

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

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STATISTICAL REVIEW AND EVALUATION CLINICAL STUDIES

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

A Phase 2 dose ranging study demonstrated a clear dose response across three micafungin doses (50 mg/day, 100 mg/day and 150 mg/day) in the rate of endoscopic cure for the treatment of esophageal candidiasis (EC). Micafungin dosed at 150 mg/day resulted in similar rates of endoscopic cure and EC relapse at 2 weeks compared to fluconazole 200 mg/day. The overall oropharyngeal candidiasis (OPC) relapse rates at 2 weeks post-treatment decreased as a function of increased micafungin dose. OPC relapse in the micafungin 150 mg dose group was numerically but not statistically greater than fluconazole 200 mg.

A single Phase 3 study demonstrated that micafungin 150 mg/day is non-inferior to fluconazole 200 mg/day in rate of endoscopic cure based on a pre-specified non-inferiority margin of 10%. EC relapse rates at two and four weeks post treatment were similar between treatment groups and commensurate to previously studied therapies for the treatment of EC. OPC relapse rates among patients cured of baseline EC and OPC signs and symptoms were statistically greater in the micafungin group compared to the fluconazole group in this study. At 4 weeks post-treatment, the rate of confirmed OPC relapse was 34.1% in the micafungin 150 mg group compared to 17.1% in the fluconazole group [95% CI around difference between micafungin and fluconazole was (8.0, 25.9)]. Sensitivity analyses including missing, death and use of antifungal therapy as relapse criteria resulted in 4 week post-treatment OPC relapse rates of 49.7% and 37.7% in the micafungin and fluconazole groups respectively resulting in a 95% CI of 1.8 to 22.3.

Based on the findings from the single Phase 3 study with supportive evidence gathered from the Phase 2 dose-ranging study, micafungin 150 mg/day appears to be as efficacious as comparator fluconazole for the treatment of EC with similar levels of EC relapse. OPC relapse rates however were shown to be statistically greater among patients treated with the proposed micafungin 150 mg/day dose compared to fluconazole 200 mg/day in the pivotal Phase 3 study. Based on efficacy, this reviewer recommends approving the micafungin 150 mg dose for treatment of EC noting ~~greater~~ greater rates of OPC relapse in the clinical section of the product label.

1.2 Brief Overview of Clinical Studies

This submission contains two randomized, controlled studies that evaluated the proposed 150 mg/day micafungin dose for treatment of EC. Study FG-463-21-09 (FG09) was a Phase II dose response, multi-center, prospective, randomized, double-blind study in adult HIV patients with confirmed esophageal candidiasis. Patients were randomized to receive either intravenous micafungin 50 mg/day, 100 mg/day, or 150 mg/day or intravenous fluconazole 200 mg/day in a 1:1:1:1 fashion and were treated for 14-21 days. The primary efficacy endpoint was endoscopic cure (mucosal grade 0) based on endoscopic assessment obtained \pm 5 days from the last dose of study drug in the full analysis set. The primary efficacy analysis consisted of evaluating the efficacy success rate among all three micafungin groups proceeded by pair-wise comparisons using the Closed Test Procedure (CTP) to measure for a dose response. No formal hypothesis comparing micafungin to comparator was specified. Relapse in clinical signs and symptoms was evaluated two weeks post-treatment in patients who were overall therapeutic successes at end of therapy (EOT).

Study 03-7-005 (005) was a Phase III, multi-center, multi-national, randomized, double-blind, non-inferiority study comparing micafungin treatment of 150 mg/day i.v. to fluconazole treatment of 200 mg/day i.v. for treatment of EC. Treatment was given for a minimum of 14 days or for 7 days following resolution of all clinical symptoms of EC up to a maximum of 42 days. Similar to study FG09, the primary efficacy endpoint was endoscopic cure (grade 0) at the end of therapy visit in the full analysis set. The pre-specified margin to demonstrate non-inferiority of micafungin to fluconazole was 10%. Relapse in clinical signs and symptoms and endoscopic grade was evaluated at 2 and 4 weeks post-therapy in patients who were overall therapeutic successes (clinical and endoscopic cure or improvement) at EOT.

1.3 Statistical Issues and Findings

The following issues were identified during this review:

- There was variation in how the Sponsor defined the population to evaluate relapse at 2 weeks in protocol and final results presented in the clinical study report (CSR) for study FG09. The protocol states that relapse was to be evaluated in patients who were overall therapeutic successes at EOT (i.e. were clinically and endoscopically cured or improved), however the EC relapse results presented in the CSR are in patients who were only clinically and endoscopically cured at EOT. The implication of this apparent deviation is nominal since qualitatively it does not change the conclusions. Furthermore, the medical and statistical reviewers have agreed that the patient population who were only cured clinically and endoscopically at EOT is the most appropriate to evaluate relapse.
- There were several missed endoscopic and clinical assessments at end of study in both study FG09 and study 005 mostly in patients who prematurely discontinued treatment due to an adverse event. These patients are treated as failures in the primary analysis.
- Use of antifungal therapy for either prophylaxis or treatment was reported for several patients during the follow-up period for both studies FG09 and 005. Only study FG09 required that use of non-prophylactic antifungal therapy during the follow-up period be criteria to count the patient as a relapse. Study 005 did not stipulate that use of antifungal therapy during the follow-up periods as criteria to determine relapse. In this review, several analyses are presented that consider the use of any antifungal therapy during the follow-up phase as criteria for both EC and OPC relapse since use of such treatment can greatly confound relapse outcomes.

2. INTRODUCTION

2.1 Overview

Esophageal candidiasis (EC) is a serious fungal infection of the esophagus marked clinically by difficult and painful swallowing (dysphagia and odynophagia), midline or retrosternal pain. EC is diagnosed endoscopically by the appearance of mucosal lesions. EC occurs in immunocompromised patients, particularly patients infected with HIV. The incidence of EC is 3%-10% in HIV-infected patients and is considered to be the second most common AIDS-defining disease after *Pneumocystis carinii* pneumonia².

Drugs currently marketed and FDA approved for the treatment of EC include Cancidas® (caspofungin acetate), Diflucan® (fluconazole), Sporanox® (itraconazole) and VFEND® (voriconazole).

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Mycamine (micafungin sodium) is the second (the first is caspofungin) in a new class of antifungals known as echinocandins. Echinocandins are semisynthetic lipopeptides with potent and broad-spectrum antifungal activity. Their activity is due to the presence of a synthetic cell-wall enzyme complex β -1, 3-D-glucan synthase, which acts by inhibiting the large polysaccharide β -1, 3-D-glucan (an essential component of the fungi cell wall providing rigidity and osmotic and structural integrity) leading to cell and eventual fungal death¹. Unlike fungal cells, human cells lack in a cell-wall thus making echinocandins good targets for fungal infections in humans.

The Sponsor conducted four clinical studies (study 97-7-003, study 98-0-047, study FG-463-21-09, and study 03-7-005) to evaluate the efficacy of micafungin in the treatment of EC. Study 98-7-003 was a multi-center study to determine the minimal effective dose and dose response of micafungin given at doses from 12.5 mg/day to 100 mg/day. Study 98-0-047 was a large non-comparative study in patients with candidemia and invasive candidiasis, which enrolled 99 patients with EC. Study FG-463-21-09 (hereafter referred to as study FG09) was a randomized, double-blind, active control, phase 2 dose response study that evaluated micafungin given at doses of 50 mg/day, 100 mg/day and 150 mg/day versus fluconazole given at 200 mg/day (approved dose) over a 14-21 day treatment period. Study 03-7-005 (hereafter referred to as Study 005) was a Phase III, randomized, double-blind, non-inferiority study of 150 mg/day micafungin versus 200 mg/day fluconazole given over a 14-21 day treatment period. A summary of these studies is in the following table:

Table 2.1 Listing of EC Studies

Protocol	Study Design	No. Randomized	Phase	Micafungin dose(s) studied mg/day	Comparator and Dose
97-7-003	MC, OL, DE	120	2	12.5, 25, 50, 75, 100	None
98-0-047	MC, OL	99*	2	50, 100	None
FG-463-21-09	MC, R, DB, AC, DR	251	2	50, 100, 150	Fluconazole 200 mg/day
03-7-005	MC, R, DB, AC	523	3	150	Fluconazole 200 mg/day

MC=multi-center, OL=open-label, DE=dose escalation, R=randomized, DB=double-blind, AC=active control

*Represents the number of patients in the per protocol population with confirmed EC (study randomized a total of 357 patients. Study was in IC and candidemia)

This review will not discuss studies 97-7-003 and 98-0-047 since neither study contained a control group nor did either study evaluate the proposed micafungin dose of 150 mg/day.

2.2 Data Sources

Studies FG09, 003 and 047 data sets analyzed during this review are located in the EDR at the following link:

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Clinical study reports for studies FG09, 003, and 047 and integrated summaries are located in the EDR at the following link:

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Study 005 was submitted with the 120-day safety update to the NDA. Data sets analyzed and the clinical study report for study 005 are located at:

\\Cdsub1\n21754\N_000\2004-08-24\UPDATE\CRT\005

\\Cdsub1\n21754\N_000\2004-08-24\UPDATE\005

FDA requested datasets:

\\Cdsub1\n21754\N_000\2005-01-10\CRT

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study Design and Endpoints

3.1.1.1 Study FG463-21-09

Study FG09 was a Phase II dose response, multi-center, prospective, randomized, double-blind study in adult HIV patients with confirmed EC. Patients were randomized to receive either intravenous micafungin 50 mg/day, 100 mg/day, or 150 mg/day or intravenous fluconazole 200 mg/day in a 1:1:1:1 fashion. Patients were treated for a minimum of 14 days and a maximum of 21 days.

Eligible patients included those with confirmed EC (histological/cytological confirmation from esophageal brushings and biopsy required at baseline but the patient could be enrolled while results were pending), age 18 years or older with a prior diagnosis of AIDS or HIV positive, no evidence of liver disease or significant renal impairment, no concomitant esophagitis caused by herpes simplex or CMV, had not received topical antifungal within 48 hrs or a systemic antifungal within 72 hrs of treatment initiation, had a life expectancy greater than 2 months, did not have EC caused by a fluconazole-resistant strain of *Candida*, and did not experience more than 3 episodes of EC requiring antifungal therapy.

