serious
1904 ZA010	Micafungin 100 mg/day	Pulmonary edema (day 10)	Day 10	Recovered day 12/death day 14	Related/serious
2408 BR005	Micafungin 100 mg/day	Cutaneous rash (day 12)	Day 12	Recovered day 17	Related/not serious
2902 BR010	Micafungin 100 mg/day	Infusion-related reaction (anaphylactic) (day 1)	Day 1	Recovered day 1	Related/serious
2909 BR010	Micafungin 100 mg/day	Anaphylactoid reaction (day 4)	Day 6	Recovered Day 6	Related/serious
3213 PE002	Micafungin 100 mg/day	Pancytopenia (day 3)	Day 12	Ongoing at study end	Related/not serious

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1202 ZA003	Micafungin 150 mg/day	Cryptococcal meningitis (day 5)	Day 5	Ongoing at study end/ death after study completion (day of death unknown)	Not Related/serious
2603 BR007	Micafungin 150 mg/day	Disseminated tuberculosis (day 13)	Day 14	Ongoing at study end	Not Related/not serious
3124 PE001	Micafungin 150 mg/dy	Rash (day 14)	Day 14	Recovered Day 19	Related/serious
1608 ZA007	Fluconazole 200 mg/day	AIDS dementia complex (day 10)	Day 10	Death day 11	Related/serious
3007 BR011	Fluconazole 200 mg/day	Meningitis (day 30)	Day 15	Ongoing at study end/death after study completion day 41	Not Related/serious
3102 PE001	Fluconazole 200 mg/day	Neutropenia (day 7)	Day 11	Recovered day 14	Related/serious
4009 ZA011	Fluconazole 200 mg/day	HIV-induced psychosis (day 9)	Day 10	Recovered with residual effects day 21	Not Related/serious

\* Treatment discontinued due to withdrawal of consent due to adverse event.

**Medical Officer Comments:** *It is not clear why more adverse events resulting in treatment discontinuation occurred in the micafungin 100 mg/day arm of this study. It is noteworthy that 3 patients enrolled at site BR010 required micafungin discontinuation due to anaphylactic or anaphylactoid reactions. Additionally, two of the patients who received micafungin 100 mg/day, (patients 1502 and 1021) withdrew consent due to the adverse events listed above). Some of the clearest associations of micafungin with an adverse reaction are depicted in this table, in which discontinuation of micafungin resulted in resolution of the event, particularly for rash, allergy, anaphylactic, and anaphylactoid reactions.*

**Other Significant Adverse Events**

**Hepatic Adverse Events**

The overall number of hepatobiliary adverse events in patients who received micafungin was 52/185 (28.1%), and 10/60 (16/7%) in patients who received fluconazole, as shown in the table below. The number of these events increased with micafungin dose. There were two patients with serious hepatic adverse events, one hepatic failure, and one case of “liver damage”, which will be discussed further below.

Laboratory abnormalities associated with the hepatic system were noted in 24/185 (13.0%) micafungin-treated patients and 7/60 (11.7%) fluconazole-treated patients. Liver function test

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abnormalities were observed in 6/64 (9.4%) patients treated with micafungin 50 mg/day, 7/62 (11.3%) patients treated with micafungin 100 mg/day, and 11/59 (18.6%) patients treated with micafungin 150 mg/day, suggesting a dose-response relationship. Overall, the number of patients with at least one hepatobiliary adverse event occurred was 12/64 (18.8%) patients treated with 50 mg/day micafungin, 19/62 (30.6%) patients treated with 100 mg/day micafungin, 21/59 (35.6%) patients treated with 150 mg/day micafungin, and 10/60 (16.7%) patients treated with fluconazole.

Table 41. Incidence of Hepatobiliary Adverse Events in Study FG463-21-09 (FAS) (adapted from Tables 13.6.1.2 and 13.6.3.3)

COSTART Term	Micafungin 50 mg/day N=64	Micafungin 100 mg/day N=62	Micafungin 150 mg/day N=59	Micafungin (all doses) N=185	Fluconazole 200 mg/day N=60
	n (%)	n (%)	n (%)	n (%)	n (%)
Increased AP	3	5	5	13	3
Increased SGOT	3	3	5	11	1
Increased SGPT	1	3	4	8	0
Bilirubinemia	1	1	1	3	0
Abnormal LFT	1	1	1	3	4
Ascites	0	0	1	1	0
Hepatomegaly	0	1	1	2	2
Hepatosplenomegaly	1	1	1	3	0
Cholecystitis	0	1	1	2	0
Jaundice	0	2	0	2	0
Bile duct disorder	0	1	0	1	0
Cholelithiasis	1	0	0	1	0
Hepatic failure	0	0	1	1	0
Liver damage	1	0	0	1	0
Total patients with hepatobiliary AEs	12 (18.8%)	19 (30.6%)	21 (35.6%)	52 (28.1%)	10 (16.7%)

FAS= full analysis set

N= number of patients in FAS; n= number of patients with adverse event

Patient could experience more than one adverse event within a body system

*Medical Officer Comments: Note that the applicant did not include ascites, hepatomegaly, hepatosplenomegaly, cholecystitis, jaundice, bile duct disorder, hepatic failure, liver damage, or cholelithiasis in enumerating hepatic adverse events in Table 13.6.3.3, resulting in different numbers in this table.*

**Narrative Summaries for Patients with Serious Hepatic Adverse Events**

**Patient Number 1008** was a 48 year old male with HIV, a CD4 count of 290 cells/mm<sup>3</sup>, with a history of pneumonia, and ongoing diarrhea and cachexia. He was not on antiretroviral therapy. He was treated with micafungin 150 mg/day for 14 days for EC. On day 13, he developed confusion and

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disorientation. On the same day, endoscopy was performed with sedation, and the patient subsequently developed respiratory failure. A CXR revealed bilateral infiltrates with a small pleural effusion, and the attending physician made a presumptive diagnosis of tuberculosis. The patient had already been receiving bactrim for “bronchitis”. The patient died on day 15, and cause of death was listed as pulmonary tuberculosis. Ongoing adverse events at the time of death included increased cough, confusion, hepatic failure, kidney failure, and respiratory failure. Laboratories performed on day 14 revealed elevated AST and ALT (both > 10 x ULN), a mild elevation of alkaline phosphatase (< 2x ULN), mildly elevated BUN 27 mg/dL mmol/L, creatinine, 1.8 mg/dL). These laboratory tests were all normal at baseline, except for the mild elevation of alkaline phosphatase, which remained unchanged. Total bilirubin was normal throughout the study. The table below shows liver function test values during the course of the study. Concomitant medications prior to hepatic failure on day 14 included betaclopramide, loperamide, and cotrimoxazole.

Hepatic laboratory values\* for Patient 1008 during study (FG-21-09)

Study Day	AST (U/L)	ALT (U/L)	Total bilirubin (mg/dL)	Albumin g/dL	Alkaline phosphate (U/L)
Baseline	40	19	0.35	2.0	125
Day 7	49	19	0.76	1.5	132
Day 14	2068	322	0.76	1.6	122

\*Normal laboratory values provided in Appendix, section 10.

***Medical Officer Comments:** Beside the evidence for hepatocellular damage (significant transaminase elevation) and the patient's low albumin, nothing in the applicant's narrative summary suggested actual liver failure or clinical evidence of hepatic failure. Prothrombin time was not measured in this study. The medical monitor suggested the following sequence of events that led to this patient's death: progressive deterioration of lung function causing the initial confusion and disorientation. The sedation given at the time of endoscopy, midazolam, caused the respiratory failure. "Liver and renal decompensation ensued, with possible progressive septicemia, resulting in multi-organ failure and death." The patient was hypotensive on day 14, with a blood pressure of 95/66 on day 14 of treatment, in comparison to 118/80 at baseline. Although this sequence of events is certainly feasible, we cannot rule out an association between the transaminitis and micafungin.*

**Patient 3103** had “liver damage” reported as a serious adverse event. This was a 26 year-old Caucasian female with HIV and a CD4 count of 90 cells/mm<sup>3</sup>, who received micafungin 50 mg/day for 14 days (700 mg total), for esophageal candidiasis. Baseline conditions included weight loss, diarrhea, cough, fever, nausea, abdominal pain, anemia, leucopenia, and hypoalbuminemia. During treatment she developed “liver damage”, considered by the investigator to be multiple liver abscesses, possibly related to non-Hodgkins lymphoma (diagnosed later on day 42). The patient had no abnormalities of AST, ALT, bilirubin, or alkaline phosphatase at any time during the study. Other adverse events included cholelithiasis, nausea, vomiting, megaloblastic anemia, worsening anemia, worsening leucopenia and fever. The latter two adverse events were considered possibly related to study drug. Concomitant medications included acetaminophen, benadryl, cotrimoxazole, isoniazid (study day 2 and ongoing), metoclopramide, ceftriaxone, metronidazole, ranitidine, ciprofloxacin, vitamin B12,

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folic acid, rifampin (day 25 and ongoing), ethambutol (day 25 and ongoing), pyrazinamide (day 25 and ongoing), fluconazole, day 26 and ongoing), acyclovir (day 26 and ongoing).

*Medical Officer Comment: The "liver damage" in this patient was actually the multiple liver abscess, or metastatic malignancy, presumably identified radiologically. This patient was also being treated for tuberculosis, which was not identified as a baseline condition or an adverse event. It is unlikely that the radiological hepatic abnormalities would be related to micafungin.*

## Hepatic Laboratory Abnormalities

The magnitude of changes in hepatic laboratories from baseline to end of therapy was assessed for patients with baseline normal to < 2.5x normal in the table below. Data were pooled for this analysis from all micafungin dose groups.

Most hepatic laboratory abnormalities at the EOT were less than 10x ULN for micafungin and fluconazole treatment groups. Similar proportions of patients had hepatic laboratory abnormalities more than 2.5x ULN in the fluconazole and pooled micafungin dose groups, with the exception of alkaline phosphatase in which a higher proportion was observed in the micafungin group. If patients with missing data at EOT are counted as having an abnormal laboratory value, 12/171 (7%), and 6/60 (10%) had abnormal AST > 2.5 x ULN in the micafungin and fluconazole treatment groups, respectively. For ALT, 17/178 (9.6%), and 7/60 (11.7%) patients in the micafungin and fluconazole treatment groups respectively, had laboratory elevations > 2.5x normal. Twenty of 175 (11.4%) and 4/59 (6.8%) patients treated with micafungin and fluconazole, respectively, had elevation of alkaline phosphatase to > 2.5x normal at the end of therapy. Elevation of total bilirubin to > 2.5x ULN occurred in 12/184 (6.5%) and 3/60 (5.0%) patients treated with micafungin and fluconazole, respectively.

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Table 42 Hepatic laboratory abnormalities at the end-of-therapy in patients with baseline normal\* hepatic laboratory values (adapted from Applicant's Table 13.7.2)

EOT laboratory value	AST		ALT		Alkaline phosphatase		Total bilirubin	
	Micafungin (all doses) N=185	Fluc 200 mg/day N=60	Micafungin (all doses) N=185	Fluc 200 mg/day N=60	Micafungin (all doses) N=185	Fluc 200 mg/day N=60	Micafungin (all doses) N=185	Fluc 200 mg/day N=60
Normal*	159	54	161	53	155	55	172	57
2.5-5 x ULN	2	1	6	3	10	1	3	1
5-10 x ULN	2	1	2	2	3	1	1	0
> 10 x ULN	1	2	1	0	0	0	0	0
No data	7	2	8	2	7	2	8	2
Total patients**	171	60	178	60	175	59	184	60

\*Normal = normal range to < 2.5x ULN

\*\*Total patients with laboratory value at both baseline and end-of therapy

Fluc= fluconazole

EOT= end of therapy

AST= aspartate aminotransferase; ALT= alanine aminotransferase; AP= alkaline phosphatase

**Medical Officer Comments:** This analysis does not take into account any hepatic laboratory abnormalities which may have occurred during or after the treatment period, but only at the end-of therapy. For micafungin-treated patients who had a normal laboratory value at baseline, 5/171 (2.9%) had further elevations of AST, 9/178 (5.1%) had further elevations of ALT, 20/175 (11.4%) had further elevations of alkaline phosphatase, and 4/184 (2.2%) had further elevation of bilirubin at the end-of therapy. For fluconazole-treated patients who had a normal laboratory value at baseline, 4/60 (6.7%), 5/60 (8.3%), 2/59 (3.4%), and 1/60 (1.7%) had further elevation of AST, ALT, alkaline phosphatase, and total bilirubin at the end-of-therapy, respectively. Overall, in comparison to the fluconazole group, patients who received micafungin were more likely to have an elevated alkaline phosphatase at the end of therapy; while the rate of elevated AST, ALT, and bilirubin were similar. This type of analysis looks at pooled laboratory changes in the population as a whole, and does not consider changes in individual patients.

