

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
21-754

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA:	Submission Date(s):
21-506	8/25/04
21-754	4/26/04, 8/26/04 (safety update)
Brand Name	Mycamine for Injection
Generic Name	Micafungin sodium (formerly FK463) for injection
Primary Reviewer	Jang-Ik Lee, Pharm.D., Ph.D.
Pharmacometrics Reviewer	Dakshina Chilukuri, Ph.D.
Team Leader	Philip Colangelo, Pharm.D., Ph.D.
OCPB Division	DPE III (HFD-880)
OND Division	ODE IV DSPIDP (HFD-590)
Sponsor	Fujisawa Healthcare, Inc.
Relevant IND(s)	55, 322
Submission Type; Code	N21-506: NME, 1P (NDA major amendment) N21-754: NME, 1S (original submission)
Formulation; Strength(s)	Lyophilized product for IV infusion; 25 and 50 mg

Proposed Indications and Doses	Adults (mg/day)
Prophylaxis of <i>Candida</i> infections in patients undergoing hematopoietic stem cell transplant (N21-506)	50
Treatment of patients with esophageal candidiasis (N21-754)	150

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I. EXECUTIVE SUMMARY

The Sponsor submitted original micafungin NDAs (N21-506) on April 29, 2002. N21-506 was approvable for the prophylaxis of *Candida* infections in patients undergoing hematopoietic stem cell transplantation. The approvable letter issued on January, 29, 2003 addressed Clinical Pharmacology and Biopharmaceutics (CPB) as well as Clinical deficiencies in N21-506. Subsequently, the Sponsor submitted a major amendment of N21-506 on August 25, 2004 and a new micafungin NDA (N21-754) in the treatment of patients with esophageal candidiasis on April 26, 2004. The two NDAs contain the same CPB information. Therefore, this review is focused on whether the Sponsor fulfilled the CPB deficiencies in the approvable letter. In addition, Dr. Chilukuri reviewed micafungin exposure-response relationships.

A. Recommendation

This reviewer recommends requesting the Sponsor to adequately assess micafungin pharmacokinetics in pediatric patients aged between 2 and 17 years. As stated in the CPB review for the original submission of N21-506, pharmacokinetic blood samples appear to be inadequately collected in the pivotal pediatric study (98-0-043) conducted in patients with febrile neutropenia. There are a number of unexplainable outlier concentrations and many samples were not collected at critical time points. In the study report, the sponsor suspected that those outlier samples were drawn from a micafungin infusion port. The manual and statistical (i.e., Tukey's procedure) methods of outlier exclusion applied by the Sponsor did not adequately resolve the pharmacokinetic discrepancies and there are still too many inconsistencies in the estimated pharmacokinetic parameter values even after the exclusion of outliers, which preclude the determination of pediatric micafungin doses based on pharmacokinetic data.

The Sponsor has fulfilled the other CPB deficiencies that were identified in the original submission of N21-506. The Sponsor adequately determined the basic parameter values, dose linearity, and time dependency in micafungin pharmacokinetics at the proposed clinical doses at steady state. The Sponsor determined the complete steady-state pharmacokinetic profiles of the most abundant metabolite (M5) and active metabolites (M1 and M2) of micafungin following multiple doses. The Sponsor adequately determined the extent of protein binding of parent compound *in vivo*. The Sponsor also adequately analyzed the effects of gender and race on micafungin pharmacokinetics. In addition, the Sponsor determined micafungin pharmacokinetics in premature infants and evaluated drug-drug interactions further.

B. Post-Marketing Commitments

The pharmacokinetics of micafungin in pediatric patients between the ages of _____ years need to be adequately determined. This may be performed as a post-approval/post-marketing commitment or a pediatric written request.

C. Summary of Clinical Pharmacology and Biopharmaceutics Findings

Basic Pharmacokinetic Parameters

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

Table 1: Micafungin pharmacokinetic parameter values (mean \pm SD) determined following an 1-hour intravenous infusion of micafungin to HIV-positive patients with esophageal candidiasis.

Time	PK Parameter	50 mg/day (n = 20)	100 mg/day (n = 20)	150 mg/day (n = 14)
After First Dose	C _{max} ($\mu\text{g/mL}$)	4.1 \pm 1.4	8.0 \pm 2.4	11.6 \pm 3.1
	AUC _T ($\mu\text{g}\cdot\text{hr/mL}$)	35.7 \pm 8.9	74.5 \pm 18.7	104.3 \pm 26.3
	AUC _{∞} ($\mu\text{g}\cdot\text{hr/mL}$)	53.4 \pm 17.8	107.9 \pm 30.7	150.6 \pm 44.6
	CL (mL/hr/kg)	19.3 \pm 5.9	19.8 \pm 5.4	20.4 \pm 5.5
	V _z (mL/kg)	401 \pm 124	388 \pm 114	407 \pm 103
	t _{1/2} (hr)	14.9 \pm 4.3	13.8 \pm 3.0	14.1 \pm 2.6
At Steady State	C _{max} ($\mu\text{g/mL}$)	5.1 \pm 1.1	10.1 \pm 2.6	16.4 \pm 6.5
	AUC _T ($\mu\text{g}\cdot\text{hr/mL}$)	54.3 \pm 13.1	115.3 \pm 24.9	166.5 \pm 40.4
	CL (mL/hr/kg)	18.1 \pm 4.2	18.1 \pm 4.3	17.5 \pm 4.8
	t _{1/2} (hr)	15.6 \pm 2.8	16.9 \pm 4.4	15.2 \pm 2.2

Micafungin Metabolites: Whereas metabolites M1 and M2 have comparable *in vitro* antifungal activity to the parent compound, metabolite M5 is inactive but most abundant (see Pharm/Tox Review and previous CPB Review in DFS). Table 2 presents pharmacokinetic parameter values for micafungin metabolites M1, M2, and M5 determined following a steady-state intravenous infusion of micafungin 50 mg, 100 mg, or 150 mg over an hour.

Table 2: Pharmacokinetic parameter values of micafungin metabolites determined following a steady-state intravenous infusion of daily micafungin doses over an hour to HIV-positive patients with esophageal candidiasis.

Metabolite	PK Parameter	50 mg/day (n = 20)	100 mg/day (n = 20)	150 mg/day (n = 14)
M1	T _{max} (hr)	12.6 \pm 12.9	6.4 \pm 8.1	4.3 \pm 6.7
	C _{max} ($\mu\text{g/mL}$)	0.31 \pm 0.14	0.62 \pm 0.25	0.93 \pm 0.34
	AUC _T ($\mu\text{g}\cdot\text{hr/mL}$)	6.0 \pm 2.1	12.1 \pm 4.0	18.1 \pm 4.7
	t _{1/2} (hr)	64.6 \pm 31.8	62.0 \pm 30.6	53.5 \pm 15.5
M2	T _{max} (hr)	22.9 \pm 24.7	21.2 \pm 22.6	26.2 \pm 26.6
	C _{max} ($\mu\text{g/mL}$)	0.08 \pm 0.02	0.10 \pm 0.03	0.14 \pm 0.04
	AUC _T ($\mu\text{g}\cdot\text{hr/mL}$)	0.98 \pm 0.69	1.81 \pm 0.55	2.57 \pm 0.77
	t _{1/2} (hr)	NC	NC	NC
M5	T _{max} (hr)	5.7 \pm 3.3	6.9 \pm 3.8	8.4 \pm 3.4
	C _{max} ($\mu\text{g/mL}$)	0.41 \pm 0.20	0.63 \pm 0.21	1.00 \pm 0.29
	AUC _T ($\mu\text{g}\cdot\text{hr/mL}$)	7.84 \pm 3.52	12.8 \pm 4.5	19.8 \pm 5.7
	t _{1/2} (hr)	22.7 \pm 4.5	25.3 \pm 5.2	24.5 \pm 9.2

NC, not calculable

Exposure to micafungin metabolites was low: M1 and M2 accounted for 11% and 2% of the systemic exposure to parent drug at steady state, respectively. M5 was the predominant metabolite in plasma with AUC τ values ranging between 6% and 24% of those for the parent compound at steady state.