Endoscopy with biopsy, brushings and fungal culture was performed at baseline (≤ 48 hrs before treatment initiation), on day 14 of treatment and EOT. Mycological assessments were made on day 14 of treatment and on EOT. Clinical assessments were made at baseline, days 3, 7, and 14 of treatment, EOT and 2-weeks post-treatment (End of Study visit). Relapse of clinical signs or symptoms was assessed at 2 week post-treatment. No endoscopy was performed at follow-up.

The primary efficacy endpoint was **endoscopic response rate**, defined as the proportion of patients with an **endoscopic grade of 0 or cleared at the EOT visit**.

Secondary efficacy assessments included the following:

- Incidence of **relapse** in patients who were overall therapeutic successes 2 weeks post-treatment. Relapse was defined as recurrence of EC as assessed by **clinical symptoms** or if the patient had received antifungal therapy during the 2 week follow-up.
- Overall therapeutic success defined as resolution or improvement in both clinical signs and endoscopic grades from baseline to EOT. Improvement of clinical signs and symptoms is defined

by reduction of 2 or more grades or the achievement of grade 0, for at least one symptom.

Improvement in endoscopic assessment is defined as an improvement of at least one grade.

- Endoscopic grade of 0 on Day 14 of treatment
- Mycological response (eradication or residual colonization) on Day 14 of treatment and at EOT
- Clinical response of 0 at EOT and at 2 week post-treatment
- Changes in the quantitative endoscopic assessment of EC compared to baseline
- Changes in the quantitative clinical assessment of EC (scores for dysphagia, odynophagia and retrosternal pain) compared to baseline
- Changes in the quantitative clinical assessment of OPC (scores for fissures, mouth pain, inflammation and plaques) compared to baseline (if applicable)
- Incidence of disease progression at EOT (clinical and endoscopic assessment) compared to baseline

Study populations as defined in the protocol include:

The **full analysis set (FAS)** consists of all randomized patients who received at least one dose of study drug. **This set is defined as the primary efficacy and safety set.**

The **per protocol set (PPS)** consists of all patients with confirmed EC who had an endoscopic assessment at baseline and end of therapy, did not receive a prohibited concomitant antifungal therapy before end of therapy, and received study drug for at least 10 days. The set is defined as a secondary analysis set.

The **confirmed EC set** consists of all patients with confirmed EC (endoscopic assessment >0 at baseline) who received at least one dose of study drug. This set is defined as a secondary analyses set.

3.1.1.2 Study 03-7-005

Study 005 was a Phase 3, multi-center, multi-national, randomized, double-blind, non-inferiority study comparing micafungin treatment of 150 mg/day i.v. to fluconazole treatment of 200 mg/day i.v. for treatment of EC. Treatment was given for a minimum of 14 days or for 7 days after resolution of all clinical symptoms of EC up to a maximum of 42 days. Patients enrolled included male or female adults (age 16 years or older) with EC confirmed (within 5 days prior to the first dose of study drug) by endoscopy and documented by clinical symptoms (e.g. dysphagia, odynophagia, and retrosternal pain). Histological and cytological and fungal culture confirmation for esophageal brushings and biopsy were required but could be pending at the time of study drug initiation. Patients who were pregnant or lactating, had evidence of liver disease, had another opportunistic fungal infections and/or were receiving acute systemic therapy for fungal infection, had received previous antifungal therapy within 48 (topical) to 72 (intravenous) hrs, or who had a history of more than two episodes of EC requiring systemic antifungal therapy were excluded from participating.

Clinical symptoms and endoscopy findings at baseline, EOT, 2-week and 4-week post-treatment visits were graded on a scale from 0 (zero) to 3 (three) where 0 represents no finding and 3 is the worse finding. Patients needed to have a baseline endoscopy score of at least a 1 to be eligible to participate.

Study populations as defined in the protocol include:

The **full analysis set (FAS)** included all randomized patients who received at least one dose of study

drug. This set was defined as the primary efficacy and safety analysis set.

The *modified full analysis (MFAS)* set included all patients in the FAS who had a positive baseline cytology or histology. This population was considered secondary by the Sponsor.

Reviewer's note: The Division considers this population equally important to the FAS and will be considered in the evaluation of the data. Also, this set is equivalent in definition to the confirmed EC set in study FG09.

The *per protocol set (PPS)* included all randomized patients who received at least 10 doses of study drug, had confirmed EC at baseline, had both a baseline and EOT endoscopy performed, and who did not have any major protocol deviation(s). Exclusion of patients based on protocol deviations was performed prior to study unblinding. This study population was considered secondary for efficacy.

This **primary efficacy endpoint was endoscopic cure**, defined as an endoscopic grade of 0 (zero) measured at the EOT visit.

Secondary endpoints included:

- Clinical success (cleared or improved) at EOT
- Mucosal success (cleared or improved) at EOT
- Overall therapeutic success at EOT. Success is defined as clinical response of cleared or improved (improvement in baseline clinical symptom(s) by a reduction of 2 or more in total grade and no increase in any symptom) and endoscopic response of cleared (grade 0) or improved (reduction of mucosal grade by at least 2).
- Relapse at 2 weeks and 4 weeks post-treatment
- Changes in the endoscopic assessment of EC (mucosal grade) at EOT compared to baseline
- Changes in clinical symptoms of EC at EOT compared to baseline
- Changes in clinical signs and symptoms of OPC at EOT compared to baseline

Clinical response was determined by an assessment of symptoms of EC (i.e., dysphagia, odynophagia, and retrosternal pain). It was defined as follows:

- **Cleared:** Complete resolution (grade=0) of all clinical symptoms.
- **Improved:** Improvement in the clinical symptom(s) from baseline by a reduction of 2 or more in the total grade and no grade increase of any symptom.
- **Unchanged:** Not considered Improved or Cleared (as defined above) and no grade increase in any clinical symptom from baseline.
- **Worse:** Deterioration (grade increase) from baseline of 1 or more clinical symptoms.
- **Not Evaluable:** No increase in any clinical symptom of EC and one or more missing end of therapy assessment(s).

Clinical success was defined as a clinical response of cleared or improved.

Mucosal (endoscopic) response reflected the grades assigned to the appearance of the esophageal mucosa on endoscopy at baseline and the end of therapy. Mucosal responses were defined as:

- **Cleared:** Mucosal grade of 0.
- **Improved:** Reduction of mucosal grade from baseline by two or more grades at the end of therapy.
- **Unchanged:** Mucosal grade greater than 0 and mucosal grade less than or equal to baseline grade, but not reduced by more than one grade.
- **Worse:** Mucosal grade increased from baseline.
- **Not Evaluable:** Patients without a baseline or end of therapy mucosal examination.

Mucosal success was defined as a mucosal response of cleared or improved.

Overall therapeutic response was based on clinical and mucosal response at the EOT compared to baseline. Overall therapeutic success was defined in the Inferential Analysis Plan (IAP) as a clinical response of cleared or improved and an endoscopic response of cleared (mucosal grade=0) or improved (reduction of mucosal grade by at least 2) at the end of therapy.

If overall therapeutic response cannot be determined due to one or more missing (not done) evaluations, the patient will be counted as a treatment failure.

Relapse was measured at 2 and 4 weeks post-treatment in patients who were overall therapeutic successes at the EOT visit. Relapse was defined as the recurrence or worsening of EC based on **clinical symptoms and endoscopic examination for any patient with a cured or improved overall therapeutic response at EOT.** Note: An endoscopy (including assessment of mucosal lesions, biopsy and brushings) was performed at these visits IF the patients had clinical symptoms of EC.

Mycological response was based on the EOT endoscopic evaluation, including the mucosal grade, fungal culture results, and histology/cytology results. Response was defined as:

- **Eradication:** A negative fungal culture and a negative histology at end of therapy.
- **Persistence (colonization):** A positive *Candida* culture, a negative histology, and a mucosal grade=0.
- **Persistence (invasive):** A positive *Candida* culture and a positive histology.
- **Not assessable:** Patients without end of therapy mucosal grade, end of therapy fungal culture, and/or end of therapy histology results.

3.1.2 Statistical Methods

3.1.2.1 Study FG463-21-09

This study was a dose ranging Phase II study evaluating three micafungin doses (50 mg/day, 100 mg/day and 150 mg/day). Fluconazole, given at the approved dose for treatment of EC, was included as a positive control. The analysis of the primary efficacy endpoint (endoscopic grade of 0 at EOT visit) was performed using the closed test principle. In the first step, the Sponsor used the Cochran-Mantel-Haenszel (CMH) test adjusting for variable pooled center to compare the three micafungin groups ($H_0: p_{50mg} = p_{100mg} = p_{150mg}$) at an alpha of 0.05. If the calculated p-value was less than or equal to 0.05 a second step was performed in which micafungin groups were tested pair-wise ($p_{50mg} = p_{100mg}$, $p_{50mg} = p_{150mg}$, $p_{100mg} = p_{150mg}$) each at an alpha of 0.05 as well as the CMH test adjusting for variable of pooled center.

The Sponsor also performed statistical comparisons between the fluconazole group and each micafungin dose group (not using the closed test principle) by calculating the difference in the rate endoscopic cures between micafungin and fluconazole. Confidence intervals around the difference in endoscopic cure were calculated, however results were considered descriptive only.

Reviewer's Note: This study was not designed nor powered to demonstrate non-inferiority of micafungin to fluconazole.

In addition to the primary efficacy analyses described above and analyses of secondary endpoints, the Sponsor also performed stratified analyses according to baseline CD4 counts, baseline endoscopic grade (categorical analyses grouping patients according to baseline grades of 0, 1, 2 or 3), and baseline EC clinical severity scores (categorical analysis grouping patients according to sum of baseline scores). Additional analyses by center and country were also performed.