The magnitude of hepatic laboratory abnormalities in patients with abnormal (>2.5 x ULN) baseline hepatic laboratory values is shown in the following table. Data was pooled from all micafungin doses for patients with a baseline laboratory abnormality

> 2.5x ULN, although patients with baseline alkaline phosphatase or total bilirubin > 2.5x normal, or transaminases > 5x ULN were to have been excluded from the study.

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Table 43. Hepatic Laboratory Abnormalities at the End of Therapy (EOT) in patients with baseline abnormal (>2.5x ULN) laboratory values (adapted from applicant's Table 13.7.2).

EOT laboratory value	AST		ALT		Alkaline phosphatase		Total bilirubin	
	Micafungin (all doses) N=185	Fluc 200 mg/day N=60	Micafungin (all doses) N=185	Fluc 200 mg/day N=60	Micafungin (all doses) N=185	Fluc 200 mg/day N=60	Micafungin (all doses) N=185	Flu 200 mg/day N=60
Normal*	7	0	5	0	2	1	0	0
2.5-5 x ULN	2	0	1	0	3	0	0	0
5-10 x ULN	3	0	0	0	2	0	0	0
> 10 x ULN	0	0	0	0	1	0	0	0
No data	2	0	1	0	2	0	1	0
Total patients*	14	0	7	0	10	1	1	0

\*Normal = normal range to < 2.5x ULN

\*\*Total patients with laboratory value > 2.5 x ULN at baseline

Fluc= fluconazole

EOT= end of therapy

AST= aspartate aminotransferase; ALT= alanine aminotransferase; AP= alkaline phosphatase; Tbili= total bilirubin

**Medical Officer Comments:** This analysis does not take into account any hepatic laboratory abnormalities which may have occurred during the treatment period, but only at the end-of therapy. For patients who received micafungin, and who had abnormal hepatic laboratory values at baseline, 3/14 (21.4 %) patients had a higher AST, 1/7 (14.3%) had a higher ALT, 3/10 (30%) had a higher alkaline phosphatase. Although the proportion of micafungin-treated patients with baseline elevations in laboratory values, and further elevations in AST, ALT, and alkaline phosphatase at the end-of therapy appears higher than in patients who had "normal" (<2.5xULN) values at baseline, the number of patients here is too small to draw that conclusion. Additionally, no comparisons with fluconazole-treated patients can be made because only 1 patient had an elevated laboratory (alkaline phosphatase) at baseline.

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### Renal Adverse Events

Renal adverse events occurred in 7/185 (3.8%) micafungin-treated patients and in 0/60 (0%) patients who received fluconazole. Renal adverse events are shown in the table below. No treatment discontinuations occurred due to renal adverse events in this study. One case of renal failure occurred in a patient who received micafungin 150 mg/day. This is the same patient, number 1008, who also had “hepatic failure” and died due to worsening tuberculosis. In this patient, kidney failure was reported as a serious adverse event on study day 13. BUN and creatinine had been normal at baseline and study day 7; while BUN was reported as 28 mg/dL, and creatinine as 1.8 mg/dL on day 14, the day prior to the patient’s death. As reviewed above (section on serious hepatic adverse events), the patient had been at least mildly hypotensive and had respiratory decompensation prior to the development of hepatic and renal failure. The only potentially nephrotoxic concomitant medication was bactrim for *Pneumocystis* prophylaxis and “bronchitis” which had been started on study day 2. None of the serious adverse events or death in this patient were attributed to micafungin.

*Medical Officer Comments: Neither the narrative summary nor the case report form provide any further details about renal failure in this patient, so it is not known if the patient became oliguric, or anuric, and there is no information on whether the patient required dialysis. Although certainly possible, because of all the confounding factors in this case, it would be difficult to attribute renal insufficiency to micafungin.*

Table 44. Renal Adverse Events (adapted from Table 13.6.3.5 and Appendix 14.3.8.1)

COSTART Term	Micafungin 50 mg/day N=64	Micafungin 100 mg/day N=62	Micafungin 150 mg/day N=59	Micafungin (all doses) N=185	Fluconazole 200 mg/day N=60
	n (%)	n (%)	n (%)	n (%)	n (%)
Increased BUN	1	1	3	5	0
Increased creatinine	2	1	1	4	0
Kidney Failure	0	0	1	1	0
Total patients with renal AE	2 (3.1%)	1 (1.6 %)	4 (6.8%)	7 (3.8%)	0 (0%)

N= number of patients in FAS; n = number of patients with adverse event

*Medical Officer Comments: It is notable that none of the patients who received fluconazole had renal laboratory abnormalities which were considered adverse events, in comparison to 7/185 (3.8%) micafungin-treated patients in this study (including the patient with renal failure described above).*

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### Hematological Adverse Events

Hematological laboratories tests reported as adverse events are shown in the following table.

Table 45. Incidence of Hematological Adverse Events in Study FG463-21-09 (adapted from Applicant's Table 13.6.1.2)

Adverse Event	Micafungin 50 mg/day N=64	Micafungin 100 mg/day N=62	Micafungin 150 mg/day N=59	Total Micafungin N=185	Fluconazole 200 mg/day N=60
	n (%)	n (%)	n (%)	n (%)	n (%)
Leukopenia	10 (15.6)	7 (11.3)	8 (13.6)	25 (13.5)	8 (13.3)
Anemia	6 (9.4)	6 (9.7)	6 (10.2)	18 (9.7)	3 (5.0)
Thrombocytopenia	2 (3.1)	3 (4.8)	3 (5.1)	8 (4.3)	2 (3.3)
Pancytopenia	0 (0)	1 (1.6)	0	1 (0.5)	0

N= number of patients in FAS; n = number of patients with adverse event

*Medical Officer Comments: Leukopenia was relatively frequent in patients treated with either micafungin or fluconazole, not unexpectedly in these patients with advanced HIV disease. Anemia was more common in each of the micafungin treatment groups than in the fluconazole group. There was, however, no reported hemolysis, hemolytic anemia, or abnormal erythrocytes in this study. Thrombocytopenia was proportionately more common among patients who received micafungin than in those treated with fluconazole; and pancytopenia was reported in a single patient who received micafungin and in no patients who received fluconazole.*

### Drug Related Hematological Adverse Events

The following table shows those hematological adverse events which the investigator considered drug-related.

Table 46. Drug-Related Hematological Adverse Events (adapted from Applicant's Table 13.6.1.3)

Adverse Event	Micafungin 50 mg/day N=64	Micafungin 100 mg/day N=62	Micafungin 150 mg/day N=59	Total Micafungin N=185	Fluconazole 200 mg/day N=60
	n (%)	n (%)	n (%)	n (%)	n (%)
Leukopenia	6 (9.4)	6 (9.7)	5 (8.5)	17 (9.2)	6 (10.0)
Anemia	2 (3.1)	3 (4.8)	2 (3.4)	7 (3.8)	2 (3.3)
Thrombocytopenia	0	1 (1.6)	0	1 (0.5)	0
Pancytopenia	0	1 (1.6)	0	1 (0.5)	0

N= number of patients in FAS; n = number of patients with adverse event

*Medical Officer Comment's: No significant differences were seen in the incidence of drug-related hematological adverse events.*

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### Serious Hematological Adverse Events

As shown in Table 37 above, three of 185 (1.6%) micafungin-treated patients, and 1/60 (1.7%) fluconazole-treated patients experienced a serious hematologic adverse event.

These included leukopenia in 2 micafungin-treated, and 1 fluconazole-treated patient, and anemia in 1 micafungin-treated patients. Narrative summaries are provided below for micafungin-treated patients with serious hematologic adverse events

### Narrative Summaries for Patients with Serious Hematologic Adverse Events

**Patient 2404** was a 29 year old male with HIV who received 14 days of micafungin 50 mg/day for esophageal candidiasis. This patient was reviewed above in the section on deaths during the study. Anemia was reported as a baseline condition. Leukopenia and anemia were reported as a serious adverse event on study day 15. Neither adverse event was considered related to micafungin. Tuberculosis was diagnosed on day 13. The cause of death was listed as respiratory failure and cardiac arrest. Hematologic laboratory values during the study are shown in the table below.

#### Hematological Laboratory Values\* for Patient 2404

Study Day	WBC (10 <sup>9</sup> /L)	Platelets (10 <sup>9</sup> /L)	Hemoglobin (g/dL)	Hematocrit (%)
Baseline	5.0	184	9.2	28.0
Day 7	4.0	287	8.7	26.0
Day 14	1.2	167	7.5	22.0

\*Normal laboratory values are provided in Appendix, section 10

***Medical Officer Comments:** The investigator considered the leucopenia and worsening anemia to be related to tuberculosis and advanced AIDS. The patient had received concomitant bactrim, efavirenz, lamivudine and zidovudine starting 3 days prior to receipt of micafungin, and continuing until day 14. Both bactrim and zidovudine have been associated with leucopenia, and zidovudine with anemia. Because of these confounding factors, it would be difficult to attribute the leucopenia or worsening anemia to micafungin in this case.*

**Patient 3113** was a 28 year old black female with HIV who received micafungin 150 mg/day for 14 days for esophageal candidiasis. Baseline conditions included pneumonia, fever, weight loss, nausea, vomiting, diarrhea, anemia and leukopenia at baseline. Leukopenia was noted as a serious adverse event on day 14, and was considered possibly related to micafungin. Hematologic laboratory values for this patient are shown in the table below. Concomitant medications included cotrimazole, tramadol, paracetamol, ranitidine, clindamycin, primaquine, folic acid, vitamin B12, diazepam, isoniazid, and others.

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**Hematologic Laboratory Values\* for Patient 3113**

Study Day	WBC (10 <sup>9</sup> /L)	Platelets (10 <sup>9</sup> /L)	Hemoglobin (g/dL)	Hematocrit (%)
Baseline	1.4	217	8.3	24.7
Day 7	1.0	223	8.1	24.0
Day 14	0.8	174	8.7	25.8
Day 21	1.1	162	8.5	25.8

\*Normal laboratory values are provided in Appendix, section 10.

***Medical Officer Comment:** Bactrim (cotrimazole) has been associated with leukopenia and other hematologic adverse reactions, while clindamycin, primaquine, and folinic acid have been associated with leukopenia less commonly. Because of the baseline leukopenia, and the concomitant medications in this patient, relating the worsening leukopenia to micafungin would be difficult.*

**Death due to Hematologic Adverse Events**

One patient died due to a hematologic adverse event in this study, **patient 2130**, who was reviewed above in section on deaths during the study. This patient received 3 days of micafungin 50 mg/day for esophageal candidiasis, and micafungin was stopped on day 3 due to cryptococcal meningitis. Thrombocytopenia was reported as a serious adverse event on day 18, but was not considered related to micafungin. Worsening leukopenia and anemia were reported as non-serious adverse events on the same day. The patient developed gastrointestinal bleeding on days 19-21, from which he recovered; but was re-hospitalized on day 31 with recurrent gastrointestinal hemorrhage, dehydration, and hemodynamic compromise. The patient died of a cardiac arrest on day 41. Hematologic laboratory values for this patient are shown in the following table. Concomitant medications prior to the day 18 included amphotericin B, bactrim, dimenhydrate, ibuprofen, ketorolac, mannitol, dexamethasone, isoniazid, ethambutol, pyrazinamide, rifampin (day 13-15), omeprazole (day 9-41), cyanocobalamin, and others.

**Hematologic Laboratory Values\* for Patient 2130**

Study Day	WBC (10 <sup>9</sup> /L)	Platelets (10 <sup>9</sup> /L)	Hemoglobin (g/dL)	Hematocrit (%)
Baseline	4.2	162	12.6	37.2
Day 4	4.4	130	11.5	34
Day 18	2.7	12	9.8	27

\*Normal laboratory values are provided in Appendix, section 10.

***Medical Officer Comments:** Although thrombocytopenia was reported as a serious adverse event on day 18, platelets had decreased by day 4. By day 18, the patient had worsening leukopenia, severe thrombocytopenia, and decreased hematocrit. The gastrointestinal bleeding was not reported until day 19, but may have accounted, in part, for the decreased hematocrit on day 18. Unfortunately, laboratory data beyond day 18 was not provided for this patient. Thrombocytopenia, leukopenia, and hemolytic anemia have occurred with rifampin; and*

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*omeprazole is also associated with uncommon hematological adverse events. Although tuberculosis was not listed as a baseline condition or adverse event for this patient, he was receiving antituberculous therapy. If this patient had disseminated tuberculosis, or another opportunistic infection or malignancy, bone marrow involvement could result in pancytopenia. Because of the multiple confounding factors in this case, it would be difficult to attribute thrombocytopenia directly to micafungin.*

### Study Drug Discontinuation due to Hematologic Adverse Events

One patient required discontinuation of micafungin due to pancytopenia (**patient 3213**); and one patient required discontinuation of fluconazole due to leukopenia (**patient 3102**), described above in section on drug-related serious adverse events) in this study. A descriptive summary for the micafungin-treated patient who developed pancytopenia is provided below.