Linearity, Accumulation, and Time Dependency in Micafungin Pharmacokinetics

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

Mass Balance

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

Protein Binding

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

Exposure-Response Relationship

Based on the dose-effectiveness analysis, it was determined that the effectiveness of micafungin increases as dose is increased and maximum effectiveness is seen at both 100 and 150 mg doses. For the purpose of analysis, multiple endpoints of effectiveness were used, which were endoscopic grade of 0 at end of therapy (EOT), clinical response at EOT, mycological response at EOT, proportion of patients showing no relapse at 2-weeks following EOT. Baseline severity of the disease was not found to affect the outcome of the treatment. The dose-relapse rate relationship indicated that the relapse rate for the 100 mg dose is 15% higher than the 150 mg

dose. This indicated that while the comparable effectiveness based on the primary and secondary endpoints were seen for the 100 and 150 mg doses, the higher relapse rate seen in the 100 mg dose group is indicative of the 150 mg dose being more appropriate for the treatment of esophageal candidiasis. The dose-toxicity analysis showed no statistically significant relationship between dose and liver enzyme elevations measured at various time points, day 7, day 14, EOT and end of study (EOS), which were 2-weeks after EOT.

Special Populations

Premature Infants: Table 3 presents micafungin pharmacokinetic parameter values determined following a single intravenous dose of 0.75, 1.5, or 3.0 mg/kg infused over 30 minutes to premature infants (Study 99-0-063).

Table 3: Pharmacokinetic parameter values (Mean \pm SD) of micafungin following a 30-min infusion of micafungin to premature infants.

Body Weight (g)	Dose (mg/kg)	N	C _{max} (μ g/mL)	AUC _{0-24hr} (μ g-hr/mL)	CL (mL/hr/kg)	t _{1/2} (hr)	V _{ss} (mL/kg)
500 - 1000	0.75	4	1.31 \pm 0.31	8.8 \pm 1.4	79.3 \pm 12.5	5.7 \pm 0.6	693 \pm 129
>1000	0.75	6	2.54 \pm 0.92	16.5 \pm 9.0	58.0 \pm 49.1	8.1 \pm 1.7	641 \pm 605
	1.5	5	4.15 \pm 1.13	34.5 \pm 5.6	38.6 \pm 8.9	8.3 \pm 2.2	440 \pm 57
	3.0	6	9.28 \pm 5.31	59.5 \pm 29.0	71.1 \pm 79.1	8.5 \pm 1.8	735 \pm 673

Micafungin concentrations were lower in smaller (500 to 1000 g) than larger (> 1000 g) infants at the same dose of 0.75 mg/kg body weight. Micafungin CL per body weight decreased with increasing body weight ($r = 0.37$). Compared with adult data (Table 1), the respective mean CL and terminal t_{1/2} of micafungin were faster and shorter in premature infants. The AUC_{0-24hr} achieved in premature infants following a single dose of 3.0 mg/kg were much smaller than that achieved in adult patients received a single dose of 150 mg.

Gender: Micafungin exposure at the same administered dose is apparently greater in females than males. When compared using pooled data determined in healthy adult subjects (Studies 03-0-175, 03-0-176, 03-0-177, and 03-0-178), the respective mean values of the C_{max} and AUC _{τ} for micafungin following a steady-state intravenous dose of 150 mg were greater by 31% and 23% but the mean value of terminal t_{1/2} was shorter by 1.5 hr in females than males (Table 4). However, the mean values of micafungin CL at steady state were similar between males and females.

Table 4: Comparison of micafungin pharmacokinetic parameters (mean \pm SD) determined following a steady-state intravenous dose of 150 mg between healthy male and female subjects.

PK Parameter	Female (n = 27)	Male (n = 80)	Female / Male Ratio
Body Weight (kg)	62.4 \pm 10.0	75.3 \pm 10.5	0.83 (p < 0.001)
C _{max} (μ g/mL)	24.7 \pm 6.3	18.8 \pm 3.0	1.31 (p = 0.002)
AUC _{τ} (μ g-hr/mL)	285 \pm 54	232 \pm 35	1.23 (p < 0.001)
CL _{ss} (mL/min/kg)	0.147 \pm 0.023	0.147 \pm 0.021	1.00 (p = 0.91)
t _{1/2} (hr)	14.2 \pm 1.6	15.7 \pm 2.5	1.5 hr* (p = 0.91)

* difference

The gender difference in the C_{max} and AUC appears to be mostly due to the difference in body weight: the mean value of baseline body weight was smaller by 17% in females than males. When compared using data determined in HIV-positive patients with esophageal candidiasis, the mean weight-adjusted values of micafungin C_{max}/Dose, AUC/Dose, and CL for males and females were comparable. Thus, micafungin dosage adjustment is not recommended based on gender difference.

Race: When compared using pooled data determined in healthy adult subjects who enrolled in drug-drug interaction studies conducted in the United States, white, black, and Hispanic subjects showed comparable mean values in micafungin pharmacokinetic parameters (Table 5). However, when compared the pooled data with the data collected in a Japanese study, Japanese showed significantly greater mean value in dose-adjusted C_{max} compared to all other racial groups by 19%, and greater mean value in dose-adjusted AUC_∞ by 26% compared to blacks. The greater mean values in the C_{max} and AUC in Japanese subjects appear to be due to smaller body weight. The mean values for weight-adjusted CL and terminal t_{1/2} were not different. Thus, micafungin dosage adjustment is not recommended based on racial difference.

Table 5: Comparison of micafungin pharmacokinetic parameters (mean ± SD) determined following a single intravenous dose of 100 mg between different races.

Study	01-0-104, 01-0-105, 01-0-110, 01-0-111			FJ-463-0004
Race	White (n = 50)	Black (n = 5)	Hispanic (n = 15)	Japanese (20)
Body Weight (kg)	75.5 ± 13.0	85.2 ± 8.0	72.8 ± 10.4	59.7 ± 7.7*
C _{max} (µg/mL)	8.30 ± 1.43	8.19 ± 1.12	8.42 ± 1.12	9.92 ± 1.13* ^
AUC _∞ (µg-hr/mL)	132 ± 23	117 ± 10[#]	125 ± 17	148 ± 19^{#, ^}
t _{1/2} (hr)	14.9 ± 1.6	13.7 ± 0.8	13.9 ± 1.5	15.1 ± 0.9
CL (mL/min/kg)	0.175 ± 0.028	0.168 ± 0.012	0.188 ± 0.025	0.193 ± 0.025

* significantly different from others, [#] different between the two comparisons, ^ adjusted to 100-mg dose

Drug-Drug Interactions

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

Effect of Micafungin on Mycophenolate Mofetil (MMF) and Fluconazole Pharmacokinetics: A steady-state intravenous dose of micafungin 150 mg did not change the extent of oral absorption of MMF and exposure to MPA following a single oral dose of MMF 1.5 g. Similarly, a steady-state intravenous dose of micafungin 150 mg did not affect fluconazole pharmacokinetics following a single oral dose of fluconazole 200 mg.

Effect of Fluconazole, MMF, Nifedipine, Rifampin, Ritonavir, and Sirolimus on Micafungin Pharmacokinetics: A single oral dose of fluconazole 200 mg, MMF 1.5 g, nifedipine 10 mg, or sirolimus 6 mg did not affect micafungin pharmacokinetics determined following a steady-state intravenous dose of micafungin 150 mg. Multiple oral doses of ritonavir 300 mg b.i.d. or rifampin 600 mg q.d. had no effect on micafungin pharmacokinetics determined following a single intravenous dose of micafungin 200 mg.

Date: _____

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II. QUESTION-BASED REVIEW

A. General Attributes

1. *What regulatory background or history information contribute to the assessment of the clinical pharmacology and biopharmaceutics of this drug?*

The Sponsor submitted original micafungin NDAs (N21-506, _____) on April 29, 2002. _____ N21-506 was approvable for the prophylaxis of _____ in patients undergoing hematopoietic stem cell transplantation. The approvable letter issued on January, 29, 2003 addressed Clinical Pharmacology and Biopharmaceutics (CPB) as well as Clinical deficiencies in N21-506. Subsequently, the Sponsor submitted a major amendment of N21-506 on August 25, 2004 and a new micafungin NDA (N21-754) in the treatment of esophageal candidiasis on April 26, 2004. The two NDAs are the same in CPB information. Therefore, this review is focused on whether the Sponsor fulfilled the CPB deficiencies in the previous submission. To fulfill the deficiencies, the Agency requested the Sponsor to;

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

In addition to the review for the deficiencies, this review includes the reviews for exposure-response relationship, additional mass balance study, additional drug-drug interaction studies, and associated analytical methods submitted in current applications.