3.1.2.2 Study 03-7-005

The Sponsor's sample size calculation was based on an assumption that the rate of endoscopic clearing (grade 0) at EOT in the micafungin 150 mg/day and fluconazole 200 mg/day groups were 90% and 87% respectively based on results from the Phase II study FG09. Based on an endoscopic cure rate of 85% and a 1-sided alpha of 0.025, 201 patients per group were required to demonstrate with at least 80% power that micafungin was non-inferior, with a pre-specified margin of 10%, to fluconazole. To ensure sufficient numbers of patients were enrolled to demonstrate NI in the modified full analysis set, the Sponsor increased the sample size to 230 patients per group.

The analysis of the primary efficacy endpoint (endoscopic grade of 0 at EOT visit) was performed by calculating the difference (micafungin-fluconazole) in endoscopic success rates at EOT. A 95% CI was calculated around the difference in success rates using the normal approximation to the binomial method. Non-inferiority of micafungin to fluconazole was defined as a lower bound of the 95% C.I. being greater than or equal to **-0.10**.

Secondary analyses of the primary endpoint were performed using the CMH test controlling for baseline mucosal grade and pooled center variables.

3.1.3 Demographics and Patient Disposition

3.1.3.1 Study FG463-21-09

A total of 251 patients (65, 64, 60 and 62 in the micafungin 50 mg/day, 100 mg/day, 150 mg/day and fluconazole groups respectively) were randomized into the study and a total of 245 patients were included in the full analysis set (all randomized patients who received at least one dose of study drug). There were six patients (2 randomized to fluconazole, 1 randomized to micafungin 150 mg/day, 2 randomized to micafungin 100 mg/day, and 1 randomized to micafungin 50 mg/day) that never received study drug (2 patients died before starting treatment, 1 patient was confirmed HIV negative, 1 patient did not have confirmed EC, 1 patient had kidney failure and 1 patient withdrew consent). Between 83% and 93% of patients had confirmed EC at baseline and received at least one dose of study drug (confirmed EC set). The PPS contained approximately 75% to 85% of all randomized patients. The total number of patients

in the per protocol defined study population is presented in Table 3.1.

Table 3.1 Study FG09 Populations

	Micafungin Dose			Fluconazole	Total
	50 mg/day	100 mg/day	150 mg/day	200 mg/day	
Randomized	65	64	60	62	251
Full Analysis Set	64 (98.5)	62 (96.9)	59 (98.3)	60 (96.8)	245 (97.6)
<i>EC not confirmed at baseline</i>	8	3	3	8	22
Confirmed EC Set	56 (86.2)	59 (92.2)	56 (93.3)	52 (83.9)	223 (88.8)
<i>Did not receive 10 doses of tri*</i>	2	9	3	2	16
<i>No endoscopic assessment at EOT*</i>	4	10	5	4	23
Per Protocol Set	52 (80.0)	48 (75.0)	51 (85.0)	48 (77.4)	199 (79.3)

Values in parenthesis represent the percentage of the total randomized patients

** Patient may have had more than one reason for exclusion from PPS*

A total of 36 (14.7%) patients prematurely discontinued treatment with a greater number (n=13, 21%) discontinuing in the micafungin 100 mg/day group compared to the other groups. Adverse events were the primary cause for treatment discontinuation [Table 3.2].

Table 3.2 Study FG09 Treatment and Study Completion Status

	Micafungin Dose			Fluconazole
	50 mg/day	100 mg/day	150 mg/day	200 mg/day
FAS	N=64	N=62	N=59	N=60
Completed Treatment	56 (87.5)	49 (79.0)	52 (88.1)	52 (86.7)
Discontinued Treatment	8 (12.5)	13 (21.0)	7 (11.9)	8 (13.3)
AE	3 (4.7)	8 (12.9)	3 (5.1)	4 (6.7)
Withdrew consent	1 (1.6)	1 (1.6)	1 (1.7)	1 (1.7)
Non-compliance	1 (1.6)	0 (0.0)	0 (0.0)	2 (3.3)
Lost to follow-up	0 (0.0)	1 (1.6)	1 (1.7)	0 (0.0)
Death	0 (0.0)	0 (0.0)	1 (1.7)	0 (0.0)
Lack of efficacy	1 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)
Prohibited medication	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.7)
Other reasons	2 (3.1)	3 (4.8)	1 (1.7)	0 (0.0)
Completed Study	54 (84.4)	50 (80.6)	51 (86.4)	53 (88.3)
Died*	3 (4.7)	3 (4.8)	3 (5.1)	1 (1.7)
During Treatment	0	0	0	0
During Follow-up**	3 (4.7)	3 (4.8)	3 (5.1)	1 (1.7)
Lost to Follow-Up	7 (10.9)	6 (9.7)	4 (6.8)	4 (6.7)
Other	0	3 (4.8)	1 (1.7)	2 (3.3)

Values in parenthesis represent percentage of FAS

Other reasons: withdrew consent due to AE (2 patients), insufficient venous access, social problems, misunderstanding of investigator, condition of patient did not allow endoscopy (1 patient each)

** In addition to these deaths, four additional patients (3 in the micafungin 50 mg/day, 1 in micafungin 150 mg/day groups) died after study completion. Reasons are stated in section 3.2.*

***Patient 1908 (150 mg/day group) was discontinued from treatment by the Sponsor due to death; she died one day after having received the last dose of study medication*

Patients ranged from 33-36 years of age with over 50% of patients being male in all treatment groups except in the micafungin 150 mg/day group. Approximately 50% of patients were Black; however there was a large representation of Caucasian patients. Over 74% of all patients had a baseline CD4 count less than 100 cells/mL with a mean value between 54 and 88 cells/mL (one-way ANOVA, p-value 0.39). The average baseline endoscopic grade was 2 and between 17 and 30% of patients had a baseline grade of 3.

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Table 3.3 Study FG09 Demographics and Baseline Infection Status

FAS	Micafungin Dose			Fluconazole
	50 mg/day N=64	100 mg/day N=62	150 mg/day N=59	200 mg/day N=60
Age (yrs)				
Mean	33	36	36	35
Range	19-33	24-35	23-36	19-34
Sex				
Male	30 (46.9)	26 (41.9)	33 (55.9)	28 (46.7)
Female	34 (53.1)	36 (58.1)	26 (44.1)	32 (53.3)
Race				
Caucasian	25 (39.1)	26 (41.9)	25 (42.4)	22 (36.7)
Black	31 (48.4)	33 (53.2)	30 (50.8)	32 (53.3)
Other*	8 (12.5)	3 (4.8)	4 (6.8)	6 (10.0)
Baseline CD4 Count				
Mean +/-SD	60.0 +/-14.5	87.6 +/- 14.6	69.5 +/- 15.1	53.8 +/-14.9
Range	0-431	0-900	0-806	0-689
<100	53 (84.1)	46 (74.2)	46 (79.3)	55 (91.7)
>=100	10 (15.9)	16 (25.8)	12 (20.7)	5 (8.3)
Not done	1	0	1	0
Baseline Endoscopic Grade				
0	0	0	0	1
1	11 (17.2)	13 (21.0)	11 (18.6)	10 (16.7)
2	42 (65.6)	37 (59.7)	37 (62.7)	31 (51.7)
3	11 (17.2)	12 (19.4)	11 (18.6)	18 (30.0)
Mean	2	2	2	2
Histology of EC Biopsy				
Positive	48 (75.0)	47 (75.8)	48 (82.8)	48 (80.0)
Negative	16 (25.0)	15 (24.2)	10 (17.2)	12 (20.0)
Not done/recorded	0	0	1	0
Cytology of EC Brushings				
Positive	56 (87.5)	55 (88.7)	54 (93.1)	51 (86.4)
Negative	8 (12.5)	7 (11.3)	4 (6.9)	8 (13.6)
Not done/recorded	0	0	1	1
Fungal culture				
Positive	58 (92.1)	61 (98.4)	57 (98.3)	58 (96.7)
<i>C. albicans</i>	57 (98.3)	61 (100.0)	57 (100.0)	58 (100.0)
<i>C. glabrata</i>	2 (3.4)	4 (6.6)	1 (1.8)	3 (5.2)
<i>C. krusei</i>	0	0	1 (1.8)	0
<i>C. tropicalis</i>	1 (1.7)	1 (1.6)	1 (1.8)	1 (1.7)
Negative	5 (7.9)	1 (1.6)	1 (1.7)	2 (3.3)
Not done/recorded	1	0	1	0
OPC	60 (93.8)	58 (93.5)	53 (89.8)	57 (95.0)

*Other includes: mulatto (15 patients), native Brazilian (2 patients), cape colored (2 patients), colored (1 patient), mestizo (1 patient). Hispanic patients were counted as Caucasian.

3.1.3.2 Study 03-7-005

A total of 523 patients were enrolled of which 265 were randomized to receive micafungin treatment and 258 were randomized to receive fluconazole treatment. There were five patients in the micafungin group that never received treatment (1 did not return for the first dose of treatment, 1 withdrew consent before first dose, 2 patients were withdrawn by investigator, 1 patient was never dispensed study drug-no reason stated) and therefore were excluded from the FAS population. This study was conducted in Brazil, Peru and South Africa in which 17% (88/518) of patients were enrolled in Brazil, 12% (62/518) of patients were enrolled in Peru and 71% (368/518) of patients were enrolled in South Africa.

The majority of patients enrolled were Black (68% in micafungin, 69% in fluconazole), approximately half were male, and the average age (yrs) was 37. Over 93% of patients enrolled in both groups were HIV positive with a mean baseline CD4 count of 109 cells/mL (micafungin group) and 111 cell/mL (fluconazole group). Over 50% of patients with HIV had CD4 counts less than 100 cells/mL (150/245, 61.2% of patients in the micafungin group and 143/241, 59.3% of patients in the fluconazole group). Only 22/260 (8.5%) patients in the micafungin group and 30/258 (11.6%) patients in the fluconazole group received antiretroviral therapy prior to study participation. The majority of patients (over 86%) in both groups had no previous episodes of EC and over 88% of patients in both groups were co-infected with OPC. Demographics and baseline conditions are outline below in Table 3.4.