**Patient 3213** was a 38 year-old female with HIV and a CD4 count of 140 cells/mm<sup>3</sup>, who received 100 mg/day micafungin, for esophageal candidiasis for 10 days. Pancytopenia had been reported at baseline, but was reported as an adverse event (not serious) on day 3, and micafungin was discontinued on study day 12. The investigator considered the worsening pancytopenia possibly related to micafungin. Other adverse events during the study included sinusitis, aphthous stomatitis, abdominal pain, fever, hyponatremia, increased AST and ALT, increased alkaline phosphatase, hypercalcemia, hypernatremia, increased LDH, hepatosplenomegaly, lymphadenopathy, jaundice, and marrow depression. The patient received a number of concomitant medications including ciprofloxacin, ethambutol, ethionamide, isoniazid, praznamide, bactrim, ceftriaxone, GCSF (days 10-11), and others. The table below shows hematological laboratory parameters for this subject during the study.

#### Hematological Laboratory Values\* for Patient 3213

Study Day	WBC (10 <sup>9</sup> /L)	Hemoglobin g/dL	Hematocrit %	Platelets (10 <sup>9</sup> /L)
Baseline	4.5	7.8	23.4	56
Day 7	2.6	2.6	26.8	15
Day 14	1.9	7.1	20.3	12
Day 24	2.0	6.9	21.1	101

WBC= total white blood cell count; ANC = absolute neutrophil count

\*Normal laboratory values are provided in Appendix, section 10.

***Medical Officer Comments:** Although no clinical narrative was provided by the Applicant because this adverse event was not considered serious, the patient apparently had tuberculosis at baseline and had been receiving a number of antituberculous drugs, including ethionamide, which is generally reserved for multi-drug-resistant tuberculosis. The worsening pancytopenia may have been related to marrow involvement by Mycobacterium tuberculosis, or other opportunistic pathogen rather than to micafungin, but without a bone marrow biopsy would be difficult to prove.*

### Allergic Reactions and Infusion-related Adverse Events

Potential infusion-related reactions, including fever, chills, and hypotension occurred in 53/185 (28.6%) micafungin-treated patients and in 17/60 (28.3%) fluconazole-treated patients. Allergic

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reactions are summarized in the table below. A higher proportion of micafungin- than fluconazole-treated patients experienced adverse events which could be considered allergic reactions.

Table 47. Allergic-type Reactions (adapted from applicant's Tables 37, and Table 13.6.1.2)

Adverse event	Micafungin 50 mg/day N=64	Micafungin 100 mg/day N=62	Micafungin 150 mg/day N=59	Micafungin (all doses) N=185	Fluconazole 200 mg/day N=60
	n (%)	n (%)	n (%)	n (%)	n (%)
Maculopapular rash	3 (4.7)	5 (8.1)	2 (3.4)	10 (5.4)	1 (1.7)
Pruritis	2 (3.1)	3 (4.8)	5 (8.5)	10 (5.4)	1 (1.7)
Rash	2 (3.1)	4 (6.5)	4 (6.8)	10 (5.4)	0 (0)
Exfoliative dermatitis	0	0	1 (1.7)	1 (0.5)	0 (0)
Allergic reaction	0	3 (4.8)	0	3 (1.6)	1 (1.7)
Eosinophilia	1 (1.6)	0	1 (1.7)	2 (1.1)	2 (3.3)
Urticaria	2 (3.1)	0	1 (1.7)	3 (1.6)	1 (1.7)
Vasodilatation	1 (1.6)	1 (1.6)	1 (1.7)	3 (1.6)	0
Facial edema	0 (0)	0 (0)	1 (1.7)	1 (0.5)	0 (0)
Anaphylactoid reaction	1 (1.6)	1 (1.6)	0	2 (1.1)	0
Total	12 (18.8)	17 (27.4)	16 (27.1)	45 (24.3)	6 (10.0)

*Medical Officer Comments: Several of the categories in the table above were added to the applicant's enumeration of allergic-like reactions. These included pustular rash, exfoliative dermatitis, and facial edema, which could all potentially be caused by an allergic reaction. Vasodilatation, which could be considered a histamine-type reaction, occurred in 3 micafungin-treated, but in none of the fluconazole-treated patients.*

### Serious Allergic Reactions

All serious allergic reactions in micafungin-treated patients are shown in the table below.

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Table 48. Incidence of Serious Allergic-type Adverse Events (adapted from Applicant's Table 13.6.2.1 and 13.6.2.2)

Serious Adverse Event	Micafungin 50 mg/day N=64	Micafungin 100 mg/day N=62	Micafungin 150 mg/day N=59	Total Micafungin N=185	Fluconazole 200 mg/day N=60
	n (%)	n (%)	n (%)	n (%)	n (%)
Allergic reaction	0	2 (3.2)	0	2 (1.1)	0
Anaphylactoid reaction	0	1 (1.6)	0	1 (0.5)	0
Rash	0	0	1 (1.7)	1 (0.5)	0

N= number of patients in FAS; n= number of patients with adverse event

Patients who experienced a serious allergic-type adverse event are listed in the following table. Narrative summaries were provided previously in the section "Study Drug Discontinuation".

Table 49. Micafungin-treated Patients with Serious Allergic Type Reactions

Patient number Investigative Site	Micafungin dose	Serious Adverse Event	Relationship to Study Drug
1606 ZA007	100 mg/day	Allergic reaction	Highly probable
2902 BR010	100 mg/day	Allergic reaction	Possible
2909 BR010	100 mg/day	Anaphylactoid reaction	Highly probable
3124 PE001	150 mg/day	Rash	Possible

**Medical Officer Comments:** As mentioned previously, the relationship of these reactions to micafungin is convincing because after drug discontinuation, the adverse event resolved in a timely manner.

### Infusion Site Reactions

Infusion site reactions, including injection site reaction, inflammation, or hemorrhage, occurred more frequently in the fluconazole arm of the study. Twenty percent (12/60) fluconazole-treated patients, and 21/185 (11.4%) micafungin-treated patients experienced at least one of these infusion site reactions. Phlebitis and thrombophlebitis, however, occurred more frequently in micafungin treated patients as shown in the table below. Phlebitis and thrombophlebitis were considered related to micafungin in 2 patients each. None of these reactions, including injection site reactions, phlebitis, and thrombophlebitis were reported as serious adverse events, and none led to treatment discontinuation in this study.

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Table 50. Incidence of Infusion Site Reactions in Study FG463-21-09 (adapted from Applicant's Tables 39 and 13.6.1.3)

Adverse Event	Micafungin 50 mg/day N=64	Micafungin 100 mg/day N=62	Micafungin 150 mg/day N=59	Total Micafungin N=185	Fluconazole 200 mg/day N=60
Any injection site reaction:	8 (12.5)	5 (8.1)	8 (13.6)	21 (11.4)	12 (20.0)
Injection site inflammation	7 (10.9)	4 (6.5)	6 (10.2)	17 (9.2)	10 (16.7)
Injection site reaction	1 (1.6)	1 (1.6)	1 (1.7)	3 (1.6)	2 (3.3)
Injection site hemorrhage	0	0	1 (1.7)	1 (0.5)	0
Vascular adverse events:					
Phlebitis	2 (3.1)	4 (6.5)	2 (3.4)	8 (4.3)	0
Thrombophlebitis	2 (3.1)	2 (3.2)	1 (1.7)	5 (2.7)	0

**Medical Officer Comments:** *If phlebitis and thrombophlebitis were included in this category, 34/185 (18.3%) micafungin-treated patients had some type of injection site reaction, similar to that observed in fluconazole-treated patients 12/60 (20%). Among the 12 fluconazole-treated patients who had an injection site reaction, 10 had injection site inflammation and none had phlebitis or thrombophlebitis; while in the micafungin-treated patients, injection site inflammation was most common reaction, followed by phlebitis.*

*These data differ from that presented in study 03-7-005, in which a higher proportion (19.6%) micafungin (150 mg/day) than fluconazole (5.0%) - treated patients experienced phlebitis or thrombophlebitis. In that study, phlebitis and thrombophlebitis were associated with the use of peripheral intravenous catheters. Data on the types of intravenous catheter used for patients in this study was not available.*

**Infections**

A higher proportion of micafungin-treated patients (56.2%) developed an infection during this study than did fluconazole-treated patients (48.3%). Bacterial infections, including tuberculosis, accounted for the majority of treatment-emergent infections (or worsening of pre-existing infections). The incidence of infections reported as adverse events is shown in the following table.

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Table 51. Incidence of Infections Reported as Adverse Events (Applicant’s Table 40)

Table 40: Incidence of Treatment-emergent Infections, Irrespective of Causality – No. Patients (%)

	Micafungin Dose			Total	Fluconazole
	50 mg/day n=64	100 mg/day n=62	150 mg/day n=59	Micafungin n=185	200 mg/day n=60
Any	38 (59.4)	33 (53.2)	33 (55.9)	104 (56.2)	29 (48.3)
Bacterial	24 (37.5)	11 (17.7)	24 (40.7)	59 (31.9)	17 (28.3)
Viral	9 (14.1)	15 (24.2)	8 (13.6)	32 (17.3)	9 (15.0)
Unknown	6 (9.4)	11 (17.7)	3 (5.1)	20 (10.8)	7 (11.7)
Fungal	5 (7.8)	4 (6.5)	4 (6.8)	13 (7.0)	3 (5.0)
Protozoal	6 (9.4)	3 (4.8)	2 (3.4)	11 (5.9)	3 (5.0)
Other	1 (1.6)	4 (6.5)	0	5 (2.7)	0

Patient population (full analysis set): all patients who received at least one dose of study drug.

The infection status was indicated with a tick-box on the case report form.

Source: Table 13.6.3.1

Further information provided by the Applicant upon request of the DSPIDP, regarding the incidence of tuberculosis and pneumonia in this study is shown in the table below. Tuberculosis was listed as a baseline condition in 52/185 (28.1%) micafungin-treated patients, and 14/60 (23.3%) patients treated with fluconazole. A total of 19/185 (10.3%) patients who received micafungin had tuberculosis reported as an adverse event in this study, with 11/19 (58%) cases occurring in patients who had tuberculosis at baseline. In the fluconazole treatment group, 4 patients had tuberculosis reported as an adverse event, none of whom had tuberculosis at baseline.

Pneumonia was reported in 18/185 (9.7%) micafungin-treated patients in comparison to 5/60 (8.3%) fluconazole-treated patients. Among the patients who received micafungin, 8/18 cases of pneumonia (44.4%) were due to *Pneumocystis jiroveci* (formerly *carinii*), and 1 case was due to tuberculosis (this case was counted as pneumonia and not tuberculosis in the database). Among fluconazole-treated patients, 1/5 (20%) cases of pneumonia were due to *Pneumocystis jiroveci* (formerly *carinii*). See discussion below regarding breakthrough fungal infections.

Table 52. Incidence of Tuberculosis and Pneumonia reported as Adverse Events in Study FG463-21-09 (adapted from attachment 11, November 12, 2004 submission).

Adverse Event (COSTART Term)	Micafungin-treated patients N=185 n (%)	Fluconazole-treated Patients N=60 n (%)
Pneumonia	18 (9.7)	5 (8.3)
Interstitial pneumonia	0	0
Tuberculosis, aggravated	18 (9.7)	4 (6.7)
Tuberculosis, reactivated	1 (0.5)	0
Pulmonary tuberculosis, reactivated	0	0

N= number of patients in FAS; n= number of patients with adverse event

**Medical Officer Comments:** The overall incidence of pneumonia is similar in the pooled micafungin and the fluconazole treatment groups. If the 11 micafungin-treated patients with tuberculosis at baseline were not included in the total patients with tuberculosis as an adverse event, the incidence of tuberculosis was similar in micafungin-treated, 4.9% (9/185) and

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*fluconazole-treated patients, 6.7% (4/60). However, the baseline incidence of tuberculosis was similar in both groups (28% for micafungin, and 23% for fluconazole), so it is not clear why proportionately patients more with tuberculosis at baseline had exacerbation of that infection in the micafungin group. There have been no specific reports in the literature regarding potential immunosuppression by the echinocandins; however, these data could suggest worsening cell-mediated immunity as a potential factor. Individual cases were not reviewed, however, to determine if other factors in these patients may have resulted in reactivation or exacerbation of tuberculosis.*

Fungal infections were reported in 12/185 (6.5%) micafungin-treated patients and 3/60 (5.0%) fluconazole-treated patients. Breakthrough fungal infections are shown in the table below.