2. *What are the proposed therapeutic indications, dosage, and route of administration?*

The Sponsor proposed to use Micafungin for Injection[®] for the prophylaxis of *Candida* infections in patients undergoing hematopoietic stem cell transplantation (N21-506) and for the treatment of patients with esophageal candidiasis (N21-754). The proposed adult _____ doses are 50 mg per day _____ for the prophylaxis indication, and 150 mg per day _____ for the treatment indication, respectively.

_____ Micafungin for Injection[™] is proposed to be administered by intravenous infusion once a day.

B. General Clinical Pharmacology

1. *What is the basis for selecting the response endpoints and how are they measured in clinical pharmacology and clinical studies?*

The primary response endpoint is endoscopic cure (endoscopic grade=0) and this is measured by endoscopic assessment of the lesions in the affected area. This was studied at EOT and 2-weeks after EOT for most clinical studies and 4-weeks after EOT in the Phase 3 study. The secondary

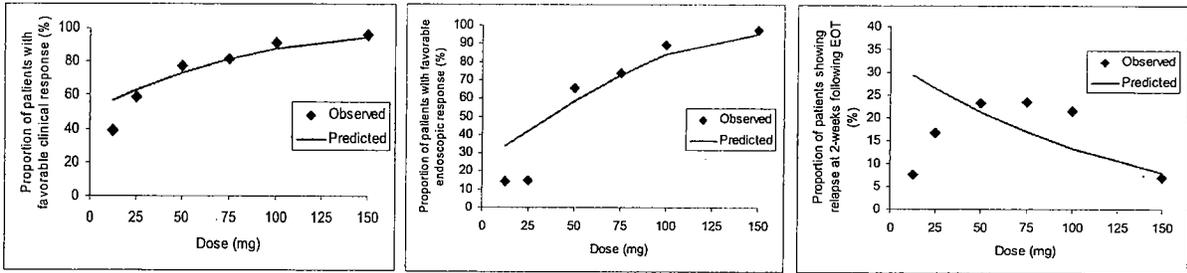
endpoint was clinical response, which was determined by resolution of disease symptoms. Most fungal infections are known to relapse in a certain proportion of patients and hence relapse was also a response endpoint and this was determined by endoscopic assessment 2 and 4-weeks after EOT.

2. Exposure-response

a. The sponsor studied various doses between 12.5 and 150 mg. What doses should be approved for the treatment of esophageal candidiasis?

Based on the pharmacometric reviewer’s (Dakshina Chilukuri, Ph.D.) analysis of the available effectiveness data for the range of doses 12.5-150 mg, the most appropriate dose of micafungin for the treatment of esophageal candidiasis is 150 mg. The reviewer found a sigmoid relationship between dose and the effectiveness endpoints as shown in Figure 1. As seen in Figure 1, there were increases in the proportion of patients with favorable clinical and endoscopic responses as the dose was increased from 12.5 to 150 mg and comparable responses between 100 and 150 mg. The dose-relapse rate relationship indicated that the relapse rate for the 100 mg dose is 15% higher than the 150 mg dose. This indicated that while the comparable effectiveness based on the primary and secondary endpoints were seen for the 100 and 150 mg doses, the higher relapse rate seen in the 100 mg dose group is indicative of the 150 mg dose being more appropriate for the treatment of esophageal candidiasis.

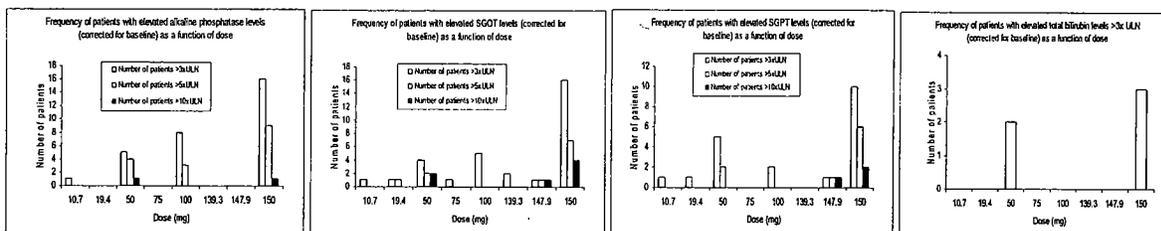
Figure 1: Plot of the dose-response relationship of micafungin for the primary endpoint of endoscopic cure (grade 0 at EOT) and secondary endpoint of clinical cure. Also plotted is the relationship of dose and relapse rate.



The effect of covariates such as dose on the elevations in liver enzyme levels normalized to baseline levels was studied. Also, an effect of time of enzyme level measurement subsequent to drug administration was studied on the elevation of the enzyme levels. The results of the analysis indicated that the enzyme levels relative to the baseline levels are not related to the dose of micafungin or the time of enzyme level measurement (duration of exposure). A detailed analysis was performed with specific emphasis on patients whose values were greater than 3 times the upper limit of normal ($3 \times \text{ULN}$), $>5 \times \text{ULN}$, $>10 \times \text{ULN}$. The relationship of dose versus these high enzyme values was performed using logistic regression in SAS. These results indicated a lack of statistically significant dose effect on the elevations in enzyme values. However, as seen below in Figure 2, a frequency plot of patients with elevated enzyme values as a function of dose indicates that a higher number of patients receiving 150 mg dose had elevated enzyme levels. This effect appears more pronounced with alkaline phosphatase, SGOT sand SGPT and can be readily seen that for the clinical dose of 150 mg micafungin is associated with

a higher number of elevations in liver enzymes. For bilirubin, none of patients had enzyme values >5x ULN and there does not seem to be a dose-related elevations of bilirubin.

Figure 2: A frequency plot of patients with elevated enzyme levels as a function of dose.



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In summary, both the 100 and 150 mg doses of micafungin resulted in comparable cure rates based on endoscopic and clinical response rates. However, patients who received the 150 mg dose had a lower rate of relapse compared to the 100 mg dose. Also a higher number of patients receiving 150 mg micafungin showed elevated liver enzyme levels (except bilirubin) compared to the patients receiving 100 mg dose. Thus, while the 150 mg dose results in better effectiveness, based on clinical and endoscopic endpoints and relapse, it also results in a higher number of patients with elevated liver enzyme elevations. In view of the higher relapse in 100 mg dose seen as a safety issue, the 150 mg micafungin dose is recommended for approval for the treatment of esophageal candidiasis. A statement in the package insert will be added indicating the potential of liver toxicity of micafungin.

b. *What is the effect of baseline condition of the disease on the effectiveness of various doses of micafungin?*

The analysis conducted by the FDA reviewer indicated that patients with baseline severity characterized by endoscopic grade '4' did not respond to micafungin differently than patients with baseline severity '1'. Hence it was concluded that there is no effect of the baseline condition of the disease on the effectiveness of micafungin.

c. *What are the characteristics of the exposure-response relationships for efficacy and safety? If relevant, indicate the time to onset of the pharmacological response or clinical endpoint.*

The applicant conducted an exposure-response study using data generated in a phase 2 study. The study was a phase 2, multicentre, prospectively randomized, reference therapy controlled, double-blind, and parallel-group study. Eligible patients were randomized 1:1:1:1 to 50, 100 or 150 mg/day micafungin or 200 mg/day fluconazole. The planned treatment period was 14 days, but was allowed to extend to 21 days for patients who did not achieve endoscopic clearance by Day 14. Pharmacokinetic profiles (assessed on Day 1 and the last day of treatment) were estimated and trough concentrations (Days 3, 7 and 14) were determined. In general, the pharmacokinetics observed in this patient population were similar to those obtained in earlier studies in adults. Micafungin exhibited linear pharmacokinetics over the dose range investigated (50 - 150 mg/day).

No differences in pharmacokinetic parameters were observed as a function of gender or race (Caucasian, Black and Mulatto). There was a difference in mean exposure between patients in

whom endoscopic clearance was observed and those in whom infection persisted. On Day 1, the respective mean AUC₂₄ values were 74 vs. 38 µg.hr/mL for the patients in whom endoscopic clearance was observed and those in whom infection persisted. The mean AUC₂₄ in the 50 mg micafungin treatment group (36 µg×hr/mL) was similar to that of the non-responders. In comparison, the corresponding values in the 100 and 150 mg treatment groups were 75 and 104 µg×hr/mL respectively. These data suggest that a daily dose of between 100 and 150 mg would appear necessary to achieve the optimal exposure associated with a therapeutic response against esophageal candidiasis in this patient population. The dose response findings based on the full analysis set of 185 patients treated with micafungin in the clinical study indicated greater effectiveness with 100 mg/day and 150 mg/day micafungin compared to 50 mg/day micafungin.