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Table 3.4 Study 005 Demographics and Baseline Conditions

Parameter	Treatment Group	
	Micafungin (N=260)	Fluconazole (N=258)
Race		
Caucasian	38 (14.6%)	35 (13.6%)
Black	176 (67.7%)	178 (69.0%)
Mestizo	32 (12.3%)	29 (11.2%)
Other	14 (5.4%)	16 (6.2%)
Gender		
Male	131 (50.4%)	116 (45.0%)
Female	129 (49.6%)	142 (55.0%)
Age (yrs)		
Mean +/- SD	37.2 +/-10.59	37.5 +/- 11.16
Range	17.0-80.0	17.0-87.0
HIV Positive	245 (94.2%)	241 (93.4)
Baseline CD4		
Mean	109.0 +/- 190.8	110.7 +/-182.2
Range	(0-1609)	(0-1419)
No. of Prior EC Episodes		
0	225 (86.5%)	225 (87.2%)
1	25 (9.6%)	23 (8.9%)
2	7 (2.7%)	6 (2.3%)
>=3	0	1 (0.4%)
Unknown	3 (1.2%)	3 (1.2%)
OPC	230 (88.5%)	229 (88.8%)
Baseline mucosal grade		
1	87 (33.5%)	96 (37.2%)
2	98 (37.7%)	99 (38.4%)
3	75 (28.8%)	63 (24.4%)

Among randomized patients, approximately 83% in both groups had a positive histology or cytology for EC at baseline (MFAS population). The per protocol population consisted of 71% and 74% of patients randomized to the micafungin and fluconazole groups respectively.

Table 3.5 Study 005 Patient Dispositions

Study Population	Treatment Group	
	Micafungin (N=265)	Fluconazole (N=258)
FAS	260 (98.1%)*	258 (100%)
MFAS	220 (83.0%)	215 (83.3%)
PPS	189 (71.3%)	192 (74.4%)

*Five patients randomized to micafungin group did not receive study drug

FAS=full analysis set=all randomized patients who rec'd at least one dose of study drug

MFAS=modified full analysis set=FAS with positive histology or cytology at baseline

PPS=per protocol set=all randomized patients who rec'd at least 10 doses of study drug, had confirmed EC at baseline, had a baseline and EOT endoscopy performed, and had no major protocol violations

A total of 204 (77%) and 214 (83%) in the micafungin and fluconazole groups respectively completed the study. The primary reasons for failure to complete the study included death and lost to follow-up.

Table 3.6 Study 005 Patient Statuses at End of Study

Status	Treatment Group	
	Micafungin (N=265)	Fluconazole (N=258)
Completed Study	204 (77.0%)	214 (83.0%)
Death	30 (11.3%)	28 (10.8%)
Lost to Follow-up	22 (8.3%)	14 (5.4%)
Other*	9 (3.4%)	2 (0.8%)

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

Approximately 89% and 91% of patients in the micafungin and fluconazole groups respectively completed the protocol specified treatment. The primary reason for premature treatment discontinuation was adverse events [Table 3.7].

Table 3.7 Study 005 Reasons for Treatment Discontinuation

Reason	Treatment Group	
	Micafungin (N=265)	Fluconazole (N=258)
Completed Treatment	232 (89.2%)	234 (90.7%)
AE	17 (6.5%)	12 (4.7%)
Trt related AE	6 (2.3%)	1 (0.4%)
AE resulting in death	10 (3.8%)	9 (3.5%)
Withdrew Consent	2 (0.8%)	0 (0.0%)
Non-compliance with Protocol		
Baseline Infection not confirmed	1 (0.4%)	0 (0.0%)
Did not return for medication	3 (1.2%)	1 (0.4%)
Other	1 (0.4%)	3 (1.2%)
Lack of efficacy	2 (0.8%)	6 (2.3%)
Other*	2 (0.8%)	2 (0.8%)

**Other: includes herpes virus infection (1 micafungin patient), non-compliance (1 micafungin patient), concomitant esophagitis caused by herpes virus (1 fluconazole patient), and patient too ill to participate (1 fluconazole patient)*

3.1.4 Efficacy Results

3.1.4.1 Study FG463-21-09

3.1.4.1.1 Primary Analyses

Endoscopic cure rates at EOT in the micafungin 50 mg/day, 100 mg/day and 150 mg/day and fluconazole

200 mg/day groups were 44/64 [68.8%, 95%CI (57.4, 80.1)], 48/62 [77.4%, 95% CI (67.0, 87.8)], 53/59 [89.8%, 95% CI (82.1, 97.5)], and 52/60 [86.7%, 95% CI (78.1, 95.3)] respectively [Table 3.8]. Using the closed testing procedure, the overall comparison [Table 3.9] among all three micafungin groups resulted in a p-value of 0.024 in the FAS and 0.019 in the confirmed EC set. Given that the overall comparison was less than 0.05, pair-wise comparisons between micafungin groups were performed. Pair-wise comparisons between micafungin 50 mg/day and 100 mg/day resulted in a p-value of 0.293 (FAS) and 0.227 (confirmed EC set), micafungin 50 mg/day vs. 150 mg/day yielded a p-value of 0.007 (FAS) and 0.006 (confirmed EC set) and micafungin 100 mg/day vs. 150 mg/day yielded a p-value of 0.075 (FAS) and 0.065 (confirmed EC set). These results demonstrate higher endoscopic cure rates observed among patients receiving 150 mg/day compared to the 50 mg/day group. 95% C.I.s for the micafungin 50, 100, 150 mg/day and fluconazole groups in the FAS are illustrated in Figure 1.

Table 3.8 Study FG09 Endoscopic Response at Test of Cure (EOT)

Endoscopic Grade at EOT	Micafungin			Fluconazole 200 mg/day
	50 mg/day	100 mg/day	150 mg/day	
<i>FAS</i>	(N=64)	(N=62)	(N=59)	(N=60)
Success	n (%)	n (%)	n (%)	n (%)
0	44 (68.8)	48 (77.4)	53 (89.8)	52 (86.7)
95% CI*	[57.4, 80.1]	[67.0, 87.8]	[82.1, 97.5]	[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	1 (1.7)
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)
<i>Per Protocol</i>	(N=52)	(N=48)	(N=51)	(N=48)
Success	n (%)	n (%)	n (%)	n (%)
0	37 (71.2)	44 (91.7)	50 (98.0)	46 (95.8)
95% CI*	[58.8, 83.5]	[80.0, 97.7]**	[89.6, 100]**	[85.8, 99.5]**
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
<i>Confirmed EC Set</i>	(N=56)	(N=59)	(N=56)	(N=52)
Success	n (%)	n (%)	n (%)	n (%)
0	37 (66.1)	45 (76.3)	50 (89.3)	46 (88.5)
95% CI*	[53.7, 78.5]	[65.4, 87.1]	[81.2, 97.4]	[79.8, 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% CI calculated based on the normal approximation to the binomial method
**95% CI calculated using exact method

Table 3.9 Study FG09 Comparison of Rate of Endoscopic Cure (Grade 0) at EOT

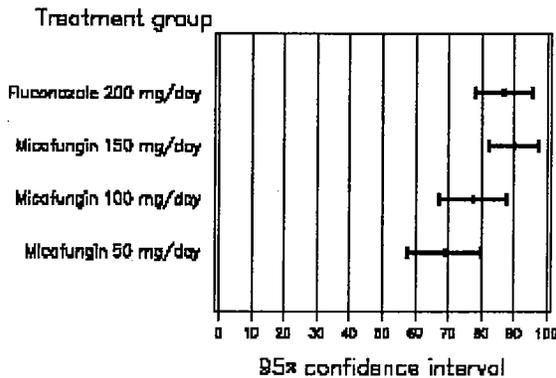
	P-value †		
	Full Analysis Set	Per Protocol Set	Confirmed EC Set
The three micafungin groups (overall)	0.024	<0.001	0.019
50 mg/day versus 100 mg/day micafungin:	0.293	0.005	0.227
50 mg/day versus 150 mg/day micafungin:	0.007	<0.001	0.006
100 mg/day versus 150 mg/day	0.075	0.135	0.065

†P-values calculated using the Cochran-Mantel-Haenzel test, adjusting for center. Centers with ≤5 patients or no patient in one or two of the three micafungin dosage groups were pooled with other small centers of the same country.

Source: Tables 13.5.1.1.1, 13.5.1.1.2, 13.5.1.1.3 of CSR

Reviewer's Note: The difference (micafungin 150 mg/day-micafungin 50 mg/day) in the rate of endoscopic cure at EOT results in a p-value of 0.004 and 95% CI of [7.0, 34.8] (normal approximation to the binomial method). This result suggests proof of efficacy of micafungin 150 mg/day to micafungin 50 mg/day (a dose that could be no better than placebo). Although this study was not intended to compare efficacy of micafungin treatments to fluconazole, the overlap of the 95% confidence intervals for the micafungin 150 mg/day and fluconazole groups on the primary endpoint provides useful information on dose determination for confirmatory testing.

Figure 1 Study FG09 C.I.s for Primary Efficacy Endpoint*



Source: Figure 1 of FG09 CSR, page 72

*Endoscopic Cure (grade 0) at EOT in full analysis set

Patients with endoscopic response of 0 by baseline grade are presented below in Table 3.10. A greater percentage (100% and 78% in the micafungin 150 mg/day and fluconazole groups respectively) with baseline endoscopic grade of 3 were cleared at the end of treatment compared to the other treatment groups suggesting a better response in these treatment groups among patients enrolled with more severe EC.