Table 53. Treatment-Emergent Fungal Infections reported as an Adverse Event (FAS) (adapted from applicant's Tables 40, and Appendix 14.4.6.2)

Fungal infection	Micafungin 50 mg/day N=64	Micafungin 100 mg/day N=62	Micafungin 150 mg/day N=59	Micafungin (all doses) N=185	Fluconazole 200 mg/day N=60
	n (%)	n (%)	n (%)	n (%)	n (%)
All	5 (7.8)	4 (6.5)	3 (5.1)	12 (6.5)	3 (5.0)
<i>Pneumocystis jirovecki</i> (formerly <i>carinii</i> ) pneumonia	4	4	1	9	1
<i>Cryptococcal</i> meningitis	1	0	1	2	2
Disseminated fungal infection	0	0	1	1	0

**Medical Officer's Comments:** *This table differs from the applicant's summary Table 40 in that 3 rather than 4 fungal infections are reported for 150 mg/day micafungin. In addition, the applicant reported only one case of *Pneumocystis carinii* pneumonia (PCP) in the 50 mg/day and 150 mg/day micafungin group and the fluconazole group, and 3 cases in the 100 mg/day micafungin group. However, the numbers listed in Table 53 were found in Appendix 14.4.6.2.*

*The overall incidence of breakthrough fungal infection, including pneumocystosis and cryptococcosis was higher in the micafungin treatment group than in the fluconazole group, despite the fact that mean CD4 count was lower in the fluconazole treatment group, although this difference was not statistically significant. Interestingly, micafungin appears to have activity against *Pneumocystis* in vitro; while these cases of new or worsening PCP suggest that at the doses studied, micafungin may not have efficacy in treatment or prevention of PCP in vivo. Micafungin is not active in vitro against *Cryptococcus*, and the breakthrough cases noted here are not unexpected. Further information regarding the single case of disseminated fungal infection is provided below.*

### Narrative summary for patient with breakthrough disseminated fungal infection

**Patient 1808** was a 50 year old male with AIDS and a CD4 count of 74 cells/mm<sup>3</sup>, who received micafungin for esophageal candidiasis for 14 days. At baseline, the patient had what the investigator

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called a “disseminated fungal infection”. Upon further review, it was found that this referred to a fungal skin infection involving most of the body surface area, with severe desquamation and pruritis. Disseminated fungal infection was listed as an adverse event on day study 8, due to worsening of skin desquamation. According to the investigator both the desquamation and pruritis improved by the end of the study, but required further treatment with griseofulvin.

***Medical Officer Comment:** This was a disseminated fungal infection involving only the skin, and not other organ systems. Most fungal skin infections are caused by Tinea species, organisms against which micafungin has no in vitro activity.*

## Conclusions Regarding Safety of Micafungin for Study FG463-21-09

1. The overall incidence of adverse events was similar in patients treated with either micafungin (89.2%) or fluconazole (93.3%).
2. The incidence of serious adverse events was somewhat higher in patients who received micafungin (13.0%) than in those who received fluconazole (8.0%)
3. Micafungin was discontinued in proportionately more patients due to adverse events (8.6%) than was fluconazole (6.7%).
4. The most common adverse events in patients who received micafungin were fever, nausea, diarrhea, headache, vomiting, abdominal pain, leukopenia, and infection.
5. Drug-related adverse events occurred in 49.7% of patients treated with micafungin, and in 43.3% patients treated with fluconazole.
5. Drug-related adverse events more common in patients who received micafungin than in those who received fluconazole included abdominal pain, fever, chills, allergic reaction, diarrhea, vomiting, anemia, increased AST, ALT, alkaline phosphatase, and LDH, somnolence, headache, maculopapular rash, rash, and pruritis.
6. A total of 9 deaths occurred during the study period among 185 patients who received micafungin, and in 1/60 patients who received fluconazole. None of the deaths occurred during treatment, and none appeared to be related to the study medication.
7. Drug related serious adverse events in patients treated with micafungin included chills, hypotension, and vomiting, dementia, rash, leukopenia, and anaphylactoid reactions.
8. Adverse events considered related to micafungin which resulted in micafungin discontinuation included anaphylactoid reactions, asthenia, dementia, rigors, nausea, vomiting and diarrhea, allergic reaction, pulmonary edema, rash, and neutropenia.
9. Proportionately more hepatobiliary adverse events were reported in micafungin-treated (28.1%) than in fluconazole-treated patients (16.7%).

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10. The incidence of elevated AST, ALT, and bilirubin reported as adverse events was similar in micafungin-treated and fluconazole treated patients; while the incidence of alkaline phosphatase elevation reported as an adverse event was higher in micafungin-treated patients.

11. Most LFT elevations were between 2.5 x and 5 x the upper limit of normal. Only a few patients in each treatment group had LFT elevations > 10 x the upper limit of normal.

12. Patients with baseline elevations of AST and ALT > 2.5 x the upper limit of normal may be at higher risk for further transaminase elevation, although the numbers of patients in this category was too low to draw firm conclusions.

13. Two serious hepatic adverse events occurred in this study, hepatic failure and liver damage. The former event appeared to be sole transaminase elevation without bilirubinemia; and the second event reflected new radiological liver abnormalities, possibly multiple abscesses or non-Hodgkin's lymphoma, without concurrent LFT abnormalities. Neither adverse event appeared to be related to micafungin, although the former case was highly confounded.

14. A higher incidence of renal adverse events was reported in patients who received micafungin than in those who received fluconazole. One serious adverse event, kidney failure was reported in the same micafungin-treated patient who had "hepatic failure". This event was actually moderate elevation of BUN and creatinine, and did not appear to be related to micafungin, although the case was highly confounded.

15. The adverse event, leukopenia, was reported at similar rates in micafungin- and fluconazole-treated patients; while proportionately higher numbers of micafungin-treated patients than fluconazole-treated patients developed anemia. No cases of hemolysis or hemolytic anemia were reported in this study. Micafungin was discontinued in one patient due to pancytopenia, and leukopenia and anemia were reported as serious adverse events in micafungin-treated patients.

16. Allergic and histamine-type reactions, including vasodilatation, flushing, and other reactions, occurred in proportionately higher numbers of patients treated with micafungin than those who received fluconazole.

17. The injection site reactions of phlebitis and thrombophlebitis occurred more frequently in patients who received micafungin than in those who received fluconazole, but no obvious dose relationship to micafungin was noted in this study.

18. The overall incidence of infections reported as adverse events was higher in micafungin-treated than in fluconazole-treated patients, due primarily to bacterial (including tuberculosis) infections. Additionally, a somewhat higher incidence of fungal infections reported as adverse events were observed in patients who received micafungin, including *Pneumocystis jirovecii* (formerly *carinii*) pneumonia and cryptococcal meningitis.

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10.1.3 Clinical Trial # 3: Study 97-7-003.

### **A Phase II Study to Determine the Minimal Effective Dose of FK463 in the Treatment of Esophageal Candidiasis in HIV Positive Patients**

**Study Objectives:** To determine the minimal effective dose of micafungin required for treatment of esophageal candidiasis (EC) in patients with HIV disease, assessed clinically. Secondary objectives included evaluation of EC treatment by endoscopic and mycological assessment, in addition to evaluation of micafungin safety.

**Rationale:** *In vitro* activity of micafungin against *Candida* species had been shown previously. In addition, phase 1 single-dose and repeat-dose studies in healthy volunteers suggested an acceptable safety profile up to 50 mg/day micafungin. This study was designed to evaluate dose-response relationships for treatment of EC with micafungin in HIV positive patients.

**Study Design:** This was a phase 2, open-label, dose de-escalation study designed to evaluate the minimum effective dose for treatment of EC with micafungin. HIV-positive patients  $\geq 18$  years old with EC received micafungin at doses of 100 mg/day, 75 mg/day, 50 mg/day, 25 mg/day, or 12.5 mg/day for 14 days. A total of 120 patients were enrolled at nine investigative sites in South Africa. The study period was May 15, 1998 to May 16, 2000.

#### **Protocol Overview**

##### **Primary Efficacy Endpoint:**

The primary efficacy endpoint was clinical response at the end of therapy. A positive response was defined as cure or improvement of clinical signs and symptoms (odynophagia, dysphagia, and retrosternal pain) of EC. Clinical response was defined as follows:

- “Cleared”: resolution of EC clinical signs and symptoms
- “Improved”: reduction in EC clinical signs and symptoms
- “Unchanged/worse”: no change or progression of EC clinical signs and symptoms

The minimum effective dose was the lowest dose of micafungin required for clinical cure or improvement in at least 65% of patients after 10 days of therapy.

##### **Secondary Efficacy Endpoints:**

Secondary efficacy endpoints included:

- Improvement in esophageal mucosal lesions at the end-of-therapy by endoscopic evaluation (endoscopic grade 0 = normal mucosa; grade 1 = individual raised plaques  $\leq 2$ mm in size; grade 2 = multiple raised plaques; grade 3 = confluent plaques and/or ulceration)
- Mycological response
- Overall success/failure
- Changes in the quantitative clinical assessment of esophagitis (odynophagia, dysphagia, retrosternal pain, and total symptom grade)

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- Clinical response of oropharyngeal candidiasis (OPC) if present at baseline (fissures, mouth pain, inflammation, and plaques)
- Clinical response at 2-weeks post-treatment
- Relapse of EC requiring the use of antifungal therapy during the 2-week post-treatment period.

## Treatment

Micafungin was administered intravenously as a 1-hour infusion once daily for 14 days (or 21 days if further treatment required). Patients received 100 mg/day, 75 mg/day, 50 mg/day, 25 mg/day, or 12.5 mg/day. The first 20 patients received 50 mg/day, determined as the initial dose level based on the previous phase 1 studies mentioned above. Dose de-escalation (with 25 mg/day and 12.5 mg/day) was to be conducted in subsequent patients if the minimal effective dose was not reached. Initial review of the doses up to 50 mg/day revealed clinical improvement in most patients, but endoscopic clearing of lesions was not demonstrated. The 2 additional doses (75 mg/day and 100 mg/day) were added to the protocol in Amendment 02 (see below). These latter doses were administered to patients sequentially (i.e. 20 patients received 75 mg/day; then 20 patients received 100 mg/day micafungin).

## Study Amendments

Amendment 01 (February 2, 1998) added overall success/failure as a secondary endpoint, added the collection of safety data, and provided updated safety data from phase 1 studies.

Amendment 02 (July 2, 1999) added the 75 mg/day and 100 mg/day micafungin dose levels, and clarified the duration of dosing and timing of end-of-therapy assessment.

## Assessments and Procedures

The following table shows the schedule for assessments and procedures in this study. Laboratory hematology evaluation included white blood cell count (WBC), with differential count, hemoglobin, hematocrit, platelet count, CD<sub>4</sub> count within 6 weeks prior to first dose of micafungin, reticulocyte count, prothrombin time (PT), and partial thromboplastin time (PTT). Serum chemistry evaluation included creatinine, blood urea nitrogen (BUN), AST, ALT, alkaline phosphatase, total bilirubin, sodium, potassium, chloride, bicarbonate, calcium, and magnesium.

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Table .1 Schedule for Study Procedures (Applicant's Table, study report, Appendix 14.1.1, study report 24 April, 2004)

PROCEDURE	BASELINE	Treatment DAY 3	Treatment DAY 7	Treatment DAY 14 <sup>a</sup> (or End of Therapy)	Post-Treatment WEEK 2 <sup>b</sup>
Informed Consent	X				
Demographics/Medical History/HIV/AIDS Status	X				
Body Weight/Height	X				
Hematology	X	X	X	X	X
Serum Chemistry	X	X	X	X	X
Total CD4 Count	X <sup>c</sup>				
Pregnancy Test (if applicable)	X				
Physical Examination	X			X	
Vital Signs	X	X	X	X	X
Infection Status Clinical Assessment Endoscopy with biopsy, brushings and fungal culture	X X	X	X	X X <sup>d</sup>	X
Treatment Evaluation				X	X
Concomitant Medications	X <sup>e</sup>	X	X	X	X <sup>f</sup>
Adverse Events		X	X	X	X <sup>f</sup>

- a Evaluable patients should receive at least 10 doses of FK463.
- b Assessments should be made 11 to 17 days after the last dose of FK463.
- c Within 6 weeks prior to the first dose of FK463.
- d Within 5 days of completing FK463 therapy. A biopsy is not required if no lesions are seen.
- e Use of antifungal agents only.
- f Adverse events will be collected through 72 hours after the last dose of FK463.