Table 6. Mean values of pharmacokinetic parameters correlated with effectiveness as measured by endoscopic grade at end of therapy.

Parameter	Units	Mean value in patients with endoscopic grade =0 (n=43)	Mean value in patients with endoscopic grade >0 (n=9)	p value*
Profile 1				
AUC ₂₄	µg*hr/mL	74.13	38.23	0.0026
C _{max}	µg/mL	8.07	4.76	0.0158
Profile 2				
AUC ₇₂	µg*hr/mL	171.55	82.49	0.0017
C _{max}	µg/mL	10.80	5.20	0.0071

* Student's t-Test: Two-Sample Assuming Equal Variances

d. *Are the dose and dosing regimen consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?*

There are no unresolved issues with respect to drug dosing and administration issues.

e. *Does this drug prolong the QT or QTc interval?*

There is no evidence of prolongation of QT and QTc intervals following the administration of micafungin alone or in combination with ritonavir (Study FG-463-21-15).

3. *What are the pharmacokinetic characteristics of the drug and its metabolite?*

a. *What are the basic pharmacokinetic parameter values of micafungin and its metabolites following the administration of the proposed clinical dose at steady state?*

Micafungin: Table 7 displays the pharmacokinetic parameter values for micafungin estimated following the first (Day 1) and steady-state (Day 14 or 21) intravenous infusion of micafungin 50 mg, 100 mg, and 150 mg a day over an hour to 54 HIV-positive patients with esophageal candidiasis (Study FG-463-21-09). The mean ± SD values of maximum concentration (C_{max}), area under the concentration-time curve within dosing interval (AUC_τ), systemic clearance (CL), and terminal half-life (t_{1/2}) for micafungin following an intravenous dose of micafungin 100 mg at steady state were 10.1 ± 2.6 µg/mL, 115 ± 25 µg-hr/mL, 18.1 ± 4.3 mL/hr/kg body weight, and 16.9 ± 4.4 hr, respectively.

Table 7: Pharmacokinetic parameter values (mean \pm SD) for micafungin determined following the first and steady-state intravenous infusion of daily micafungin doses over an hour to HIV-positive patients with esophageal candidiasis (Study FG-463-21-09).

Time	PK Parameter	50 mg/day (n = 20)	100 mg/day (n = 20)	150 mg/day (n = 14)
After First Dose	C _{max} ($\mu\text{g/mL}$)	4.1 \pm 1.4	8.0 \pm 2.4	11.6 \pm 3.1
	AUC _T ($\mu\text{g}\cdot\text{hr/mL}$)	35.7 \pm 8.9	74.5 \pm 18.7	104.3 \pm 26.3
	AUC _{∞} ($\mu\text{g}\cdot\text{hr/mL}$)	53.4 \pm 17.8	107.9 \pm 30.7	150.6 \pm 44.6
	CL (mL/hr/kg)	19.3 \pm 5.9	19.8 \pm 5.4	20.4 \pm 5.5
	V _z (mL/kg)	401 \pm 124	388 \pm 114	407 \pm 103
	t _{1/2} (hr)	14.9 \pm 4.3	13.8 \pm 3.0	14.1 \pm 2.6
At Steady State*	C _{max} ($\mu\text{g/mL}$)	5.1 \pm 1.1	10.1 \pm 2.6	16.4 \pm 6.5
	AUC _T ($\mu\text{g}\cdot\text{hr/mL}$)	54.3 \pm 13.1	115.3 \pm 24.9	166.5 \pm 40.4
	CL (mL/hr/kg)	18.1 \pm 4.2	18.1 \pm 4.3	17.5 \pm 4.8
	t _{1/2} (hr)	15.6 \pm 2.8	16.9 \pm 4.4	15.2 \pm 2.2

* Day 14 or Day 21

Micafungin Metabolites: Whereas metabolites M1 and M2 have comparable *in vitro* antifungal activity to the parent compound, metabolite M5 is inactive but most abundant (see Pharm/Tox Review and previous CPB Review in DFS). Table 8 displays pharmacokinetic parameter values for micafungin metabolites (M1, M2, and M5) estimated following a steady-state (Day 14 or Day 21) intravenous infusion of micafungin 50, 100, and 150 mg (Study FG-463-21-09). The terminal t_{1/2} of M1 was longer than the t_{1/2} of parent compound but remained relatively constant across the dose range studied, with a mean value of 62 hours at the micafungin dose of 100 mg. The terminal t_{1/2} of M5 was shorter than that of M1 but still longer than that of parent compound, with a mean value of 25 hours at the micafungin dose of 100 mg.

Table 8: Pharmacokinetic parameter values (mean \pm SD) of micafungin metabolites determined following a steady-state intravenous infusion of daily micafungin doses over an hour to HIV-positive patients with esophageal candidiasis (Study FG-463-21-09).

Metabolite	PK Parameter	50 mg/day (n = 20)	100 mg/day (n = 20)	150 mg/day (n = 14)
M1	T _{max} (hr)	12.6 \pm 12.9	6.4 \pm 8.1	4.3 \pm 6.7
	C _{max} ($\mu\text{g/mL}$)	0.31 \pm 0.14	0.62 \pm 0.25	0.93 \pm 0.34
	AUC _T ($\mu\text{g}\cdot\text{hr/mL}$)	6.0 \pm 2.1	12.1 \pm 4.0	18.1 \pm 4.7
	t _{1/2} (hr)	64.6 \pm 31.8	62.0 \pm 30.6	53.5 \pm 15.5
M2	T _{max} (hr)	22.9 \pm 24.7	21.2 \pm 22.6	26.2 \pm 26.6
	C _{max} ($\mu\text{g/mL}$)	0.08 \pm 0.02	0.10 \pm 0.03	0.14 \pm 0.04
	AUC _T ($\mu\text{g}\cdot\text{hr/mL}$)	0.98 \pm 0.69	1.81 \pm 0.55	2.57 \pm 0.77
	t _{1/2} (hr)	NC	NC	NC
M5	T _{max} (hr)	5.7 \pm 3.3	6.9 \pm 3.8	8.4 \pm 3.4
	C _{max} ($\mu\text{g/mL}$)	0.41 \pm 0.20	0.63 \pm 0.21	1.00 \pm 0.29
	AUC _T ($\mu\text{g}\cdot\text{hr/mL}$)	7.84 \pm 3.52	12.8 \pm 4.5	19.8 \pm 5.7
	t _{1/2} (hr)	22.7 \pm 4.5	25.3 \pm 5.2	24.5 \pm 9.2

NC, not calculable

Exposure to micafungin metabolites was low. As determined in Study FG-463-21-09, plasma concentrations of M1 were low with its AUC_τ values on Day 1 being less than 0.01% of the parent compound's (Table 9). The values were approximately 11% of the parent compound's at steady state (Day 14 or 21) in all treatment groups indicating accumulation of this metabolite relative to micafungin. Plasma concentrations of M2 on Day 1 were not quantifiable for any subject over any dose level. The AUC_τ values for M2 at Day 14 or 21 were approximately 2 % of the values for parent drug. M5 was the predominant metabolite in plasma with its AUC_τ values between 7% and 10% of those for parent compound on Day 1. The ratio of M5 to parent compound ranged between 6% and 24% at steady state.

Table 9: Comparison of C_{max} and AUC values between micafungin and its metabolites determined following the first and steady-state (Day 14 or 21) intravenous infusion of micafungin over an hour to HIV-positive patients with esophageal candidiasis (Study FG-463-21-09).