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Table 3.10 Study FG09 Patients with EOT Endoscopic Grade 0 by Baseline Endoscopic Grade

	Micafungin Dose						Fluconazole 200 mg/day		
	50 mg/day		100 mg/day		150 mg/day		N	n (%)	
	N	n (%)	N	n (%)	N	n (%)			
<i>FAS</i>	<i>n=64</i>		<i>n=62</i>		<i>n=59</i>			<i>n=60</i>	
BEG	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 (100.0)	18	14 (77.8)
<i>PPS</i>	<i>n=52</i>		<i>n=48</i>		<i>n=51</i>			<i>n=48</i>	
BEG	0	0	-	0	-	0	-	0	-
	1	9	7 (77.8)	1 0	9 (90.0)	8	8 (100.0)	5	5 (100.0)
	2	34	24 (70.6)	3 1	30 (96.8)	32	31 (96.9)	28	27 (96.4)
	3	9	6 (66.7)	7	5 (71.4)	11	11 (100.0)	15	14 (93.3)

BEG=baseline endoscopic grade

Source: Tables 13.5.1.2.1.1 and 13.5.1.2.1.2

3.1.4.1.2 Secondary Analyses

Clinical Clearance at EOT

The rates of clinical clearance in the FAS (73%, 84%, 86% and 88% in the micafungin 50 mg, 100 mg, 150 mg and fluconazole groups respectively) were consistent with the endoscopic cure rates at EOT with a higher rate of clearance in the micafungin 100 and 150 mg/day groups compared to the micafungin 50 mg/day group.

Mycological Outcome at EOT

The rates of mycological eradication [Table 3.11] were 35.1% (20/57), 78.3% (36/46) and 57.1% (28/49) in the micafungin 50 mg, 100 mg and 150 mg/day groups respectively and 67.3% (35/52) in the fluconazole group. The Sponsor performed two-sided Cochran-Armitage tests^{3,4} to measure for possible trends across micafungin groups. This test yielded a descriptive p-value of 0.019 in the mycological eradication rate in the FAS.

Table 3.11 Study FG09 Mycological Response at EOT

	Micafungin Dose						Fluconazole	
	50 mg/day		100 mg/day		150 mg/day		200 mg/day	
	N	n (%)	N	n (%)	N	n (%)	N	n (%)
Full Analysis Set	n=64		n=62		n=59		n=60	
Eradication	57	20 (35.1)	46	36 (78.3)	49	28 (57.1)	52	35 (67.3)
Colonization		15 (26.3)		6 (13.0)		7 (14.3)		4 (7.7)
Invasive based on:		22 (38.6)		4 (8.7)		14 (28.6)		13 (25.0)
Positive cytology		1 (1.8)		2 (4.3)		6 (12.2)		7 (13.5)
Positive histology and/or fungal culture		21 (36.8)		2 (4.3)		8 (16.3)		6 (11.5)
Per Protocol Set	n=52		n=48		n=51		n=48	
Eradication	50	13 (26.0)	42	33 (78.6)	46	26 (56.5)	46	30 (65.2)
Colonization		15 (30.0)		5 (11.9)		6 (13.0)		4 (8.7)
Invasive based on:		22 (44.0)		4 (9.5)		14 (30.4)		12 (26.1)
Positive cytology		1 (2.0)		2 (4.8)		6 (13.0)		6 (13.0)
Positive histology and/or fungal culture		21 (42.0)		2 (4.8)		8 (17.4)		6 (13.0)

Source: Tables 13.5.1.6.1 and 13.5.1.6.2

Overall Therapeutic Success at EOT

Overall therapeutic success in the FAS (complete resolution or improvement in clinical signs and symptoms and endoscopic grades from baseline to EOT) rates were higher in the micafungin 150 mg/day (91.5 %, 54/59) group compared to the micafungin 50 mg/day (79.7%, 51/64) group. A similar rate (91.7%, 55/60) was observed in the fluconazole group. The micafungin 100 mg/day had a rate of 83.9% (52/62).

EC Relapse at 2 weeks post-treatment

As per the protocol, a relapse is indicated if a patient develops a worsening of disease (significant increase in clinical assessment by 2 or more grades or grade 3) and/or needs additional antifungal treatment (excluding prophylaxis) during the follow-up period.

Among patients who were clinically and endoscopically cured at EOT (39, 48, 50 and 51 patients in the micafungin 50 mg, 100 mg, 150 mg and fluconazole groups respectively), there were 1, 5, 3 and 0 patients who had a recurrence of EC at the 2 week assessment. Patients who relapsed along with endoscopy grade and severity at baseline, EOT and EOS (2 week follow-up) are presented in Table 3.12.

Table 3.12 Study FG09 EC Relapse at 2-weeks post-treatment

Patient No.	Therapy †	Endoscopy Grade		Esophageal candidiasis severity grade ‡		
		Baseline	EOT	Baseline	EOT	EOS
Micafungin, 50 mg/day						
3109	OEC, OP	2	0	2	0	1
Micafungin, 100 mg/day						
1301	None	3	0	5	0	2
2307	None	2	0	6	0	3
2403	OEC	1	0	4	0	0
3211	OEC, OP	2	0	7	0	4
4014	None	1	0	6	0	4
Micafungin, 150 mg/day						
3006	OEC	2	0	0	0	0
3113	OEC, OP	2	0	6	0	2
4001	None	2	0	6	0	6

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

EOT: end of therapy; EOS: End of study-2 week follow-up

† Non-prophylactic antifungal medication during follow-up phase; OEC: primary treatment was for esophageal candidiasis; OP: primary treatment was for oropharyngeal candidiasis

‡ The sum of scores for dysphagia, odynophagia and retrosternal pain, each graded on a scale of 0-3

Relapse: For patients with an endoscopy grade and clinical response of 0 at end of therapy, the patient showed a total symptom score for esophageal candidiasis or oropharyngeal candidiasis > 0 at the follow-up visit or the patient received antifungal medication during follow-up phase

Source: Table 13.5.4.1.1.1, Appendix 14.4.5.6

At the 2 week follow-up visit there was no EC relapse information for 8, 3, 3, and 6 patients in the micafungin 50 mg, 100 mg, 150 mg and fluconazole groups respectively who were clinically and endoscopically cured at EOT. When treating these missed assessments as relapses, the relapse rates are 9/39 (23.1%), 8/48 (16.7%), 6/50 (12.0%), and 6/51 (11.8%) for micafungin 50 mg, 100 mg, 150 mg and fluconazole in the FAS. No statistically significant trend was observed among the three micafungin groups.

Reviewers' Note: *The Sponsor also summarized rates of EC worsening among patients who were only clinically improved at EOT. This summary (located in Table 13.5.4.1.2.2) provides no additional data regarding EC relapse and it is unclear from the summary what criteria for EC (cured or improved) were used. Furthermore, it is felt by the medical reviewer that the most clinically appropriate group to evaluate relapse is in the clinically and endoscopically cured (cleared) patients and not in improved patients.*

EC relapse and antifungal use at 2 weeks post-treatment

Of 188 patients who were endoscopically and clinically cured at EOT, there were 18 patients (5, 6, 5, and 2 for micafungin 50, 100, 150 and fluconazole 200 respectively) who received antifungal treatment (including prophylaxis) during the study. Among these patients, 15 (4, 5, 4, 2 micafungin 50, 100, 150

and fluconazole 200 respectively) had not relapsed at the 2-week follow-up visit. Given the confounding effects of antifungal treatment and EC relapse these 15 patients were treated as relapses in an additional analysis. When counting confirmed relapse, missing, and use of antifungal therapy during 2 week follow-up as relapse, the overall EC relapse rates were 13/39 (33.3%), 13/48 (27.1%), 10/50 (20.0%), and 8/51 (15.7%) for micafungin 50 mg, 100 mg, 150 mg and fluconazole 200 mg. A summary of all EC relapse information is presented in Table 3.13.

Table 3.13 Study FG09 Summary of EC relapse

	Micafungin 50 mg	Micafungin 100 mg	Micafungin 150 mg	Fluconazole
Endo and clinically cured at EOT*	N=39	N=48	N=50	N=51
EC relapse at 2 weeks				
Relapse	1 (2.6)	5 (10.4)	3 (6.0)	0 (0.0)
Missing	8 (20.5)	3 (6.3)	3 (6.0)	6 (11.8)
No relapse but rec'd AFT **	4 (10.3)	5 (10.4)	4 (8.0)	2 (3.9)
Total EC relapse at 2 wks***	13 (33.3)	13 (27.1)	10 (20.0)	8 (15.7)

* Subset of patients who were both endoscopically and clinically cured at EOT

**Patients who received systemic antifungal therapy during 2 week follow-up period and had no EC relapse at follow-up

*** Sum of EC relapses, missing and use of systemic antifungal therapy during 2 week f/u period but counted as no relapse

Values in parenthesis are percentages of endoscopic and clinical cure subset

OPC relapse at 2 week follow-up in patients who were OPC and EC cures at EOT

At EOT, there were 179 patients who were cleared of baseline OPC and EC signs and symptoms. At the 2 week follow-up visit, there were 23/38, 28/45, 32/46 and 39/50 patients who received micafungin 50 mg, 100 mg, 150 mg and fluconazole 200 mg respectively who remained cleared of all OPC symptoms; however among these patients there were 3, 4, 3 and 2 in the micafungin 50 mg, 100 mg, 150 mg and fluconazole groups respectively who received antifungal therapy during the follow-up period. The following table presents the OPC relapse results and considers missing and use of antifungal therapy as criteria for relapse.