Patients were required to meet the following inclusion and exclusion criteria:

**Inclusion Criteria:**

- Informed consent of patient or legally authorized representative prior to study entry
- Patient with HIV or AIDS and  $\geq 18$  years old  
 Negative pregnancy test in females of child-bearing potential
- Patient with esophageal candidiasis documented by clinical signs and symptoms, and confirmed endoscopically within 5 days prior to first dose of micafungin
- Patient with sufficient venous access to allow administration of intravenous micafungin and monitoring of safety variables

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### Exclusion Criteria:

- Pregnancy or nursing
- Abnormal liver function test values at baseline, including AST or ALT > 2.5 x upper limit of normal (ULN); total bilirubin > 2.5 x ULN; alkaline phosphatase > 2.5 x ULN
- Serum creatinine > 2.0 mg/dL
- Active opportunistic infection (or receiving acute therapy for opportunistic infection)
- Acute or chronic hepatitis or cirrhosis
- History of allergy, hypersensitivity, or any serious reaction to echinocandins
- Receipt of an oral topical (non-systemic) antifungal agent within 48 hours, or a systemic antifungal agent within 72 hours of the first dose of micafungin
- Requirement for topical or systemic antifungal therapy for conditions other than EC
- Abnormalities which precluded esophageal endoscopy
- Presence of a concomitant condition that could create an additional risk for the patient ( in the opinion of the investigator or medical monitor)
- Receipt of another investigational drug (other than one to treat HIV)

*Medical Officer Comments: Concomitant antifungal agents, including topical and systemic antifungal medications were prohibited during the treatment phase, but were permitted during the 2 week post-treatment period. Receipt of antifungal agent during this timeframe could confound the analysis of relapse.*

### Criteria for Study Withdrawal

Reasons for study withdrawal included the following:

- Occurrence of unacceptable toxicity
- Progression of infection
- Diagnosis of EC not confirmed
- Patient required therapy with another antifungal agent
- Patient withdrew consent
- Investigator decision that it was in patient's best interest to discontinue

Patients who prematurely discontinued therapy were evaluated at the 2-week post-treatment visit. Discontinuation of therapy was permitted after a patient received 10 doses of micafungin if esophageal endoscopy was performed within 5 days of the last dose.

### Safety Evaluation

Safety evaluation included assessment of adverse events, laboratory profiles, vital signs, and chest X-rays). An adverse event was defined as any reaction, side effect, or other untoward event, regardless of relationship to study drug, which occurred during the clinical trial. A serious adverse event was defined as any adverse event that resulted in death, was life-threatening, resulted in a persistent or significant disability or congenital anomaly/birth defect, required inpatient hospitalization, prolonged existing hospitalization, or required intervention to prevent any of the above. Adverse events were recorded through 72 hours after receipt of the last dose of micafungin; and ongoing adverse events

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were followed until the event stabilized or as long as necessary to ensure patient safety. Adverse events were coded by body system using a modified Coding Symbols for Thesaurus of Adverse Reaction Terms (COSTART) dictionary.

## Statistical Consideration

No formal sample size determination was performed. The targeted enrollment was 20 patients in each dosing group. If < 13/20 (65%) enrolled patients experienced a successful clinical outcome, then no further dose-reduction was to be performed.

## Statistical Analysis Populations

**Full Analysis Set (FAS):** All patients who received at least one dose of study drug. The FAS was the analysis set for safety evaluation.

**Per Protocol Set (PPS):** All patients with confirmed EC (positive histology or cytology) at baseline, who received at least 10 doses of micafungin, or who was discontinued for treatment failure. The PPS was considered the primary analysis set for efficacy evaluation.

*Medical Officer Comments: The FAS (analogous to ITT population) was appropriately designated for the safety analysis. In this review, efficacy will be evaluated using both the FAS and PPS.*

## Statistical Methods

For the primary endpoint, the rate of successful clinical response was compared at the lowest and highest dose level, and a two-sided 95% confidence interval around the treatment difference was performed. Additionally, a trend test was performed to assess a linear trend in the clinical response rates by dose level. Clinical response rates were also evaluated using logistic regression analysis.

## Study Results

### Patient Disposition

A total of 120/120 (100%) patients were enrolled in this study, and received at least one dose of micafungin and were included in the FAS. Overall, 84/120 (70%) enrolled patients met the criteria for inclusion in the PPS. Thirty six of 120 patients were considered non-evaluable, and were excluded from the Per Protocol analysis). Twenty excluded patients received fewer than 10 doses of study medication; and 13 of these 20 patients discontinued due to an adverse event or death, 6 patients withdrew consent, and 1 patient was discontinued by the investigator due to non-compliance. Sixteen of 36 patients excluded from the PPS received at least 10 doses of micafungin, but did not have a positive histology or cytology to confirm EC at baseline. Patient distribution by dose level and analysis population is shown in the table below.

Table 2. Overall Patient Distribution by Micafungin dose and Analysis Population (Applicant's Table 1, study report, 24 April, 2004)

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	FK463 Dose Level (mg/day)					
	12.5	25.0	50.0	75.0	100.0	Total
<b>All Enrolled Patients</b>	26	22	26	22	24	120
<b>Full Analysis Set</b>	26 100.0%	22 100.0%	26 100.0%	22 100.0%	24 100.0%	120 100.0%
<b>Per Protocol Set</b>	18 69.2%	13 59.1%	15 57.7%	19 86.4%	19 79.2%	84 70.0%

Patient base: all enrolled patients, irrespective of whether FK463 was administered (all enrolled patients); all patients who received at least 1 dose of FK463 (full analysis set); all patients who had a positive histology or cytology at baseline and received at least 10 doses of FK463 or discontinued due to treatment failure (per protocol set).

Protocol deviations included enrollment of patients despite one or more elevated liver function tests at baseline in the 12.5 mg/day treatment group (4 patients), the 25 mg/day group (2 patients), the 50 mg/day group (3 patients), the 75 mg/day group (5 patients), and the 100 mg/day group (2 patients). Additionally 1 patient in the 75 mg/day group was enrolled despite a baseline creatinine of > 2.0 mg/dL; and 5 patients were enrolled despite not having a pregnancy screening test performed prior to enrollment (4 patients in the 12.5 mg/day group and 1 patient in the 50 mg/day group).

*Medical Officer Comments: Patient distribution by micafungin dose level was fairly even in both analysis sets, although the 25 mg/day and 50 mg/day dosing groups had the fewest patients in the PPS.*

**Reasons for Treatment Discontinuation**

A total of 29/120 (24.2%) patients discontinued therapy. Sixteen of 120 (13.3 %) patients discontinued micafungin due to an adverse event; 3/120 (2.5%) discontinued due to lack of efficacy, and 10/120 (8.3%) discontinued for administrative reasons. These data are shown in the table below.

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Table 3. Reason for Patient Discontinuation (Applicant's Table 3, study report)

	FK463 Dose Level (mg/day)					
	12.5 (n=26)	25.0 (n=22)	50.0 (n=26)	75.0 (n=22)	100.0 (n=24)	Total (n=120)
<b>Completed Therapy</b>	19 73.1%	17 77.3%	17 65.4%	19 86.4%	19 79.2%	91 75.8%
<b>Discontinued Therapy</b>	7 26.9%	5 22.7%	9 34.6%	3 13.6%	5 20.8%	29 24.2%
<b>Adverse Event</b>	2 7.7%	2 9.1%	5 19.2%	3 13.6%	4 16.7%	16 13.3%
<b>Lack of Efficacy</b>	1 3.8%	2 9.1%	0 0.0%	0 0.0%	0 0.0%	3 2.5%
<b>Administrative*</b>	4 15.4%	1 4.5%	4 15.4%	0 0.0%	1 4.2%	10 8.3%

Patient base: all patients who received at least 1 dose of FK463 (full analysis set).

A patient may have discontinued therapy, but was still considered to have completed the study.

\*administrative reasons included withdrawal of consent in 9 patients, and withdrawal by investigator due to patient noncompliance in 1 patient.

*Medical Officer Comments: Reasons for treatment discontinuation were similar among the micafungin treatment groups.*

**Study Completion**

A total of 89/120 (74.2%) patients completed the study, 13/120 (10.8%) patients died prior to study completion, 13/120 (10.8%) were lost to follow-up, and 5/120 (4.2%) patients withdrew consent for the study. Patient status at the end of study for all enrolled patients is shown in the table below.

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Table 4. Study Completion (FAS) (Applicant's Table 2, study report, 24 April, 2004)

Patient Status at End-of-Study	FK463 Dose Level (mg/day)					
	12.5 (n=26)	25.0 (n=22)	50.0 (n=26)	75.0 (n=22)	100.0 (n=24)	Total (n=120)
Completed Study	18 69.2%	17 77.3%	20 76.9%	18 81.8%	16 66.7%	89 74.2%
Death	3 11.5%	3 13.6%	2 7.7%	2 9.1%	3 12.5%	13 10.8%
Lost to Follow-Up	2 7.7%	2 9.1%	3 11.5%	2 9.1%	4 16.7%	13 10.8%
Other†	3 11.5%	0 0.0%	1 3.8%	0 0.0%	1 4.2%	5 4.2%

Patient base: all enrolled patients.

† Other: included five patients who withdrew consent prior to completing the study.

A patient may have discontinued therapy, but was still considered to have completed the study.

*Medical Officer Comments: Similar numbers and proportion of patients died, were lost to follow-up, or withdrew consent in each of the micafungin dosing groups.*

**Patient Demographics**

Baseline characteristics of patients with regard to age, race/ethnic background, gender and weight are summarized in the table below. Overall, 52% of patients were male, and 84% were black, with a mean age of 34 years, and a mean CD<sub>4</sub> count of 91 cells/mm<sup>3</sup>.

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Table 5. Baseline Patient Demographics (FAS) (applicant's Table 13.2.1.1, study report, 24 April, 2004)

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PARAMETER	CATEGORY	MICAFUNGIN DOSE LEVEL					TOTAL (N=120)
		12.5 MG/DAY (N=26)	25.0 MG/DAY (N=22)	50.0 MG/DAY (N=26)	75.0 MG/DAY (N=22)	100.0 MG/DAY (N=24)	
GENDER	MALE	12 (46.2%)	17 (77.3%)	15 (57.7%)	8 (36.4%)	10 (41.7%)	62 (51.7%)
	FEMALE	14 (53.8%)	5 (22.7%)	11 (42.3%)	14 (63.6%)	14 (58.3%)	58 (48.3%)
RACE	CAUCASIAN	2 (7.7%)	4 (18.2%)	5 (19.2%)	2 (9.1%)	1 (4.2%)	14 (11.7%)
	BLACK	23 (88.5%)	18 (81.8%)	19 (73.1%)	20 (90.9%)	21 (87.5%)	101 (84.2%)
	OTHER	1 (3.8%)	0 (0.0%)	2 (7.7%)	0 (0.0%)	2 (8.3%)	5 (4.2%)
AGE (YEARS)	N	26	22	26	22	24	120
	MEAN	36.0	31.8	33.4	34.6	34.1	34.1
	STD	8.60	6.18	6.74	10.41	9.29	8.34
	MEDIAN	33.5	33.5	33.5	35.5	33.0	34.0
	MIN	22.0	20.0	22.0	18.0	23.0	18.0
	MAX	57.0	41.0	49.0	59.0	57.0	59.0
HEIGHT (CM)	N	26	19	24	22	23	114
	MEAN	164.2	167.5	166.0	162.9	165.0	165.0
	STD	9.87	9.20	10.72	6.21	11.48	9.67
	MEDIAN	165.5	168.0	167.5	163.0	162.0	165.0
	MIN	143.0	145.0	150.0	155.0	151.0	143.0
	MAX	182.0	183.0	186.0	193.0	191.0	191.0
WEIGHT (KG)	N	26	22	26	22	24	120
	MEAN	48.8	52.4	55.3	53.0	51.5	52.2
	STD	13.32	13.37	14.23	16.30	9.12	13.38
	MEDIAN	46.5	51.5	51.6	50.5	50.5	49.6
	MIN	32.0	32.0	36.0	31.0	35.0	31.0
	MAX	79.5	77.0	83.2	95.0	68.0	95.0
CD4 COUNT	N	24	19	22	22	24	111
	MEAN	121.0	59.8	78.1	130.0	63.0	91.3
	STD	153.53	55.66	104.99	255.46	136.88	157.45
	MEDIAN	63.7	54.0	36.0	30.7	18.5	34.0
	MIN	0.6	5.0	5.0	3.1	4.0	0.6
	MAX	499.4	200.0	396.0	1044.7	671.0	1044.7

**Medical Officer Comments:** The 25 mg/day micafungin group had significantly more males, 77.3% (17/22) than females enrolled, 22.7% (5/22), and the 75 mg/day group had more females, 63.6% (14/22) than males, 36.4% (8/22); otherwise gender distribution within groups was balanced. No differences in racial/ethnic distribution were observed between groups. Overall, patients appeared evenly distributed by age and weight. Overall, patients in this study had advanced HIV disease, with the median CD<sub>4</sub> count below 100 for each treatment group. Some differences were observed in baseline CD<sub>4</sub> counts between groups, with the highest mean CD<sub>4</sub> counts in the 12.5 mg/day and 75 mg/day groups.