PK Parameter	Dose (mg/day)	Time	Absolute Value (Mean)				Ratio to Micafungin		
			Micafungin	M1	M2	M5	M1	M2	M5
C _{max} (µg/mL)	50 (n = 20)	Day 1	4.07	0.06	NC	0.20	0.01	< 0.01	0.05
		Day 14 or 21	5.08	0.31	0.08	0.41	0.06	0.02	0.08
	100 (n = 20)	Day 1	8.04	0.08	NC	0.36	0.01	< 0.01	0.04
		Day 14 or 21	10.10	0.62	0.10	0.63	0.06	0.01	0.06
	150 (n = 14)	Day 1	11.56	0.11	NC	0.53	0.01	< 0.01	0.05
		Day 14 or 21	16.40	0.93	0.14	1.00	0.06	0.01	0.06
AUC _τ (µg·hr/mL)	50 (n = 20)	Day 1	35.7	NC	NC	3.66	< 0.01	< 0.01	0.10
		Day 14 or 21	54.25	5.96	0.98	7.84	0.11	0.02	0.14
	100 (n = 20)	Day 1	74.49	NC	NC	6.57	< 0.01	< 0.01	0.09
		Day 14 or 21	115.26	12.12	1.81	12.77	0.11	0.02	0.11
	150 (n = 14)	Day 1	104.32	NC	NC	9.77	< 0.01	< 0.01	0.09
		Day 14 or 21	166.46	18.07	2.57	19.75	0.11	0.02	0.12

NC, not calculable

b. Based on pharmacokinetic parameters, what is the degree of linearity and accumulation in the dose-concentration relationship?

Micafungin pharmacokinetics are apparently linear over the proposed daily dose range of 50 mg to 150 mg administered once daily: all coefficients (r) for the correlation between micafungin dose, and micafungin C_{max} or AUC at Day 1 and at steady state displayed in Table 7 were > 0.99. Micafungin accumulation ratios (ratio of micafungin AUC_τ at steady state to AUC_τ at Day 1 presented in Table 7) were 1.52, 1.55, and 1.60 at daily micafungin doses of 50, 100, and 150 mg, respectively.

c. How do the pharmacokinetic parameters change with time following repeated dosing?

The mean values of systemic CL and terminal t_{1/2} estimated following an intravenous infusion of micafungin over an hour at steady state were not meaningfully different from the values estimated at Day 1 (Table 7). The ratios of micafungin AUC_τ at steady state to AUC_∞ at Day 1 at daily micafungin doses of 50 mg, 100 mg, and 150 mg were 1.11, 1.14, and 1.16, respectively (Table 7). The mean trough concentrations of micafungin measured at Days 3, 7, and 14 remained relatively stable, and the mean trough concentrations of micafungin metabolites were

comparable when measured at Days 7 and 14 (Table 10). This supports that no considerable accumulation of micafungin and its metabolites occurs with micafungin administrations at the daily dose range of 50 to 150 mg.

Table 10: Micafungin trough concentrations (mean \pm SD) determined following repeated intravenous infusions of micafungin over an hour for 14 days or longer to HIV-positive patients with esophageal candidiasis (Study FG-463-21-09).

Dose (mg/day)	Time (Day)	Micafungin ($\mu\text{g/mL}$)	M1 ($\mu\text{g/mL}$)	M2 ($\mu\text{g/mL}$)	M5 ($\mu\text{g/mL}$)
50 (n = 20)	1	0.78 \pm 0.27	< 0.05	< 0.05	0.17 \pm 0.07
	3	1.18 \pm 0.81	0.09 \pm 0.02	< 0.05	0.24 \pm 0.10
	7	1.10 \pm 0.33	0.19 \pm 0.05	< 0.05	0.30 \pm 0.12
	14	1.06 \pm 0.28	0.22 \pm 0.04	< 0.05	0.30 \pm 0.16
100 (n = 20)	1	1.65 \pm 0.73	0.07*	< 0.05	0.31 \pm 0.11
	3	2.84 \pm 1.58	0.18 \pm 0.05	< 0.05	0.47 \pm 0.18
	7	3.84 \pm 4.18	0.42 \pm 0.13	< 0.05	0.63 \pm 0.40
	14	2.51 \pm 0.57	0.48 \pm 0.12	0.07 \pm 0.02	0.62 \pm 0.30
150 (n = 14)	1	2.21 \pm 0.64	0.11*	< 0.05	0.51 \pm 0.17
	3	3.97 \pm 3.22	0.27 \pm 0.06	< 0.05	0.81 \pm 0.43
	7	4.53 \pm 3.51	0.65 \pm 0.18	0.05 \pm 0.04	0.84 \pm 0.49
	14	3.53 \pm 2.27	0.46 \pm 0.40	0.07 \pm 0.06	0.83 \pm 0.07

* not calculable SD

d. What are the characteristics of drug excretion (mass balance)?

Following a single intravenous infusion of ^{14}C -micafungin 25 mg to healthy subjects (Study FG-463-21-14), total radioactivity was eliminated primarily in the feces, accounting for a mean of 71.0% (n = 6; range, 64.7% - 77.5%) of the administered dose by the end of the continuous collection period (28 days post dose). Excretion *via* the feces was very slow with a mean recovery of 60.6% (range, 55.5% - 65.8%) at 14 days post dose. Excretion *via* urine accounted for a mean of 11.6% (range, 9.4% - 14.1%) of the dose by the end of the collection period. Total radioactivity in feces and urine by the end of the collection period accounted for a mean of 82.5% (range, 76.4% - 87.9%) of the dose. On Day 34, a mean of 0.19% of the dose was recovered in 24 hr period. The recovery reduced to a mean of 0.06% by the final collection interval (Day 55). Extrapolation of the fecal excretion data suggested that overall recovery between Days 29 and 55 accounted for a mean of 4.9% of the administered dose.

The mean C_{max} of total radioactivity observed at the end of the infusion was similar to that of parent drug (Table 11). However, the mean AUC of total radioactivity were approximately 6-fold greater than that of parent drug. The mean terminal t_{1/2} of total radioactivity was much longer than that of parent drug. By 24 hours post dose, plasma concentrations of total radioactivity decreased to a mean of 0.78 $\mu\text{g-eq/mL}$ (range, 0.60 - 1.04 $\mu\text{g-eq/mL}$) and further decreased to 0.45 $\mu\text{g-eq/mL}$ (range, 0.34 - 0.63 $\mu\text{g/mL}$) by 72 hours post dose. By 28 days post dose, the mean concentration decreased to 0.11 $\mu\text{g-eq/mL}$ (range, 0.07 - 0.16 $\mu\text{g eq/mL}$) and by 55 days post dose, concentrations were close to or below the limit of quantitation. The greater systemic exposure observed for total radioactivity appears to reflect the formation of radiolabeled metabolites or breakdown products which persist in the circulation longer than the parent drug.

Concentrations of parent drug were up to 23-fold greater than corresponding estimates for metabolite M5. The median time to Cmax (Tmax) was substantially longer for M5 compared with parent drug, suggesting relatively slow formation of M5. The terminal t½ was also longer for M5 compared with parent drug. No quantifiable concentrations of M1 and M2 metabolites were reported at the dose studied.

Table 11: Pharmacokinetics parameter values of micafungin and total radioactivity following an intravenous dose of ¹⁴C-micafungin 25 mg to 6 healthy subjects (Study FG-463-21-14).

PK Parameter	Micafungin	M5	Total Radioactivity
Tmax (hr)		11.0 ± 1.7	1.0 ± 0.0
Cmax (µg/mL)	2.22 ± 4.30	0.097 ± 0.028	2.30 ± 0.43
AUCt (µg·hr/mL)	29.2 ± 6.2	2.31 ± 1.55	170 ± 44
AUC∞ (µg·hr/mL)	31.5 ± 5.4	6.28*	184 ± 50^
CL (mL/min)	14.3 ± 2.4		
Vss (L)	16.9 ± 3.5		
Vz (L)	18.2 ± 3.7		
t½ (hr)	14.7 ± 1.0	32.0*	340 ± 52^

* N = 2, ^ N = 5

e. *What are the characteristics of protein binding?*

Micafungin binding was determined in human plasma samples obtained from healthy subjects and those with severe renal dysfunction (creatinine clearance <30 mL/min) who received an intravenous dose of micafungin 100 mg (Study 01-0-110). Micafungin concentrations in plasma were 5.8 to 11.2 µg/mL at the end of 1-hour infusion and 2.2 µg/mL to 5.2 at 8 hours post dose. The mean values for micafungin binding to plasma protein were 99.8% at the end of infusion and at 8 hours post dose (Table 12). Micafungin protein binding in subjects with severe renal impairment was similar to that of healthy subjects with normal renal function.