Table 3.14 Study FG09 OPC Relapse at 2 week follow-up

	Micafungin 50 mg	Micafungin 100 mg	Micafungin 150 mg	Fluconazole
OPC & EC Grade 0 at EOT	N=38	N=45	N=46	N=50
OPC Status at 2 week f/u				
No relapse (OPC grade 0)	23 (60.5)	28 (62.2)	32 (69.6)	39 (78.0)
Relapse (OPC grade > 0)	7 (18.4)	14 (31.1)	12 (26.1)	5 (10.0)
Missing	8 (21.1)	3 (6.7)	2 (4.3)	6 (12.0)
No relapse but rec'd AFT *	3 (7.9)	4 (8.9)	3 (6.5)	2 (4.0)
Total OPC relapse at 2 weeks**	18 (47.4)	21 (46.7)	17 (37.0)	13 (26.0)

Values in parenthesis represent percent of subset of patients who were cured of OPC and EC at EOT

**Patients who received systemic antifungal therapy during 2 week follow-up period and had no OPC relapse at follow-up*

*** Sum of OPC relapses, missing and use of systemic antifungal therapy during 2 week f/u period but counted as no relapse*

Note: The difference in total OPC relapse was not statistically significant (Fisher's Exact Test) between micafungin 150 mg and fluconazole

Note: The test for trend across the three micafungin arms is statistically insignificant

3.1.4.2 Study 03-7-005

3.1.4.2.1 Primary Analyses

At EOT, the endoscopic cure rates (in the FAS) in the micafungin and fluconazole groups were 228/260 (87.7%) and 227/258 (88.0%), resulting in a difference (micafungin-fluconazole) of -0.3%, 95% CI [-5.9, 5.3]. The endoscopic cure rates in the modified full analysis set (all FAS patients with positive baseline cytology or histology) were 191/220 (86.8%) and 188/215 (87.4%) for micafungin and fluconazole respectively, resulting in a difference (micafungin-fluconazole) in success rates of -0.6%, 95% CI [-6.9, 5.7]. Per protocol set results in the micafungin and fluconazole groups were 183/189 (96.8%) and 182/192 (94.8%), difference of 2.0, 95% CI [-2.0, 6.1]. These results [Table 3.15] demonstrate non-inferiority in the rate of endoscopic cure, based on a margin of 10%, of micafungin 150 mg/day to fluconazole 200 mg/day. Among the patients not evaluable at EOT, the majority prematurely discontinued treatment due to an adverse event.

Table 3.15 Study 005 Primary Efficacy (Endoscopic cure) at EOT

Outcome	Treatment		Treatment Difference (Mica-Fluconazole)	95% CI
	Micafungin	Fluconazole		
Endoscopic Cure at EOT				
<u>FAS</u>	(N=260)	(N=258)		
Success	228 (87.7%)	227 (88.0%)	-0.3	(-5.9, 5.3)
Failure	32 (12.3%)	31 (12.0%)		(-6.3, 5.7)*
Mucosal grade >0	7 (2.7%)	10 (3.9%)		
Not Evaluable	25 (9.6%)	21 (8.1%)		
<u>MFAS</u>	(n=220)	(n=215)		
Success	191 (86.8%)	188 (87.4%)	-0.6	(-6.9, 5.7)
Failure	29 (13.2%)	27 (12.6%)		(-7.4, 6.1)*
Mucosal grade >0	6 (2.7%)	10 (4.7%)		
Not Evaluable	23 (10.5%)	17 (7.9%)		
<u>PPS</u>	(n=189)	(n=192)		
Success	183 (96.8%)	182 (94.8%)	2.0	(-2.0, 6.1)
Failure	6 (3.2%)	10 (5.2%)		(-2.5, 6.6)*
Mucosal grade >0	6 (3.2%)	10 (5.2%)		

FAS=full analysis set=all randomized patients who rec'd at least one dose of study drug

MFAS=modified full analysis set=FAS with positive histology or cytology at baseline

PPS=per protocol set=all randomized patients who rec'd at least 10 doses of study drug, had confirmed EC at

baseline, had a baseline and EOT endoscopy performed, and had no major protocol violations

95% CI calculated using normal approximation to the binomial method

**95% CI calculated using normal approximation to the binomial with continuity correction-Sponsor's calculation*

3.1.4.2.2 Secondary Analyses

Clinical outcome at EOT

The rates of clinical success (clearance or improvement in baseline clinical signs and symptoms) at EOT were similar (94.2% and 94.6% in micafungin and fluconazole respectively) between the two groups. Rates of clinical clearance in the FAS were 91.9% in both groups and 90.9% and 92.6% in the micafungin and fluconazole groups respectively in the MFAS. The primary reason for clinical failure was non-evaluability at EOT.

Table 3.16 Study 005 Clinical Responses at EOT

Outcome	Treatment		Treatment Difference (Mica-Fluconazole)	95% CI
	Micafungin	Fluconazole		
Clinical Response at EOT				
FAS	(N=260)	(N=258)		
Success	245 (94.2%)	244 (94.6%)	-0.3	(-4.3, 3.6)
Cleared	239 (91.9%)	237 (91.9%)		(-4.7, 4.0)*
Improved	6 (2.3%)	7 (2.7%)		
Failure	15 (5.8%)	14 (5.4%)		
Unchanged	2 (0.8%)	3 (1.2%)		
Worse	0	1 (0.4%)		
Not Evaluable	13 (5.0%)	10 (3.9%)		
MFAS	(n=220)	(n=215)		
Success	206 (93.6%)	206 (95.8%)	-2.2	(-6.4, 2.0)
Cleared	200 (90.9%)	199 (92.6%)		(-6.8, 2.5)*
Improved	6 (2.7%)	7 (3.3%)		
Failure	14 (6.4%)	9 (4.2%)		
Unchanged	1 (0.5%)	1 (0.5%)		
Worse	0	1 (0.5%)		
Not Evaluable	13 (5.9%)	7 (3.3%)		
PPS	(n=189)	(n=192)		
Success	187 (98.9%)	189 (98.4%)	0.5	(-2.4, 3.6)**
Cleared	184 (97.4%)	183 (95.3%)		(-2.3, 3.3)*
Improved	3 (1.6%)	6 (3.1%)		
Failure	2 (1.1%)	3 (1.6%)		
Unchanged	1 (0.5%)	1 (0.5%)		
Worse	0	1 (0.5%)		
Not Evaluable	1 (0.5%)	1 (0.5%)		

FAS=full analysis set=all randomized patients who rec'd at least one dose of study drug

MFAS=modified full analysis set=FAS with positive histology or cytology at baseline

PPS=per protocol set=all randomized patients who rec'd at least 10 doses of study drug, had confirmed EC at

baseline, had a baseline and EOT endoscopy performed, and had no major protocol violations

**95% CI calculated using normal approximation to the binomial with continuity correction*

***95% CI calculated using exact method*

Mycological outcome at EOT

The following table [Table 3.17] shows that between 76% and 80% of patients who had a mucosal grade of 0 at EOT also had eradication of baseline pathogens. There were approximately 18% to 23% of patients who were endoscopically cleared at EOT but still had mycological persistence/colonization.

Table 3.17 Study 005 Mycological Responses by Endoscopic Response at EOT in MFAS

	Endoscopic Outcome at EOT			
	Micafungin N=220		Fluconazole N=215	
	Success (n=191)	Failure (n=29)	Success (n=188)	Failure (n=27)
Mycological Response at EOT				
Eradication	145 (75.9)	3 (10.3)	151 (80.3)	4 (14.8)
Persistence/Colonization	43 (22.5)	1 (3.5)	33 (17.6)	1 (3.7)
Persistence/Invasive	3 (1.6)	3 (10.3)	4 (2.1)	6 (22.2)
Not Evaluable	0	22 (75.9)	0	16 (59.3)

Overall therapeutic success at EOT

The rates of overall therapeutic successes (clinical and endoscopic response of cleared or improved at EOT) were 227 for micafungin and 225 for fluconazole based on the following combinations of outcomes demonstrating that the majority of patients that were endoscopically cured were also clinically cured.

Mucosal Outcome	Clinical Outcome	Micafungin N=260	Fluconazole N=258
Cleared	Cleared	223	220
Cleared	Improved	4	3
Improved	Cleared	1	1
	Total	227	225

EC relapse at 2 and 4 weeks post-treatment

The Sponsor assessed EC relapse at 2 and 4 weeks post-treatment in patients who were overall therapeutic successes at EOT. The Sponsor's analysis [Table 3.18] considering missing as failures resulted in a 2 week EC relapse rate of 15.4% in the micafungin group and 11.1% in the fluconazole group. Relapse through the 4 week follow-up period was 26.0% and 23.1% in the micafungin and fluconazole groups respectively.

Table 3.18 Study 005 Relapse Rate at Post-Treatment Periods ***

<u>Post-Treatment Visit</u>	<u>Treatment</u>		<u>P-value, 95% CI*</u>
	<u>Micafungin</u>	<u>Fluconazole</u>	
<u>FAS</u>			
Relapse at 2-wk visit	35/227 (15.4%)	25/225 (11.1%)	0.18, [-1.9, 10.6]
Relapse at 4-wk visit**	24/192 (12.5%)	27/200 (13.5%)	0.77, [-7.7, 5.7]
Relapse through week 4	59/227 (26.0%)	52/225 (23.1%)	0.48, [-5.1, 10.8]
<u>MHIS</u>			
Relapse at 2-wk visit	29/190 (15.3%)	23/187 (12.3%)	0.40, [-4.0, 9.9]
Relapse at 4-wk visit	20/161 (12.4%)	24/164 (14.6%)	0.56, [-9.6, 5.2]
Relapse through week 4	49/190 (25.8%)	47/187 (25.1%)	0.88, [-8.1, 9.5]
<u>PRisit</u>			
Relapse at 2-wk visit	27/182 (14.8%)	23/181 (12.7%)	0.56, [-5.0, 9.2]
Relapse at 4-wk visit	19/155 (12.3%)	23/158 (14.6%)	0.55, [-9.8, 5.2]
Relapse through week 4	46/182 (25.3%)	46/181 (25.4%)	0.98, [-9.1, 8.8]

Source: Study 005 CSR, Table 11, page 81

*Calculated around the difference (micafungin-fluconazole) using the Normal Approximation to the Binomial Method

**Relapses at 2 weeks not included in 4 week assessment

*** Incidence of relapse in patients with overall therapeutic success (cleared or improved clinical response and cleared or improved mucosal response) at EOT. Missing values are treated as relapse.

Reviewer's Note: The population used to assess relapse, i.e. the overall therapeutic success population, is not considered by the medical reviewer to be the most appropriate population given that it includes patients who were only improved clinically and/or endoscopically. As a result, additional analysis, presented below, assesses relapse in only patients who were cured either endoscopically or endoscopically and clinically at EOT.