**Baseline Status of Esophageal Candidiasis**

In the PPS, all patients had histology and/or cytology (obtained at baseline endoscopy) positive for fungal elements, confirming EC at baseline. A total of 83/84 (98.8%) in the PPS had *Candida albicans* isolated at baseline, and 1 patient did not have a baseline fungal culture performed. Additionally, one patient had baseline *Candida tropicalis* in addition to *C. albicans*. Baseline EC endoscopic grade and symptom scores are shown in the following table.

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Table .6 Baseline Esophageal Candidiasis scores (PPS) (adapted from Applicant’s Tables 13.4.9.2 and 13.4.11.2, study report, 24 April, 2004)

Baseline Parameter	Micafungin 12.5 mg/day	Micafungin 25 mg/day	Micafungin 50 mg/day	Micafungin 75 mg/day	Micafungin 100 mg/day
Endoscopic grade* (mean± SD)	2.6 ± 0.7	2.4 ± 1.0	1.9 ± 0.8	2.2 ± 0.7	2.6 ± 0.8
Baseline EC symptom score**	5.3 ± 2.8	5.1 ± 2.4	4.3 ± 1.8	5.3 ± 2.7	5.1 ± 2.3

\*Endoscopic grade was assessed on scale of 0-3

\*\* EC symptom score was assessed on scale of 0-9

**Prior and Concomitant Antifungal Therapy**

None of the patients in the PPS set received systemic antifungal therapy in the 2 weeks prior to the first dose of micafungin; while 11 patients received topical (non-systemic) antifungal therapy during this time period. None of the patients were to receive topical antifungal agents within 48 hours of the first dose of micafungin or systemic antifungal agents within 72 hours. Additionally, patients were to be discontinued from micafungin if they received another antifungal agent during the treatment period.

*Medical Officer Comments: The data regarding post-treatment receipt of other antifungal medications was not summarized by the Applicant in this study.*

**Other Concomitant Medications**

In the PPS, 7/84 (8.3%) patients received antiretroviral therapy during the study, 1 patient in the 12.5 mg/day micafungin group, 2 in the 25 mg/day group, 3 in the 50 mg/day group, 1 in the 100 mg/day group, and none in the 75 mg/day group.

*Medical Officer Comments: Esophageal candidiasis is prone to relapse in patients whose HIV status is not improved, so because most patients in this study were not receiving antiretroviral therapy, their HIV disease would be expected to progress toward more severe immunosuppression, and these patients would be expected to have recurrent EC, sometimes even with chronic antifungal prophylaxis.*

**Efficacy**

**Primary Efficacy Endpoint: Clinical Response**

A favorable clinical response (clearing or improvement of EC symptoms) was observed in all patients in the 75 mg/day and 100 mg/day micafungin treatment groups. In the 50 mg/day group, 1 patient did not have baseline symptoms of EC (but had positive histology on endoscopy), so only 14 patients in that group were evaluated. Fourteen of 14 patients in that group had a positive clinical response. One patient of 13 (7.7%) was unchanged or worse in the 25 mg/day group, and 6/18 (33.3%) patients failed in the 12.5 mg/day treatment group. These results are summarized in the table below.

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Table 7. Clinical Response at End-of-Therapy (PPS) (adapted from Applicant's Table 6, study report, 24 April, 2004)

	Micafungin Dose Level (mg/day)				
	12.5 (n=18)	25.0 (n=13)	50.0 (n=15)	75.0 (n=19)	100.0 (n=19)
<b>Positive Clinical Response</b>	12 66.7%	12 92.3%	14† 93.3%	19 100.0%	19 100.0%
<b>Cleared</b>	6 33.3%	7 53.8%	13 86.7%	16 84.2%	18 94.7%
<b>Improved</b>	6 33.3%	5 38.5%	1 6.7%	3 15.8%	1 5.3%
<b>Unchanged or Worse</b>	6 33.3%	1 7.7%	0 0.0%	0 0.0%	0 0.0%

Patient base: all patients who had a positive histology or cytology at baseline and received at least 10 doses of micafungin or discontinued due to treatment failure (per protocol set).

† Patient Number 101005 did not have clinical signs and symptoms of disease at baseline.

The end of therapy response was based on the last available post-baseline response up to 5 days after the last dose.

Positive clinical response: cleared or improved.

Cleared: resolution of clinical signs and symptoms.

Improved: reduction of clinical signs and symptoms.

Unchanged or worse: no change or progression of clinical signs or symptoms.

**Medical Officer Comments:** A clear dose-response was observed for clinical clearing of EC symptoms, with the lowest response rate in the 12.5 mg/day micafungin group, and the highest response rate in the 100 mg/day micafungin group. When the response was "cleared" or "improved" the dose response relationship was still present, but not as apparent (66.7 % cleared or improved in the 12.5 mg/day group compared to 92-93% in the 25 and 50 mg/day groups, and 100% in the 75 and 100 mg/day groups). A Cochran-Armitage test for trend demonstrated a statistically significant trend for the latter outcome.

**Minimal Effective Dose**

All of the doses tested met the criterion that treatment resulted in clinical cure or improvement in > 65% patients, so no minimal effective dose could be established.

**Medical Officer Comments:** In the 12.5 mg/day group, only 66.7% of patients had an overall positive clinical response, and only 33.3% had resolution of EC symptoms ("cleared"); while in the 25 mg/day group, 53.8% patients had resolution of EC symptoms, compared to 86.7% in

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*the 50 mg/day group. Thus, the minimal effective dose as defined by clinical "clearing" in > 65% patients would be in the range of 12.5 to 50 mg/day micafungin.*

## Secondary Efficacy Endpoints

### Changes in Esophageal Symptom Scores

Changes in EC symptom scores were generally the least in the 12.5 mg/day micafungin group, and the highest in the 100 mg/day group. These data are shown in the table below.

Table 8. Changes in Esophageal Symptom Score (PPS) at EOT

Parameter	Micafungin 12.5 mg/day N=18	Micafungin 25 mg/day N=13	Micafungin 50 mg/day N=15	Micafungin 75 mg/day N=19	Micafungin 100 mg/day N=19
Dysphagia score (mean ± SD)	-9 ± 1.1	-1.5 ± 0.9	-1.4 ± 0.7	-1.8 ± 1.0	-1.8 ± 0.8
Odynophagia score (mean ± SD)	-9 ± 1.2	-1.2 ± 0.9	-1.4 ± 0.6	-1.3 ± 1.2	-1.6 ± 1.0
Retrosternal pain score (mean ± SD)	-8 ± 1.2	-1.2 ± 1.0	-1.4 ± 0.7	-1.5 ± 0.9	-1.6 ± 1.0

SD = standard deviation

*Medical Officer Comments: Quantitative symptom scores may not be as useful as overall clinical judgment as to whether the patient has symptomatically cleared or improved.*

### Esophageal Mucosal Lesions

Endoscopic grade at the end of therapy is shown in the following table.

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Table 9. Endoscopic Response at End-of-Therapy (PPS) (data from Applicant's Table 13.4.5.2 study report, 24 April, 2004)

Baseline Endoscopic grade	Favorable Endoscopic Response (cleared or improved) at EOT				
	Micafungin 12.5 mg/day N=18	Micafungin 25 mg/day N=13	Micafungin 50 mg/day N=15	Micafungin 75 mg/day N=19	Micafungin 100 mg/day N=19
Grade 0	0/0	1*/1	0/0	0/0	0/0
Grade 1	2/2	1/1	5/5	3/3	3/3
Grade 2	2/3	2/3	5/6	9/9	2/2
Grade 3	8/13	8/8	4/4	7/7	13/19
Total patients with favorable endoscopic response	12/18 (66.7)	12/13 (92.3)	14/15 (93.3)	19/19 (100)	18/19 (94.7)
Baseline Endoscopic Grade	Endoscopic Resolution (cleared) at EOT				
Grade 0	0/0	0/1	0/0	0/0	0/0
Grade 1	1/2	1/1	5/5	2/3	3/3
Grade 2	2/3	2/3	4/6	8/9	2/2
Grade 3	3/13	4/8	4/4	6/7	12/19
Total patients with endoscopic resolution at baseline	6 (33.3)	7 (53.8)	13 (86.7)	16 (84.2)	17 (89.5)

\*at baseline 1 patient had no visible plaques on endoscopy, but had a positive histology and thus was included in the PPS.

*Medical Officer's Comments: Using either measure of a favorable endoscopic response ("cleared and improved" or "cleared") efficacy increased with micafungin dose. However, endoscopic resolution ("cleared") at the end-of-therapy is more discriminatory for potential differences between dosing groups than combining endoscopic clearing (grade 0) and improvement (the Applicant's stated secondary response measure). Notably, the differences in efficacy between doses are most apparent in patients with the most severe EC at baseline (grade 3). This endpoint supports the clinical endpoint (primary) in this study.*

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**Mycological Response**

Patients with mycological eradication (fungal culture and histology negative) or residual colonization (negative histology and positive fungal culture) had a favorable mycological response to therapy. Mycological response at EOT is shown in the table below.

Table 10. Mycological Response at EOT (PPS) (adapted from Applicant's Table 7, study report, 24 April, 2004)

	Micafungin Dose Level (mg/day)					Total (n=84)
	12.5 (n=18)	25.0 (n=13)	50.0 (n=15)	75.0 (n=19)	100.0 (n=19)	
<b>Eradication or Residual Colonization</b>	5 27.8%	0 0.0%	7 46.6%	14 73.7%	17 89.5%	43 51.2%
<b>Persistence (invasive)</b>	12 66.7%	9 69.2%	4 26.7%	4 21.1%	2 10.5%	31 36.9%
<b>Not Done†</b>	1 5.6%	4 30.8%	4 26.7%	1 5.3%	0 0.0%	10 11.9%

Patient base: all patients who had a positive histology or cytology at baseline and received at least 10 doses of micafungin or discontinued due to treatment failure (per protocol set).

Eradication: negative histology/culture and negative fungal culture result.

Residual colonization: negative histology/culture and positive fungal culture result.

Persistence (invasive): positive histology/culture and negative or positive fungal culture result.

Not done: Of the 10 patients who did not have an end of therapy histology or cytology, 6 patients had clearing and 4 patients had improvement of clinical signs and symptoms at the end of therapy. Two patients (numbers 301015 and 401007) did not have an end of therapy endoscopy performed. Of the 8 patient who had endoscopy performed at EOT, 3 patients had clearing of mucosal lesions, 1 had improvement, 3 patients had no change, and 1 patient had worsening of mucosal lesions at the end of therapy.

*Medical Officer Comment: This analysis supports the primary endpoint (clinical response), in that a dose-response was observed for mycological response. Eradication or residual colonization was higher as the micafungin dose increased with the exception of the 25 mg/day dosing group, where mycological success (eradication or colonization) was achieved in 0/13 patients; while in the 12.5 mg/day group, 5 of 18 patients had mycological success. This can most likely be explained by the small numbers of patients in each group, and the fact that 4 patients did not have mycological evaluation in the 25 mg/day group in comparison to only 1 patient the 12.5 mg/day group.*

**Overall Success of Treatment**

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Overall treatment success was defined as improvement or clearing in both clinical symptoms and endoscopic grade at the end of therapy. Overall success of therapy is shown in the following table.

Table 11. Overall Treatment Success (FAS and PPS) (adapted from applicant's Tables 13.4.13.1 and 13.4.13.2, study report, 24 April, 2004)

Overall Treatment Response	Micafungin 12.5 mg/day	Micafungin 25 mg/day	Micafungin 50 mg/day	Micafungin 75 mg/day	Micafungin 100 mg/day
FAS	N=26	N=22	N=26	N=22	N=24
Success	17 (65.4)	18 (81.8)	16 (61.5)	19 (86.4)	18 (75.0)
PPS	N=18	N=13	N=15	N=19	N=19
Success	13 (72.2)	11 (84.6)	12 (80.0)	18 (94.7)	17 (89.5)

*Medical Officer Comments: The dose-response relationship seen for other endpoints is not seen in this analysis. There may be a plateau effect at 75 and 100 mg/day. However, the numbers are small in this study, and small differences in the number of successes translate into larger proportional differences. Clearly, the 75 mg/day and 100 mg/day micafungin groups had higher response rates than the 12.5 mg, 25 mg and 50 mg/day treatment groups in the PPS. These differences are not as apparent for the FAS.*

**Relapse at 2 weeks Post-Treatment**

Relapse was evaluated in patients who had clearing or improvement of clinical symptoms of EC at the end of therapy, as shown in the applicant's analysis below. A total of 50% (38/76) patients remained free of EC signs and symptoms 2 weeks post-treatment.