Table 12. Comparison of the plasma protein binding of micafungin between renally impaired patients (creatinine clearance [CrCL] range, < 30 mL/min) and matched healthy controls (CrCL range, > 4 mL/min) at 1 hour and 8 hours after start of infusion of micafungin 100 mg (N = 9 each, Study 01-0-110).

Time (hr)	Protein Binding Parameter	Severe Dysfunction (Mean ± SD)	Normal Function (Mean ± SD)	Difference (%)	Mean Ratio (%)
1	Plasma (µg/mL)	7.88 ± 2.00	8.04 ± 1.48	-1.9	98.0
	Ultrafiltrate (ng/mL)	18.03 ± 3.57	17.64 ± 3.93	2.2	102.2
	% Bound	99.77 ± 0.04	99.77 ± 0.07	0.0	100.0
	% Unbound	0.24 ± 0.04	0.23 ± 0.07	4.0	104.3
8	Plasma (µg/mL)	3.66 ± 1.01	3.75 ± 0.47	-23	97.6
	Ultrafiltrate (ng/mL)	8.26 ± 1.38	7.83 ± 1.42	5.4	105.5
	% Bound	99.76 ± 0.06	99.79 ± 0.05	0.0	99.7
	% Unbound	0.24 ± 0.06	0.21 ± 0.05	11.8	114.3

Micafungin binding was also determined in human plasma samples obtained from healthy subjects and those with moderate hepatic dysfunction (Child-Pugh score 7 - 9) who received an intravenous dose of micafungin 100 mg (Study 01-0-111). Micafungin concentrations in plasma were 5.3 to 9.7 µg/mL at the end of 1-hour infusion and 2.3 to 4.8 µg/mL at 8 hours post dose. The mean values for micafungin binding to plasma protein were 99.8% at the end of 1-hour infusion and at 8 hours post dose (Table 13). Micafungin protein binding in subjects with moderate hepatic dysfunction was similar to that of healthy subjects with normal hepatic function.

Table 13. Comparison of the plasma protein binding parameters of micafungin between patients with moderate hepatic dysfunction (Child-Pugh score 7 - 9) and normal hepatic function at 1 and 8 hours after start of infusion of micafungin 100 mg (N = 8 each group, Study 01-0-111).

Time (hr)	Protein Binding Parameter	Moderate Dysfunction (Mean ± SD)	Normal Function (Mean ± SD)	Difference (%)	Mean Ratio (%)
1	Plasma (µg/mL)	7.06 ± 1.66	8.62 ± 0.90	-1.93	98.1
	Ultrafiltrate (ng/mL)	13.92 ± 2.63	17.32 ± 2.42	2.18	102.2
	% Bound	99.80 ± 0.03	99.80 ± 0.02	-0.01	100.0
	% Unbound	0.20 ± 0.03	0.20 ± 0.02	3.98	104.0
8	Plasma (µg/mL)	3.16 ± 0.65	3.91 ± 0.56	-2.27	97.7
	Ultrafiltrate (ng/mL)	5.73 ± 1.27	7.37 ± 0.99	5.40	105.4
	% Bound	99.82 ± 0.04	99.81 ± 0.03	-0.03	100.0
	% Unbound	0.18 ± 0.04	0.19 ± 0.03	11.80	111.8

In vitro studies, micafungin was highly bound (> 99%) to plasma proteins primarily to albumin and, to a lesser extent, to alpha-1-acid glycoprotein. The extent of plasma protein binding was independent of micafungin concentrations at the concentration range from 10 to 100 µg/mL. Micafungin does not displace bilirubin binding to albumin. The blood to plasma ratio of micafungin was reported to be 0.82 to 0.85 and independent of micafungin concentrations over the range from 0.1 to 10 µg/mL. The percent transfer into human red blood cells was calculated as 33.2% to 35.1%.

C. Intrinsic Factors

1. What intrinsic factors (age, gender, and race) influence exposure and/or response?

a. Age (Pediatric Patients)

Micafungin pharmacokinetics were not adequately determined in pediatric patients aged between 2 and 17 years. As stated in the CPB review for the original submission of N21-506 in DFS as of January 23, 2003 (see section 4.2 General Clinical Pharmacology, page 15), pharmacokinetic blood samples appear to be inadequately collected in the pivotal pediatric study (98-0-043) conducted in patients with febrile neutropenia. There are a number of unexplainable outlier concentrations and many samples were not collected at critical time points (e.g., at the end of infusion and at 24 hour post infusion). In the study report, the sponsor suspected that those outlier samples were drawn from micafungin infusion port. The manual and statistical (i.e., Tukey's procedure) methods of outlier exclusion applied by the Sponsor did not adequately resolve the pharmacokinetic discrepancies: there are still too many inconsistencies in

the estimated pharmacokinetic parameter value even after the exclusion of outliers, which preclude the determination of pediatric micafungin doses based on pharmacokinetics.

Micafungin pharmacokinetics were determined following a single dose of 0.75, 1.5, or 3.0 mg/kg infused over 30 minutes to premature infants (age, up to 8 weeks) receiving an antifungal therapy (Study 99-0-063, Table 14).

Table 14: Pharmacokinetic parameter values of micafungin following a single intravenous infusion of micafungin over 30 minutes to premature infants (Study, 99-0-063).

Weight (g)	Dose (mg/kg)	n	Statistics	C _{max} (µg/mL)	AUC _{0-24hr} (µg-hr/mL)	CL (mL/hr/kg)	t _{1/2} (hr)	V _{ss} (mL/kg)
500 - 1000	0.75	4	Mean ± SD	1.31 ± 0.31	8.8 ± 1.4	79.3 ± 12.5	5.7 ± 0.6	693 ± 129
			Median (Range)	1.31	9.05	79.4	5.8 ±	685
>1000	0.75	6	Mean ± SD	2.54 ± 0.92	16.5 ± 9.0	58.0 ± 49.1	8.1 ± 1.7	641 ± 605
			Median (Range)	2.41	16.4	37.4	8.3	426
>1000	1.5	5	Mean ± SD	4.15 ± 1.13	34.5 ± 5.6	38.6 ± 8.9	8.3 ± 2.2	440 ± 57
			Median (Range)	4.29	31.6	40.0	8.4	442
>1000	3.0	6	Mean ± SD	9.28 ± 5.31	59.5 ± 29.0	71.1 ± 79.1	8.5 ± 1.8	735 ± 673
			Median (Range)	9.67	59.2	42.2	8.6	507

Based on the Sponsor's rough statistical analysis, the C_{max} and AUC_{0-24hr} of micafungin increased in proportion to dose (r = 0.69 and 0.62, respectively). Micafungin concentrations were lower in smaller (500 to 1000 g) than larger (> 1000 g) infants. The difference in micafungin C_{max} for the two groups was significant (p = 0.036), but the differences in AUC_{0-24hr} and clearance were not significant (p = 0.13 and 0.71, respectively). Micafungin clearance per body weight decreased with increasing body weight (r = 0.37). Micafungin clearance did not change with increasing gestational age, post-conceptual age, or with increasing age from birth (r < 0.1). The relationship between albumin levels and micafungin clearance was positively correlated (r = 0.42).

Compared with adult data (Table 7), the respective mean CL and terminal t_{1/2} of micafungin were faster (approx. 8 versus 14 hour) and shorter (approx. 50 versus 20 mL/hr/kg) in premature infants. The AUC_{0-24hr} achieved in premature infants following a single dose of 3.0 mg/kg were much smaller that achieved in adult patients (approx. 60 versus 104 µg-hr/mL).

b. Gender

Micafungin exposure at the same administered dose is apparently greater in females than males. When compared using pooled data determined in healthy adult subjects who enrolled in drug-drug interaction studies conducted for current submission (i.e., 03-0-175, 03-0-176, 03-0-177, and 03-0-178), the respective mean values of the C_{max} and AUC_t for micafungin following a steady-state intravenous dose of 150 mg without interaction drug coadministration were greater by 31% and 23% but the mean value of terminal t_{1/2} was shorter by 1.5 hr in females than males

(Table 15). However, the mean values of micafungin CL at steady state were similar between males and females. The gender difference in the C_{max} and AUC appears to be mostly due to the difference in body weight: the mean value of baseline body weight was smaller by 17% in females than males.

Table 15: Comparison of micafungin pharmacokinetic parameters (mean ± SD) determined following a steady-state intravenous dose of 150 mg between healthy male and female subjects.