Of additional interest during the review was to access the rate of relapse in a) patients who met the primary endpoint of endoscopic cure at EOT and b) patients who were endoscopically and clinically cured at EOT. Rates of confirmed EC relapse were consistently greater in the micafungin group compared to the fluconazole group in all populations evaluated; however there were no statistically significant differences observed. Total EC relapse rates (sum of confirmed EC relapse, missing, death, and antifungal use but counted as no relapse by the Sponsor) up through 4 weeks in patients that were endoscopically cured were 32.5% and 29.1% for micafungin and fluconazole respectively. In the subset of patients who were endoscopically and clinically cured, the overall EC relapse rates were 17.9% and 13.6% in micafungin and fluconazole groups respectively. These analyses were performed by the reviewer and are presented below in Table 3.19.

Table 3.19 Study 005 Post-Treatment EC Relapse

FAS	Micafungin 150 mg/day	Fluconazole 200 mg/day	% Difference, 95% CI [±]
2 week follow-up Assessment			
Endoscopic Cure at EOT[†]	N=228	N=227	
Death	10	9	
LTF/missing	15	10	
No EC Relapse	190 (3 rec'd AFT ^{***})	200 (3 rec'd AFT ^{***})	
EC Relapse	13 (5.7%)	8 (3.5%)	
Total Relapse[‡]	41 (18.0%)	30 (13.2%)	4.8, [-1.9, 11.4]
Endoscopic and Clinical Cure at EOT[*]	N=223	N=220	
Death	10	9	
LTF/missing	14	10	
No EC Relapse	186 (3 rec'd AFT ^{***})	193 (3 rec'd AFT ^{***})	
EC Relapse	13 (5.8%)	8 (3.6%)	
Total Relapse[‡]	40 (17.9%)	30 (13.6%)	4.3, [-2.5, 11.1]
4 week Follow-Up Assessment			
Endoscopic Cure at EOT[†]	188 ^{**}	199 ^{**}	
Death	3	7	
LTF/missing	4	5	
No EC Relapse	165 (10 rec'd AFT ^{***})	172 (6 rec'd AFT ^{***})	
EC Relapse	16 (8.5%)	15 (7.5%)	
Total Relapse[‡]	33 (17.6%)	33 (16.6%)	0.87, [-6.5, 8.5]
Total Relapse up to week 4^{#‡}	74/228 (32.5%)	66/227 (29.1%)	3.4, [-5.1, 11.9]
Endoscopic and Clinical Cure at EOT[*]	184	192	
Death	2	6	
LTF/missing	3	5	
No EC Relapse	163 (12 rec'd AFT ^{***})	169 (9 rec'd AFT ^{***})	
EC Relapse	16 (8.7%)	12 (6.3%)	
Total Relapse[‡]	33 (17.9%)	32 (16.7%)	1.3, [-6.4, 8.9]
Total Relapse up to week 4^{#‡}	73/223 (32.7%)	62/220 (28.2%)	4.6, [-4.0, 13.1]

[†] Primary efficacy endpoint

[‡] Sum of confirmed relapses, missing, LTF, deaths and receipt of antifungal therapy (in patients counted as no relapse at follow-up assessment)

[±] 95%CI calculated around the difference (Micafungin-fluconazole) using the normal approximation to the binomial method (uncorrected)

[#] Cumulative relapses up to end of study (week 4)

^{*} Patients who were both endoscopic cures (grade 0) and clinical cures at end of therapy

^{**} Three patients excluded from week 4 follow-up. Amendment 1 requiring 4 week follow-up approved after these patients completed the study.

^{***} Patients who received systemic antifungal therapy during the follow-up period but were counted as no relapse at follow-up assessment

OPC relapse at 2 and 4 weeks post-treatment

Although not analyzed as a secondary endpoint in the Sponsor's analysis, OPC status at follow-up visits was collected and thus evaluated during this review. OPC relapse was evaluated by the reviewer in a subset of patients who had baseline OPC and were cured of OPC (OPC grade 0 out of 12) and of EC at the end of treatment assessment. At baseline, there were 230/260 (88.5%) and 229/259 (88.4%) patients with OPC and EC in the micafungin and fluconazole groups respectively. Among these patients, there were 179/230 (77.8%) and 175/229 (76.4%) who had a grade 0 (cured) for OPC and EC at EOT.

At 2 weeks post-treatment, there were 35/179 (19.6%) and 9/175 (5.7%) confirmed cases of OPC relapse in the micafungin and fluconazole groups respectively. This resulted in a statistically significant difference (micafungin-fluconazole) of 13.8%, 95% CI [7.1, 20.6]. When including missing, death and use of systemic antifungal treatment the total 2 week relapse rate is 53/179 (29.6%) and 28/175 (16.0%) in the micafungin and fluconazole groups respectively.

At 4 weeks post-treatment, there was a total of 61 and 30 confirmed OPC relapses in the micafungin and fluconazole groups respectively resulting in a statistically significant difference of 16.9%, 95% CI [8.0, 25.9]. An additional analysis including missing, death, and use of systemic antifungal treatment during the 4 week period resulted in overall relapse rates of 89/179 (49.7%) and 66/175 (37.7%) for micafungin and fluconazole groups respectively. The 95% CI around the difference (12.0%) in these two rates was 1.8. to 22.3, which is statistically significant since it excludes zero. A summary of the OPC relapse analyses are summarized below in Table 3.20.

Table 3.20 Study 005 OPC Relapse at 2 and 4 weeks post-treatment

	Micafungin 150 mg N=179	Fluconazole 200 mg N=175	% Difference, 95% CI [±]
OPC & EC Grade 0 at EOT			
OPC Status at 2 week follow-up			
No relapse or AFT Use (OPC grade 0)	126 (70.4)	147 (84.0)	
Relapse (OPC grade > 0)	35 (19.6)	10 (5.7)	13.8, [7.1, 20.6]
Missing	14 (7.8)	15 (8.6)	
No relapse but rec'd AFT Therapy*	4 (2.2)	3 (1.7)	
Total OPC relapse at 2 weeks**	53/179 (29.6)	28/175 (16.0)	13.6, [5.0, 22.2]
OPC Status at 4 week follow-up[†]			
No relapse of AFT use (OPC grade 0)			
Total Relapse (OPC grade > 0)	61 (34.1)	30 (17.1)	16.9, [8.0, 25.9]
Total Missing	20 (11.2)	29 (16.6)	
Total No relapse but rec'd AFT Therapy***	8 (4.5)	7 (4.0)	
Total OPC relapse up to 4 weeks**	89/179 (49.7)	66/175 (37.7)	12.0, [1.8, 22.3]

Values in parenthesis are the percents of patients who were cured of OPC and EC at EOT

*Patients who received systemic antifungal therapy during 2 week follow-up period and had no OPC relapse at follow-up

** Sum of OPC relapses, missing and use of systemic antifungal therapy but counted as no relapse

***Patients who received systemic antifungal therapy during 4 week follow-up period and had no OPC relapse at follow-up

[†] Summary over entire 4 week follow-up period

± 95%CI calculated around the difference (micafungin-fluconazole) using the normal approximation to the binomial method (uncorrected)

An additional analysis looked at OPC relapse in the subset of patients who were cured of OPC at EOT (did not consider EC status at EOT). At EOT, there were 192/230 (83.5%) and 188/229 (82.1%) patients cured of baseline OPC. Among these patients, 36/192 (18.8%) and 10/188 (5.3%) relapsed at 2 weeks. Cumulative relapse rates at 4 weeks were 63/192 (32.8%) and 32/188 (17.0%) resulting in a difference (micafungin-fluconazole) of 15.8%, 95% CI [7.3, 24.3].

When treating missing and use of systemic antifungal therapy as relapse, the two week OPC relapse rates were 62/192 (32.3%) for micafungin 34/188 (18.1%) for fluconazole, difference (micafungin-fluconazole) of 14.2%, 95% CI [5.6, 22.8]. The cumulative 4 week OPC relapse rates for micafungin and fluconazole respectively were 100/192 (52.1%) and 74/188 (39.4%) with a difference (micafungin-fluconazole) of 12.7%, 95% CI [2.8, 22.7].

3.2 Evaluation of Safety

3.2.1 Study FG 463-21-09

The rate of treatment-emergent adverse events in the micafungin 50 mg, 100 mg, 150 mg and fluconazole groups was 87.5%, 91.9%, 88.1%, and 93.3% respectively. Among these events, 50%, 54.8%, 44.1% and 43.3% for micafungin 50 mg, 100 mg, 150 mg and fluconazole were thought to be drug related respectively. Serious adverse events occurred in 15.6%, 11.3%, 11.9% and 8.3% for micafungin 50 mg, 100 mg, 150 mg and fluconazole respectively. Of particular interest to this class of drugs is their effect on hepatic function. In this study, the incident of treatment-emergent hepatic adverse events, irrespective of causality, was 9.4%, 11.3%, 18.6% and 11.7% for micafungin 50 mg, 100 mg, 150 mg and fluconazole respectively. Of additional interest was the rate of treatment-emergent renal adverse events, which occurred in 3.1%, 1.6%, 6.8% and 0% in the micafungin 50 mg, 100 mg, 150 mg and fluconazole groups respectively.

3.2.2 Study 03-7-005

The incidence of any treatment-emergent adverse event was 77.7% and 72.1% in the micafungin 150 mg and fluconazole 200 mg groups respectively. Among these events, 27.7% and 21.3% were thought to be drug related for the micafungin and fluconazole groups respectively. The rate of serious adverse events was 13.5% and 9.3% for micafungin and fluconazole respectively with the most frequent events being pneumonia (2.3% of micafungin and 1.6% for fluconazole), AIDS (1.9% micafungin and 0.8% fluconazole) and kidney failure (1.2% micafungin and 1.2% fluconazole). Incidence of hepatic adverse events was 6.5% and 5.0% in the micafungin and fluconazole groups respectively with the most common events of abnormal liver function tests (1.9% micafungin, 0.8% fluconazole) and alkaline phosphatase increase (2.3% micafungin and 1.9% fluconazole). Renal related adverse events occurred in 3.1% of micafungin treated patients and 2.3% of fluconazole treated patients with one event of kidney failure in the micafungin group thought to be related to study drug.