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Table.12 Relapse of Esophageal Candidiasis at 2-weeks Post-Treatment (PPS) (Applicant's Table 8, study report, 24 April, 2004)

	FK463 Dose Level (mg/day)					
	12.5 (n=18)	25.0 (n=13)	50.0 (n=15)	75.0 (n=19)	100.0 (n=19)	Total (n=84)
End of Therapy Cleared or Improved	12	12	14	19	19	76
Relapse†	1/12 8.3%	2/12 16.7%	3/14 21.4%	4/19 21.1%	7/19 36.8%	17/76 22.4%
No Evidence of Disease at Week 2 Posttreatment	7/12 58.3%	4/12 33.3%	9/14 64.3%	11/19 57.9%	7/19 36.8%	38/76 50.0%

Patient base: all patients who had a positive histology or cytology at baseline and received at least 10 doses of FK463 or discontinued due to treatment failure (per protocol set).

† Patients who experienced either recurrence or worsening of disease following the end of therapy assessment.

Cleared: resolution of clinical signs and symptoms.

Improved: reduction of clinical signs and symptoms.

*Medical Officer's Comments: In this analysis, the relapse rate increased with increasing micafungin dose. In the medical officer's opinion, relapse analysis is more appropriate in the subset of patients who had resolution of EC signs and symptoms ("cleared") at EOT, rather than in those who were clinically "cleared or improved", as discussed below.*

In the PPS, 34/60 (56.7%) patients who were clinically cleared at the EOT, remained disease-free at 2 weeks post-treatment; while 16/60 (26.7%) patients had EC recurrence, and 10/60 (16.7%) patients were not evaluated. In the medical officer's analysis below, patients who had documented EC recurrence or patients who were not evaluated were counted as relapses, totaling 26/60 (43.3%) overall.

In the FAS, of the 80 patients who were clinically cleared at the EOT, 49 (61.3%) remained disease-free at 2 weeks post-treatment, 17/80 (21.3%) had documented EC recurrence, 14/80 (17.5%) were not evaluated. When patients with documented recurrence and patients not evaluated were counted as relapses, 31/80 (38.8%) patients overall relapsed at 2 weeks post-treatment. The following table shows the EC status at 2-weeks post-treatment for those who had clinical "clearing" at the end-of-therapy.

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Table 12. Relapse of Esophageal Candidiasis (in patients who had clinical resolution of EC at EOT) (FAS and PPS) (adapted from applicant's Tables 13.4.7.1 and 13.4.7.2)

Analysis Population	Clinical status 2 weeks post-treatment	Micafungin 12.5 mg/day	Micafungin 25 mg/day	Micafungin 50 mg/day	Micafungin 75 mg/day	Micafungin 100 mg/day	Total
PPS		N=6	N=7	N=13	N=16	N=18	N=60
	No disease	4 (66.7%)	3 (42.9 %)	9 (69.3%)	11 (68.8%)	7 (38.9%)	34 (56.7%)
	Recurrence	1 (16.7%)	1 (14.3%)	3 (23.1%)	4 (25.0%)	7 (38.8%)	16 (26.6%)
	Not evaluated	1 (16.7%)	3 (42.9%)	1 (7.7%)	1 (6.3%)	4 (22.2%)	10 (16.7%)
	<b>Total Relapse*</b>	<b>2 (33.3)</b>	<b>4 (57.1)</b>	<b>4 (30.8)</b>	<b>5 (31.3)</b>	<b>11 (61.1)</b>	<b>26 (43.3%)</b>
FAS		N=9	N=13	N=19	N=18	N=21	N=80
	No disease	7 (77.8%)	9 (69.2%)	13 (68.4%)	12 (66.7%)	8 (38.1%)	49 (31.0%)
	Recurrence	1 (11.1%)	1 (7.7%)	4 (21.1%)	4 (22.2%)	7 (33.3%)	17 (21.3%)
	Not evaluated	1 (11.1%)	3 (23.1%)	2 (10.5%)	2 (11.1%)	6 (28.6%)	14 (17.5%)
	<b>Total Relapse*</b>	<b>2 (22.2)</b>	<b>4 (30.8)</b>	<b>6 (31.5)</b>	<b>6 (33.3)</b>	<b>13 (61.9)</b>	<b>31 (38.8%)</b>

N= number of patients who had clinical resolution ("cleared") EC at EOT

*Medical Officer Comments: In this analysis, relapse rates (including missing values as relapse) had no relationship to micafungin dose in either analysis population, the FAS or PPS. This may be due, in part, to the relatively small numbers of patients in each treatment group and the even smaller numbers of patients cleared or improved at EOT.*

*These relapse rates do not reflect use of systemic antifungal agents in the post-treatment period, and patients who received systemic antifungal therapy, either for prophylaxis or treatment, should be considered as having EC relapse, as was done in studies 03-7-005 and FG463-21-09. These relapse rates are higher than that observed in those studies, probably because the 150 mg/day micafungin dose was not used in this study.*

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### Efficacy Conclusions:

1. Micafungin was effective for treatment of esophageal candidiasis, with a dose-response relationship noted for the primary endpoint (clinical clearing or improvement at the end-of-therapy), but was more pronounced when clinical resolution of symptoms at the end-of-therapy was used as the endpoint.
2. The secondary study endpoints, endoscopic response, mycological response, and overall treatment response, all supported the conclusion drawn with the primary endpoint, clinical response at end-of-therapy.
3. Relapse rates in patients who had clinical resolution of EC at end-of-therapy occurred in 38.8% patients in the FAS, and in 43.3% patients overall in the PPS. There was no obvious micafungin treatment dose relationship for EC relapse.

### Safety Evaluation

#### Drug Exposure

A summary of micafungin exposure in the FAS is shown in the table below. The overall mean duration of micafungin therapy was 13.2 days, and was similar for each of the treatment groups. The median duration of therapy was 14.0 days overall, and for each of the treatment groups except for the 100 mg/day dose (median 12.0 days).

Table 13. Summary of Micafungin Exposure (FAS) (adapted from Applicant's Table 13.3.1, study report 24 April, 2004)

Parameter	Micafungin 12.5 mg/day N=26	Micafungin 25 mg/day N=22	Micafungin 50 mg/day N=26	Micafungin 75 mg/day N=22	Micafungin 100 mg/day N=24	Micafungin Total N=120
Mean days of Micafungin (mean $\pm$ SD)	12.6 $\pm$ 5.6	13.5 $\pm$ 3.7	12.3 $\pm$ 5.8	15.5 $\pm$ 5.1	12.3 $\pm$ 4.3	13.2 $\pm$ 5.1
Median days micafungin (range)	14.0 (1-21)	14.0 (5-21)	14.0 (1-23)	14.0 (3-21)	12.0 (3-21)	14.0 (1-23)
Cumulative dose micafungin (mean $\pm$ SD)	152.9 $\pm$ 70.6	323.9 $\pm$ 89.1	596.2 $\pm$ 267.2	1142.0 $\pm$ 384.5	1220.8 $\pm$ 431.4	675.2 $\pm$ 513.4

SD = standard deviation

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**Medical Officer Comments:** *The maximum duration of therapy under the study protocol was 21 days, and in the 50 mg/day group the maximum range of therapy was 23 days, so a protocol violation likely occurred in that group.*

## Adverse Events

Adverse events were evaluated in all patients who received at least 1 dose of micafungin, who comprised the FAS. Adverse events that occurred in the study are categorized in the following table. Drug-relatedness was determined by the investigator, and included those events possibly or probably related to study drug.

Table 14. Summary of Adverse Events (AEs) in FAS (adapted from Applicant's Tables 13.5.1.1, 13.5.2.1, 13.5.3.1, 13.5.4.1, 13.5.3.2, 13.5.4.2, and 13.5.5)

Safety Parameter	Micafungin 12.5 mg/day N=26	Micafungin 25 mg/day N=22	Micafungin 50 mg/day N=26	Micafungin 75 mg/day N=22	Micafungin 100 mg/day N=24	Micafungin Total N=120
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
All AEs	15 (57.7)	16 (72.7)	20 (76.9)	18 (81.8)	21 (87.5)	90 (75.0)
Drug-related AEs	7 (26.9)	8 (36.4)	8 (30.8)	3 (13.6)	9 (37.5)	35 (29.2)
SAEs	3 (11.5)	3 (13.6)	4 (15.4)	4 (18.2)	4 (16.7)	18 (15.0)
Drug-related SAEs	1 (3.8)	0	0	0	0	1 (0.8)
Discontinuations due to AEs	2 (7.7)	2 (9.1)	5 (19.2)	3 (13.6)	4 (16.7)	16 (13.3)
Discontinuations due to drug- related AEs	0	0	1 (3.8)	0	1 (4.2)	2 (1.7)
Deaths (total)	3 (11.5)	3 (13.6)	2 (7.7)	2 (9.1)	3 (12.5)	13 (10.8)

SAE= serious adverse event

**Medical Officer Comments:** *A dose relationship was noted for all adverse events, and serious adverse events, with an increasing proportion of patients experiencing adverse events with increasing micafungin dose for these parameters. There was no apparent dose-relationship for drug-related adverse events, discontinuations, or deaths.*

## All Adverse Events

The following table lists all adverse events which occurred in this study. A total of 90/120 (75.0%) patients overall had at least one adverse event. The proportion of patients with at least one adverse event increased slightly with each higher micafungin dose.

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Table 15. Incidence of Adverse Events in FAS (Applicant's Table 13.5.1.1, study report, 24 April, 2004)

COSTART BODY SYSTEM (1)	COSTART TERM	FK463 DOSE LEVEL					TOTAL (N=120)
		12.5 mg/DAY (N=26)	25.0 mg/DAY (N=22)	50.0 mg/DAY (N=26)	75.0 mg/DAY (N=22)	100.0 mg/DAY (N=24)	
ANY AE		15 (57.7%)	16 (72.7%)	20 (76.9%)	19 (81.8%)	21 (87.5%)	90 (75.0%)
BODY AS A WHOLE	ANY AE	2 ( 7.7%)	8 (36.4%)	8 (30.8%)	8 (36.4%)	14 (58.3%)	40 (33.3%)
	FEVER	0	3 (13.6%)	3 (11.5%)	3 (13.6%)	9 (37.5%)	18 (15.0%)
	CHILLS	0	1 ( 4.5%)	2 ( 7.7%)	1 ( 4.5%)	3 (12.5%)	7 ( 5.8%)
	ABDOMINAL PAIN	1 ( 3.8%)	1 ( 4.5%)	0	2 ( 9.1%)	1 ( 4.2%)	5 ( 4.2%)
	SEPSIS	0	2 ( 9.1%)	2 ( 7.7%)	0	1 ( 4.2%)	5 ( 4.2%)
	BACK PAIN	0	0	2 ( 7.7%)	2 ( 9.1%)	0	4 ( 3.3%)
	CELLULITIS	2 ( 7.7%)	1 ( 4.5%)	1 ( 3.8%)	0	0	4 ( 3.3%)
	ASTHENIA	0	1 ( 4.5%)	0	1 ( 4.5%)	0	2 ( 1.7%)
	FLU SYNDROME	0	0	0	1 ( 4.5%)	1 ( 4.2%)	2 ( 1.7%)
	NECK PAIN	0	0	0	1 ( 4.5%)	1 ( 4.2%)	2 ( 1.7%)
	ABSCESS	0	0	0	1 ( 4.5%)	0	1 ( 0.8%)
	AIDS	0	1 ( 4.5%)	0	0	0	1 ( 0.8%)
	ALLERGIC REACTION	0	0	0	0	1 ( 4.2%)	1 ( 0.8%)
	INFECTION	0	0	0	1 ( 4.5%)	0	1 ( 0.8%)
	PRURITUS	0	0	0	0	1 ( 4.2%)	1 ( 0.8%)
	PAIN	0	1 ( 4.5%)	0	0	0	1 ( 0.8%)
	PROCEDURAL COMPLICATION	0	0	1 ( 3.8%)	0	0	1 ( 0.8%)
	TUBERCULOSIS REACTIVATED	0	0	0	0	1 ( 4.2%)	1 ( 0.8%)
CARDIOVASCULAR SYSTEM	ANY AE	2 ( 7.7%)	3 (13.6%)	7 (26.9%)	2 ( 9.1%)	6 (25.0%)	20 (16.7%)
	PHLEBITIS	1 ( 3.8%)	0	1 ( 3.8%)	1 ( 4.5%)	2 ( 8.3%)	5 ( 4.2%)
	TACHYCARDIA	0	1 ( 4.5%)	1 ( 3.8%)	0	3 (12.5%)	5 ( 4.2%)
	CHEST PAIN	0	0	2 ( 7.7%)	1 ( 4.5%)	0	3 ( 2.5%)
	VASODILATION	1 ( 3.8%)	0	1 ( 3.8%)	0	1 ( 4.2%)	3 ( 2.5%)
	HYPERTENSION	0	1 ( 4.5%)	1 ( 3.8%)	0	0	2 ( 1.7%)
	HYPOTENSION	0	1 ( 4.5%)	0	0	1 ( 4.2%)	2 ( 1.7%)
	PALPITATION	0	0	1 ( 3.8%)	1 ( 4.5%)	0	2 ( 1.7%)
	DEEP THROMBOPHLEBITIS	0	0	1 ( 3.8%)	0	0	1 ( 0.8%)
	SYNCOPE	0	0	1 ( 3.8%)	0	0	1 ( 0.8%)
	VASCULAR HEADACHE	0	0	1 ( 3.8%)	0	0	1 ( 0.8%)
DIGESTIVE SYSTEM	ANY AE	8 (30.8%)	7 (31.8%)	10 (38.5%)	10 (45.5%)	9 (37.5%)	44 (36.7%)
	DIARRHEA	3 (11.5%)	1 ( 4.5%)	3 (11.5%)	7 (31.8%)	3 (12.5%)	17 (14.2%)
	VOMITING	2 ( 7.7%)	2 ( 9.1%)	3 (11.5%)	2 ( 9.1%)	6 (25.0%)	15 (12.5%)
	NAUSEA	1 ( 3.8%)	4 (18.2%)	3 (11.5%)	1 ( 4.5%)	4 (16.7%)	13 (10.8%)
	LIVER FUNCTION TESTS ABNORMAL	3 (11.5%)	4 (18.2%)	2 ( 7.7%)	0	0	9 ( 7.5%)
	DYSPEPSIA	0	0	2 ( 7.7%)	0	0	2 ( 1.7%)
	GASTROINTESTINAL HEMORRHAGE	1 ( 3.8%)	0	0	1 ( 4.5%)	0	2 ( 1.7%)