PK Parameter	Female (n = 27)	Male (n = 80)	Female / Male Ratio
Body Weight (kg)	62.4 ± 10.0	75.3 ± 10.5	0.83 (p < 0.001)
C _{max} (µg/mL)	24.7 ± 6.3	18.8 ± 3.0	1.31 (p = 0.002)
AUC _T (µg-hr/mL)	285 ± 54	232 ± 35	1.23 (p < 0.001)
CL _{ss} (mL/min/kg)	0.147 ± 0.023	0.147 ± 0.021	1.00 (p = 0.91)
t _{1/2} (hr)	14.2 ± 1.6	15.7 ± 2.5	1.5 hr* (p = 0.91)

* difference

When compared using the pooled data determined in healthy adult subjects who enrolled in drug-drug interaction studies for the original NDA submission (i.e., 01-0-104, 01-0-105, 01-0-110, and 01-0-111), the mean values of the weight-adjusted CL, weight-adjusted V_{ss}, and terminal t_{1/2} for micafungin following a single intravenous dose of 100 mg without interaction drug coadministration were similar in males and females (Table 16). Even though the mean values of the C_{max} and AUC were greater in females by approximately 13%, this gender difference appears to be due to the difference in body weight: the mean body weight was smaller by 11% in females than males.

Table 16: Comparison of micafungin pharmacokinetic parameters (mean ± SD) determined following a single intravenous dose of 100 mg between healthy male and female subjects.

PK Parameter	Female (n = 22)	Male (n = 48)	Female / Male Ratio
Body Weight (kg)	69.7 ± 11.9	78.3 ± 11.8	0.89 (p = 0.01)
C _{max} (µg/mL)	9.04 ± 0.99	7.98 ± 1.36	1.13 (p = 0.002)
AUC _∞ (µg-hr/mL)	140 ± 22	124 ± 19	1.13 (p = 0.003)
t _{1/2} (hr)	14.2 ± 1.5	14.8 ± 1.6	0.6* (p = 0.12)
CL (mL/min/kg)	0.178 ± 0.031	0.177 ± 0.026	1.00 (p = 0.87)
V _{ss} (L/kg)	0.201 ± 0.027	0.211 ± 0.023	0.95 (p = 0.11)

* difference

When compared using data determined in HIV-positive patients with esophageal candidiasis who enrolled in Study FG-463-21-09, the mean weight-adjusted values of micafungin C_{max}/Dose, AUC/Dose, and CL for males and females were comparable (Table 17).

Table 17: Micafungin pharmacokinetics (mean \pm SD) determined following the intravenous administration of micafungin 50, 100, or 150 mg over an hour at steady state to HIV-positive male and female patients with esophageal candidiasis (Study FG-463-21-09).

Time	Gender	N	C _{max} /Dose ($\mu\text{g/mL}$)/(mg/kg)	AUC _{24hr} /Dose ($\mu\text{g}\cdot\text{hr/mL}$)/(mg/kg)	CL (mL/hr)/kg
Day 1	Male	27	4.2 \pm 1.3	36.8 \pm 8.7	20.6 \pm 5.9
	Female	27	4.1 \pm 1.0	38.1 \pm 9.3	19.8 \pm 5.1
Day 14 or 21	Male	27	5.3 \pm 1.2	58.6 \pm 13.2	18.0 \pm 4.4
	Female	27	5.4 \pm 1.3	59.3 \pm 15.5	17.9 \pm 4.3

c. Race

Micafungin pharmacokinetics are similar between different racial groups. When compared using pooled data determined in healthy adult subjects who enrolled in drug-drug interaction studies conducted in the United States for the original NDA submission (i.e., 01-0-104, 01-0-105, 01-0-110, and 01-0-111), whites, blacks, and Hispanics showed comparable mean values in micafungin pharmacokinetic parameters (Table 18). However, when compared the pooled data with the data collected in a Japanese study (FJ-463-0004), Japanese showed significantly greater mean value in dose-adjusted C_{max} compared to all other racial groups by 19%, and greater mean value in dose-adjusted AUC_∞ by 26% and in weight-adjusted V_{ss} by 19% compared to blacks. The greater mean values in the C_{max} and AUC in Japanese subjects appear to be due to smaller body weight: the mean values for weight-adjusted CL and terminal t_{1/2} were not different. The reason for the greater V_{ss} in Japanese compared to black subjects is not known.

Table 18: Comparison of micafungin pharmacokinetic parameters (mean \pm SD) determined following a single intravenous dose of 100 mg between races.

Study	01-0-104, 01-0-105, 01-0-110, 01-0-111			FJ-463-0004
Race	White (n = 50)	Black (n = 5)	Hispanic (n = 15)	Japanese (20)
Body Weight (kg)	75.5 \pm 13.0	85.2 \pm 8.0	72.8 \pm 10.4	59.7 \pm 7.7*
C _{max} ($\mu\text{g/mL}$)	8.30 \pm 1.43	8.19 \pm 1.12	8.42 \pm 1.12	9.92 \pm 1.13* ^
AUC _∞ ($\mu\text{g}\cdot\text{hr/mL}$)	132 \pm 23	117 \pm 10 [#]	125 \pm 17	148 \pm 19 ^{#, ^}
t _{1/2} (hr)	14.9 \pm 1.6	13.7 \pm 0.8	13.9 \pm 1.5	15.1 \pm 0.9
CL (mL/min/kg)	0.175 \pm 0.028	0.168 \pm 0.012	0.188 \pm 0.025	0.193 \pm 0.025
V _{ss} (L/kg)	0.207 \pm 0.024	0.197 \pm 0.026 [#]	0.212 \pm 0.023	0.234 \pm 0.023 [#]

* significantly different from others, [#] different between the two comparisons, ^ adjusted to 100-mg dose

When compared using pharmacokinetic data determined in 106 healthy adult subjects who enrolled in drug-drug interaction studies conducted for current submission (i.e., 03-0-175, 03-0-176, 03-0-177, and 03-0-178), the mean values of the C_{max}, AUC_τ, terminal t_{1/2}, and CL for micafungin following a steady-state intravenous dose of 150 mg without interaction drug coadministration were similar (p > 0.05) between Caucasians (n = 90) and blacks (n = 16). When compared using data determined in HIV positive patients with esophageal candidiasis who enrolled in Study FG-463-21-09, the mean weight-adjusted values of micafungin C_{max}/Dose, AUC/Dose, and CL for Caucasians, blacks, and Mulattos were comparable (Table 19).

Table 19: Effect of race on micafungin pharmacokinetics (mean \pm SD) determined following the intravenous administration of micafungin 50 mg, 100 mg, or 150 mg over an hour at steady state to HIV-positive patients with esophageal candidiasis (Study FG-463-21-09).

Time	Race	N	C _{max} /Dose ($\mu\text{g/mL}$)/(mg/kg)	AUC _{24hr} /Dose ($\mu\text{g}\cdot\text{hr/mL}$)/(mg/kg)	CL (mL/hr)/kg
Day 1	Caucasian	18	4.1 \pm 1.1	37.1 \pm 9.4	20.8 \pm 6.9
	Black	30	4.1 \pm 1.2	37.2 \pm 9.0	20.1 \pm 4.8
	Mulatto	5	5.1 \pm 1.0	42.2 \pm 6.0	17.7 \pm 3.1
Day 14 or 21	Caucasian	18	5.3 \pm 1.3	60.4 \pm 14.0	17.5 \pm 4.6
	Black	30	5.3 \pm 1.3	58.5 \pm 14.2	17.9 \pm 3.9
	Mulatto	5	5.6 \pm 1.1	60.4 \pm 14.0	17.7 \pm 5.2

d. Population Pharmacokinetics of Micafungin

The Sponsor submitted a summary report of micafungin population pharmacokinetics analyzed using nonlinear mixed-effect model (NONMEM). The analysis is based on 5 small and early pharmacokinetic studies conducted in Japan. The report was not reviewed in depth because the report is submitted in a brief summary format and is not likely to provide additional information for the clinical use of micafungin in the United States: (1) the analysis includes only Japanese subjects, (2) most studies were conducted using doses lower than proposed clinical doses, (3) only peak and trough concentrations were measured in one study, and (4) two studies (FJ-463-0004 and FJ-463-0005) were already reviewed with the original submission (see the CPB review of N21-506 in DFS as of January 23, 2003).