For a detailed safety review, including discussion regarding hepatic and renal safety, please refer to medical officer's review and ODS consult.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

Subgroup analysis by gender, race and age of the primary endpoint (endoscopy grade 0 at EOT) did not result in numeric differences between the two treatment groups in study 005 [Table 4.1] or study FG09 [Table 4.2].

Table 4.1 Subgroup Analysis of Primary Endpoint-Study 005

	Micafungin 150 mg/day N=260	Fluconazole 200 mg/day N=258
Gender		
Male	114/131 (87.0)	101/116 (87.1)
Female	114/129 (88.6)	126/142 (88.7)
Race		
Black	156/176 (88.6)	160/178 (89.9)
Caucasian	32/38 (84.2)	28/35 (80.0)
Mestizo	26/32 (81.3)	24/29 (82.8)
Other	14/14 (100)	15/16 (93.8)
Age		
<30	54/61 (88.5)	61/64 (95.3)
30-39	99/110 (90.0)	89/102 (87.3)
40-49	53/62 (85.5)	49/59 (83.1)
>=50	22/27 (81.5)	28/33 (84.9)

Table 4.2 Subgroup Analysis of Primary Endpoint-Study FG09

	Micafungin 50 mg/day	Micafungin 100 mg/day	Micafungin 150 mg/day	Fluconazole 200 mg/day
Age				
<35	28/40 (70.0)	22/28 (78.6)	22/25 (88.0)	30/32 (93.8)
>=35	16/24 (66.7)	26/34 (76.5)	31/34 (91.2)	22/28 (78.6)
Race				
Caucasian	14/25 (56.0)	22/26 (84.6)	23/25 (92.0)	18/22 (81.8)
Black	27/31 (87.1)	24/33 (72.7)	26/30 (86.7)	28/32 (87.5)
Gender				
Male	17/30 (56.7)	21/26 (80.8)	30/33 (90.9)	24/28 (85.7)
Female	27/34 (79.4)	27/36 (75.0)	23/26 (88.5)	28/32 (87.5)

4.2 Other Special/Subgroup Populations

In study 005, the Sponsor's fitted exploratory logistic model including patients with HIV found that the odds of endoscopic cure was 2.6 greater in patients with a baseline CD4 count ≥ 100 compared to patients with baseline CD4 count < 100 . Within treatment groups, the odds of endoscopic cure for patients with baseline CD4 count ≥ 100 was 2.75 and 2.30 for micafungin and fluconazole respectively suggesting no

treatment interaction.

In both studies, baseline CD4 (treated continuously) was shown to be a significant predictor of outcome. In subgroup analysis (baseline CD4 \geq 100 and <100) there were no differences between treatment groups (study 005) and among treatment groups (study FG09) observed.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The statistical issues associated with this submission are minimal and mainly related to the Sponsor's handling of patients who received antifungal therapy during the study in the relapse analyses. An additional concern is the rate of missing clinical assessment at the end of therapy visits in both studies. This issue is related to the study conduct and occurred mostly in patients who had prematurely discontinued treatment due to an adverse event. These issues do not affect the efficacy conclusions for either study or the overall conclusions for this submission.

Micafungin dose response for the treatment of EC was demonstrated in the Phase 2 study FG09 with escalating endoscopic response rates of 68.8%, 77.4%, and 89.9% in the micafungin 50 mg, 100 mg and 150 mg groups respectively. The fluconazole control group had a similar response rate to the micafungin 150 mg group of 86.7% suggestive that the target micafungin dose is 150 mg/day. Rates of EC and OPC relapse in study FG09 decreased as a function of increasing micafungin dose. The rate of total EC relapse (including missing, death, and use of antifungal therapy as relapse) was similar between the micafungin 150 mg group and the fluconazole 200 mg group. The OPC relapse rate in the micafungin 150 mg group was numerically but not statistically greater than the fluconazole group at 2 weeks post-treatment. A summary of the main efficacy conclusions is in Table 5.1.

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Table 5.1 Study FG09 Efficacy Results

Outcome	Micafungin			Fluconazole
	50 mg/day	100 mg/day	150 mg/day	200 mg/day
Endoscopic Grade at EOT in FAS[†]	44/64 (68.8)	48/62 (77.4)	53/59 (89.9)	52/60 (86.7)
	<i>95% CI*</i> [57.4, 80.1]	[67.0, 87.8]	[82.1, 97.5]	[78.1, 95.3]
EC Relapse at 2 Week F/U**	13/39 (33.3)	13/48 (27.1)	10/50 (20.0)	8/51 (15.7)
OPC Relapse at 2 Week F/U***	18/38 (47.4)	21/45 (46.7)	17/46 (37.0)	13/50 (26.0)

[†] Primary efficacy endpoint

* 95% CI calculated based on the normal approximation to the binomial method

** Sum of EC relapses, missing and use of systemic antifungal therapy during 2 week f/u period but counted as no relapse evaluated in patients who were clinically and endoscopically cured at EOT

*** Sum of OPC relapses, missing and use of systemic antifungal therapy during 2 week f/u period but counted as no relapse evaluated in patients who were cured of OPC and EC at EOT

The Phase 3 confirmatory study 005 demonstrated non-inferiority (within a pre-specified 10% margin) of micafungin 150 mg/day to fluconazole 200 mg/day in the rate of endoscopic cure [Table 5.2]. The observed difference (micafungin-fluconazole) in the full analysis set was -0.3, 95% CI [-5.9, 5.3]. The rate of EC relapse was similar between the two treatment groups with the most conservative measure (including missing, death, and use of antifungal therapy during follow-up as relapse) resulting in an overall rate of 32.7% and 28.2% in the micafungin and fluconazole groups respectively. OPC relapse up through the end of study (week 4 post-treatment) was, however statistically greater in the micafungin group compared to the fluconazole group in every analysis performed (i.e. relapse only, relapse plus death, missing and use of antifungal therapy as relapse). The calculated difference in overall OPC relapse (sum of OPC relapse, death, missing, and use of antifungal therapy) up through week 4 between micafungin and fluconazole was 12.0% resulting in a 95% CI of 1.8 to 22.3. Although OPC relapse was a secondary measure in study 005 this finding is significant and should be reflected in the product label. A summary of the main efficacy conclusions follows.

Table 5.2 Study 005 Efficacy Results

Outcome	Treatment		% Difference, 95% CI [±]
	Micafungin 150 mg/day	Fluconazole 200 mg/day	
Endoscopic Cure at EOT*	228/260 (87.7)	227/258 (88.0)	-0.3, [-5.9, 5.3]
Total EC Relapse up to week 4^{#†}	73/223 (32.7)	62/220 (28.2)	4.6, [-4.0, 13.1]
Total OPC relapse up to week 4^{#**}	89/179 (49.7)	66/175 (37.7)	12.0, [1.8, 22.3]

[±] 95%CI calculated around the difference (Micafungin-fluconazole) using the normal approximation to the binomial method (uncorrected)

* Primary efficacy endpoint

Cumulative relapses up to end of study (week 4)

[†] Sum of confirmed EC relapses, missing, LTF, deaths and receipt of antifungal therapy (in patients counted as no relapse at follow-up assessment) evaluated in patients who were endoscopically and clinically cured at EOT

** Sum of OPC relapses, missing and use of systemic antifungal therapy but counted as no relapse in patients who were EC and OPC cures at EOT

Results from both studies demonstrate that the micafungin 150 mg/day dose is as efficacious, in terms of endoscopic and clinical outcomes, as comparator fluconazole for the treatment of esophageal candidiasis. Rates of EC relapse in the micafungin 150 mg/day groups were similar to those observed in fluconazole groups. OPC relapse rates were significantly greater in the micafungin 150 mg/day group compared to fluconazole in the single pivotal study. The results seen for OPC relapse are somewhat consistent with those observed in studies conducted with a similar echinocandin, caspofungin. These consistencies suggest a class related effect related to OPC outcome, which is possibly related to the molecular size of echinocandins. These large compounds are possibly not readily absorbed into tissue, thus resulting in a higher rate of relapse in tissue related fungal infections.

5.2 Conclusions and Recommendations

A Phase 2 dose ranging study demonstrated a clear dose response across three micafungin doses (50 mg/day, 100 mg/day and 150 mg/day) in the rate of endoscopic cure for the treatment of esophageal candidiasis (EC). Micafungin dosed at 150 mg/day resulted in similar rates of endoscopic cure and EC relapse at 2 weeks compared to fluconazole 200 mg/day. The overall oropharyngeal candidiasis (OPC) relapse rates at 2 weeks post-treatment decreased as a function of increased micafungin dose. OPC relapse in the micafungin 150 mg dose group was numerically but not statistically greater than fluconazole 200 mg.

A single Phase 3 study demonstrated that micafungin 150 mg/day is non-inferior to fluconazole 200 mg/day in rate of endoscopic cure based on a pre-specified non-inferiority margin of 10%. EC relapse rates at two and four weeks post treatment were similar between treatment groups and commensurate to previously studied therapies for the treatment of EC. OPC relapse rates among patients cured of baseline EC and OPC signs and symptoms were statistically greater in the micafungin group compared to the fluconazole group in this study. At 4 weeks post-treatment, the rate of confirmed OPC relapse was 34.1% in the micafungin 150 mg group compared to 17.1% in the fluconazole group [95% CI around difference between micafungin and fluconazole was (8.0, 25.9)]. Sensitivity analyses including missing, death and use of antifungal therapy as relapse criteria resulted in 4 week post-treatment OPC relapse rates of 49.7% and 37.7% in the micafungin and fluconazole groups respectively resulting in a 95% CI of 1.8 to 22.3.

Based on the findings from the single Phase 3 study with supportive evidence gathered from the Phase 2 dose-ranging study, micafungin 150 mg/day appears to be as efficacious as comparator fluconazole for the treatment of EC with similar levels of EC relapse. OPC relapse rates however were shown to be statistically greater among patients treated with the proposed micafungin 150 mg/day dose compared to fluconazole 200 mg/day in the pivotal Phase 3 study. Based on efficacy, this reviewer recommends approving the micafungin 150 mg dose for treatment of EC noting ~~greater~~ greater rates of OPC relapse in the clinical section of the product label.

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