(1) WITHIN A BODY SYSTEM PATIENTS MAY REPORT MORE THAN ONE ADVERSE EVENT.

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COSTART BODY SYSTEM (1)	COSTART TERM	FKM3 DOSE LEVEL					TOTAL (N=120)	
		12.5 mg/DAY (N=26)	25.0 mg/DAY (N=22)	50.0 mg/DAY (N=26)	75.0 mg/DAY (N=22)	100.0 mg/DAY (N=24)		
DIGESTIVE SYSTEM	RECTAL DISORDER	0	0	0	2 ( 9.1%)	0	2 ( 1.7%)	
	CONSTIPATION	0	0	1 ( 3.8%)	0	0	1 ( 0.8%)	
	GASTROENTERITIS	0	0	0	0	1 ( 4.2%)	1 ( 0.8%)	
	GASTROINTESTINAL DISORDER	1 ( 3.8%)	0	0	0	0	1 ( 0.8%)	
	GINGIVITIS	1 ( 3.8%)	0	0	0	0	1 ( 0.8%)	
	HEPATITIS	0	0	0	0	1 ( 4.2%)	1 ( 0.8%)	
	MOUTH ULCERATION	1 ( 3.8%)	0	0	0	0	1 ( 0.8%)	
	PEPTIC ULCER HEMORRHAGE	1 ( 3.8%)	0	0	0	0	1 ( 0.8%)	
	VIRAL HEPATITIS	0	1 ( 4.5%)	0	0	0	1 ( 0.8%)	
HEMIC AND LYMPHATIC SYSTEM	ANY AE	0	3 (13.6%)	0	4 (18.2%)	0	7 ( 5.8%)	
	ANEMIA	0	2 ( 9.1%)	0	2 ( 9.1%)	0	4 ( 3.3%)	
	LEUKOPENIA	0	0	0	2 ( 9.1%)	0	2 ( 1.7%)	
	LYMPHADENOPATHY	0	1 ( 4.5%)	0	1 ( 4.5%)	0	2 ( 1.7%)	
INJECTION SITE REACTION	ANY AE	1 ( 3.8%)	0	0	0	0	1 ( 0.8%)	
	INJECTION SITE PAIN	1 ( 3.8%)	0	0	0	0	1 ( 0.8%)	
METABOLIC AND NUTRITIONAL DISORDERS	ANY AE	1 ( 3.8%)	5 (22.7%)	1 ( 3.8%)	0	5 (20.8%)	12 (10.0%)	
	ALKALINE PHOSPHATASE INCREASED	0	1 ( 4.5%)	0	0	2 ( 8.3%)	3 ( 2.5%)	
	HYPOKALEMIA	0	2 ( 9.1%)	0	0	1 ( 4.2%)	3 ( 2.5%)	
	DEHYDRATION	1 ( 3.8%)	0	0	0	1 ( 4.2%)	2 ( 1.7%)	
	HYPERKALEMIA	0	0	0	0	2 ( 8.3%)	2 ( 1.7%)	
	SCOT INCREASED	0	2 ( 9.1%)	0	0	0	2 ( 1.7%)	
	HYPERNATREMIA	0	0	0	0	1 ( 4.2%)	1 ( 0.8%)	
	HYPOGLYCEMIA	0	1 ( 4.5%)	0	0	0	1 ( 0.8%)	
	THIRST	0	0	1 ( 3.8%)	0	0	1 ( 0.8%)	
	UREMIA	0	0	0	0	1 ( 4.2%)	1 ( 0.8%)	
	MUSCULOSKELETAL SYSTEM	ANY AE	0	2 ( 9.1%)	1 ( 3.8%)	0	0	3 ( 2.5%)
		CRAMPS	0	1 ( 4.5%)	1 ( 3.8%)	0	0	2 ( 1.7%)
		ARTHRALGIA	0	1 ( 4.5%)	0	0	0	1 ( 0.8%)
SYNOVITIS		0	1 ( 4.5%)	0	0	0	1 ( 0.8%)	
NERVOUS SYSTEM		ANY AE	3 (11.5%)	5 (22.7%)	7 (26.9%)	4 (18.2%)	8 (33.3%)	27 (22.5%)
	HEADACHE	2 ( 7.7%)	4 (18.2%)	3 (11.5%)	3 (13.6%)	4 (16.7%)	16 (13.3%)	
	CONFUSION	0	1 ( 4.5%)	0	1 ( 4.5%)	1 ( 4.2%)	3 ( 2.5%)	
	CONVULSION	0	0	1 ( 3.8%)	1 ( 4.5%)	0	2 ( 1.7%)	

(1) WITHIN A BODY SYSTEM PATIENTS MAY REPORT MORE THAN ONE ADVERSE EVENT.

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Clinical Review

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

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

Table 15. (continued) Incidence of Adverse Events in FAS (continued) (Applicant's Table 13.5.1.1, study report, 24 April, 2004)

COSTART BODY SYSTEM (1)	COSTART TERM	FM463 DOSE LEVEL					TOTAL (N=120)
		12.5 mg/DAY (N=26)	25.0 mg/DAY (N=22)	50.0 mg/DAY (N=26)	75.0 mg/DAY (N=22)	100.0 mg/DAY (N=24)	
NERVOUS SYSTEM	DISSIMISS	0	0	1 (3.8%)	0	1 (4.2%)	2 (1.7%)
	NEUROUSNESS	0	0	0	0	2 (8.3%)	2 (1.7%)
	PARAESTHESIA	0	0	1 (3.8%)	1 (4.5%)	0	2 (1.7%)
	THINKING ABNORMAL	0	0	2 (7.7%)	0	0	2 (1.7%)
	ANXIETY	0	0	1 (3.8%)	0	0	1 (0.8%)
	DEPRESSION	0	0	0	0	1 (4.2%)	1 (0.8%)
	DYSTONIA	0	1 (4.5%)	0	0	0	1 (0.8%)
	GRAND MAL CONVULSION	0	0	0	0	1 (4.2%)	1 (0.8%)
	NEUROPATHY	1 (3.8%)	0	0	0	0	1 (0.8%)
	SLEEP DISORDER	0	0	0	0	1 (4.2%)	1 (0.8%)
RESPIRATORY SYSTEM	ANY AE	2 (7.7%)	1 (4.5%)	7 (26.9%)	3 (13.6%)	10 (41.7%)	23 (19.2%)
	PNEUMONIA	2 (7.7%)	1 (4.5%)	2 (7.7%)	2 (9.1%)	2 (8.3%)	9 (7.5%)
	COUGH INCREASED	0	0	1 (3.8%)	2 (9.1%)	2 (8.3%)	5 (4.2%)
	PULMONARY TUBERCULOSIS	0	0	1 (3.8%)	0	4 (16.7%)	5 (4.2%)
	REACTIVATED						
	RHEUMATISM	0	0	2 (7.7%)	0	1 (4.2%)	3 (2.5%)
	DYSPIA	0	0	1 (3.8%)	0	1 (4.2%)	2 (1.7%)
	RESPIRATORY DISORDER	0	0	0	0	2 (8.3%)	2 (1.7%)
	BRONCHITIS	0	0	1 (3.8%)	0	0	1 (0.8%)
	PULMONARY EMBOLUS	0	0	0	1 (4.5%)	0	1 (0.8%)
	RESPIRATORY FAILURE	0	0	0	0	1 (4.2%)	1 (0.8%)
	RHINITIS	0	0	1 (3.8%)	0	0	1 (0.8%)
	SINUSITIS	0	0	0	0	1 (4.2%)	1 (0.8%)
	SKIN AND APPENDAGES	ANY AE	1 (3.8%)	1 (4.5%)	3 (11.5%)	3 (13.6%)	5 (20.8%)
RASH		0	1 (4.5%)	3 (11.5%)	2 (9.1%)	2 (8.3%)	8 (6.7%)
HERPES SIMPLEX		1 (3.8%)	0	0	0	1 (4.2%)	2 (1.7%)
SWEATING		0	0	1 (3.8%)	1 (4.5%)	0	2 (1.7%)
PRURITUS		0	0	0	1 (4.5%)	0	1 (0.8%)
URTICARIA		0	0	0	0	1 (4.2%)	1 (0.8%)
VESTITULOBULLOUS RASH		0	0	0	0	1 (4.2%)	1 (0.8%)
SPECIAL SENSES		ANY AE	2 (7.7%)	0	3 (11.5%)	0	0
	OTITIS MEDIA	2 (7.7%)	0	1 (3.8%)	0	0	3 (2.5%)
	EAR PAIN	0	0	1 (3.8%)	0	0	1 (0.8%)
	TASTE DERIVERSION	0	0	1 (3.8%)	0	0	1 (0.8%)
	VESTIBULAR DISORDER	0	0	1 (3.8%)	0	0	1 (0.8%)
UROGENITAL SYSTEM	ANY AE	0	1 (4.5%)	1 (3.8%)	1 (4.5%)	2 (8.3%)	5 (4.2%)

(1) WITHIN A BODY SYSTEM PATIENTS MAY REPORT MORE THAN ONE ADVERSE EVENT.

COSTART BODY SYSTEM (1)	COSTART TERM	FM463 DOSE LEVEL					TOTAL (N=120)
		12.5 mg/DAY (N=26)	25.0 mg/DAY (N=22)	50.0 mg/DAY (N=26)	75.0 mg/DAY (N=22)	100.0 mg/DAY (N=24)	
UROGENITAL SYSTEM	URINARY TRACT INFECTION	0	0	1 (3.8%)	0	1 (4.2%)	2 (1.7%)
	CYSTITIS	0	0	0	1 (4.5%)	0	1 (0.8%)
	KIDNEY FAILURE	0	1 (4.5%)	0	0	0	1 (0.8%)
	KIDNEY PAIN	0	0	0	0	1 (4.2%)	1 (0.8%)
	PYELONEPHRITIS	0	0	0	0	1 (4.2%)	1 (0.8%)

**Medical Officer Comments:** There was no clear relationship between micafungin dose and any specific adverse event, although some events occurred at somewhat higher frequencies with the 100 mg/day dose (fever, tachycardia, vomiting, pulmonary tuberculosis), than with the lower doses of micafungin.

**Common Adverse Events**

The most common adverse events were fever (15.0%), diarrhea (14.2%), headache (13.3%), vomiting (12.5%), and nausea (10.8%). Common adverse events are shown in the table below.

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