2. Based upon what is known about exposure-response relationships and their variability, and the groups studied; what dosage regimen adjustments are recommended for each of these subgroups?

The dose-response analysis performed by the pharmacometrics reviewer and the exposure response analysis conducted by the applicant indicate that the 100 mg and 150 mg doses provide comparable rate of cure. However, the 150 mg dose group is associated with a lower rate (15%) of relapse compared to the 100 mg dose group. In view of these findings, the applicant’s proposed dosage regimen of 150 mg/day is appropriate and no dosage regimen adjustments are recommended based on the dose-response analysis.

D. Extrinsic Factors

1. Are there any in vivo drug-drug interaction studies that indicate the exposure-response relationships are different when drugs are co-administered?

Nifedipine-Micafungin Interaction

A steady-state intravenous dose of micafungin increased nifedipine exposure following a single oral dose. In a fixed-sequence drug interaction study (03-0-178) conducted in 26 healthy subjects, a single oral dose of nifedipine 10 mg was administered on Day 1 followed by a 1-week washout period. A daily dose of micafungin 150 mg was administered on 15 successive days (Days 8 through 22) as 1-hour intravenous infusion. A second single dose of nifedipine 10 mg

was administered concomitantly with the 15th dose of micafungin on Day 22. When administered in combination with micafungin, the C_{max} and AUC_∞ of nifedipine were increased by 42% (geometric mean ratio [GMR], 141.5%; 90% confidence interval [CI], 116.4% - 172.0%) and 18% (GMR, 117.9%; 90% CI, 106.4% - 130.7%), respectively (Table 20).

Table 20: Effect of a steady-state intravenous dose of micafungin 150 mg on nifedipine pharmacokinetics (mean ± SD) following a single oral dose of nifedipine 10 mg (Study 03-0-178, n = 26).

Pharmacokinetic Parameter	Nifedipine Alone (Day 1)	In Combination with Micafungin (Day 22)	Day 22 / Day 1	
			GMR (%)	90% CI (%)
T _{max} * (hr)	1.5 (0.4 - 3.0)	0.7 (0.3 - 2.0)	0.8 [^]	
C _{max} (ng/mL)	54.9 ± 26.0	84.6 ± 52.7	141.5	116.4 - 172.0
AUC _∞ (ng-hr/mL)	188 ± 98	224 ± 113	117.9	106.4 - 130.7
CL/F (L/hr)	63.4 ± 24.8	54.9 ± 25.5	84.8	76.5 - 94.0
V _z /F (L)	495 ± 219	605 ± 537	102.7	82.7 - 127.6
t _{1/2} (hr)	5.9 ± 2.8	7.4 ± 4.6	1.5 [^]	

* median (range); [^] mean difference; GMR, geometric mean ratio; CI, confidence interval

However, a single oral dose of nifedipine 10 mg did not affect micafungin pharmacokinetics following a steady-state intravenous dose of 150 mg. The 90% CIs for the GMR of Day 22 (micafungin + nifedipine) to Day 21 (micafungin alone) with respect to the C_{max} and AUC_{0-24hr} of micafungin were within the range of 80% to 125% (Table 21). The mean C_{max} and AUC values for micafungin metabolites were similar when administered alone and coadministered with nifedipine.

Table 21: Effect of a single oral dose of nifedipine 10 mg on micafungin pharmacokinetics (mean ± SD) following an intravenous dose of micafungin 150 mg at steady state (Study 03-0-178, n = 26).

Pharmacokinetic Parameter	Micafungin Alone (Day 21)	In Combination with Nifedipine (Day 22)	Day 22 / Day 21	
			GMR (%)	90% CI (%)
C _{max} (ng/mL)	21.4 ± 4.9	21.7 ± 4.9	101.4	98.9 - 104.0
AUC _{0-24hr} (ng-hr/mL)	253 ± 50	250 ± 48	98.7	97.6 - 99.9
t _{1/2} (hr)	15.5 ± 1.6	16.05 ± 3.403		

* median (range); [^] mean difference; GMR, geometric mean ratio; CI, confidence interval

Sirolimus-Micafungin Interaction

A steady-state intravenous dose of micafungin increased sirolimus exposure following a single oral dose. In a fixed-sequence drug interaction study (03-0-175) conducted in 26 healthy subjects, a single oral dose of sirolimus 6 mg was administered on Day 1 followed by a 1-week washout period. A daily dose of micafungin 150 mg was administered on 15 successive days (Days 8 through 22) as 1-hour intravenous infusion. A second single dose of sirolimus (6 mg) was administered concomitantly with the 15th dose of micafungin on Day 22. When administered in combination with micafungin, the AUC_{0-72hr} of sirolimus was increased by 21% (GMR, 121.1%; 90% CI, 112.1% - 130.9%; Table 22). However, the C_{max} of sirolimus was not affected by micafungin coadministration (GMR, 101.6%; 90% CI, 92.5% - 111.5%). The

apparent oral CL (CL/F) and apparent Vz (Vz/F) of sirolimus were decreased by 20% (GMR, 79.7%; 90% CI, 73.0% - 87.0%) and 13% (GMR, 86.9%; 90% CI, 79.4% - 95.2%), respectively.

Table 22: Effect of a steady-state intravenous oral of micafungin 150 mg on sirolimus pharmacokinetics (mean ± SD) following a single oral dose of sirolimus 6 mg (Study 03-0-175, n = 26).

Pharmacokinetic Parameter	Sirolimus Alone (Day 1)	In Combination with Micafungin (Day 22)	Day 22 / Day 1	
			GMR (%)	90% CI (%)
Tmax* (hr)	1.5 (1.0 - 6.0)	1.5 (0.9 - 6.0)		
Cmax (ng/mL)	17.4 ± 4.9	17.8 ± 5.3	101.6	92.5 - 111.5
AUC _{0-72hr} (ng-hr/mL)	233 ± 53	284 ± 77	121.1	112.1 - 130.9
CL/F (L/hr)	19.0 ± 5.1	15.3 ± 4.4	79.7	73.0 - 87.0
Vz/F (L)	1483 ± 439	1287 ± 354	86.9	79.4 - 95.2
t _{1/2} (hr)	54.9 ± 12.3	59.5 ± 11.4		

* median (range); GMR, geometric mean ratio; CI, confidence interval

However, a single oral dose of sirolimus 6 mg did not affect micafungin pharmacokinetics following a steady-state intravenous dose of micafungin 150 mg. The 90% CIs for the GMR of Day 22 (micafungin + sirolimus) to Day 21 (micafungin alone) with respect to the Cmax and AUC_{0-24hr} of micafungin were within the range of 80% to 125% (Table 23). The mean Cmax and AUC values for micafungin metabolites were similar when administered alone and coadministered with sirolimus.

Table 23: Effect of a single oral dose of sirolimus 6 mg on micafungin pharmacokinetics (mean ± SD) following intravenous administration of micafungin 150 mg at steady state (Study 03-0-175, n = 26).

Pharmacokinetic Parameter	Micafungin Alone (Day 21)	In Combination with sirolimus (Day 22)	Day 22 / Day 21	
			GMR (%)	90% CI (%)
Cmax (ng/mL)	17.5 ± 3.0	17.6 ± 2.9	100.5	98.4 - 102.6
AUC _{0-24hr} (ng-hr/mL)	223 ± 37	224 ± 37	100.2	98.9 - 101.6
t _{1/2} (hr)	15.1 ± 2.5	15.9 ± 2.1		

GMR, geometric mean ratio; CI, confidence interval

Mycophenolate Mofetil (MMF)-Micafungin Interaction

A steady-state intravenous dose of micafungin did not affect exposure to mycophenolic acid (MPA) or MPA glucuronide (MPAG). In a fixed-sequence drug interaction study (03-0-176) conducted in 27 healthy adult subjects, a single oral dose of MMF 1500 mg was administered on Day 1 followed by a 1-week washout period. A daily dose of micafungin 150 mg was administered on 15 successive days (Days 8 through 22) as a 1-hour intravenous infusion. A second single oral dose of MMF (1.5 g) was administered concomitantly with the 15th dose of micafungin on Day 22. The 90% CIs for the GMR of Day 22 (MMF + micafungin) to Day 1 (MMF alone) with respect to the Cmax and AUC_{0-72hr} of MPA and MPAG were within the range of 80% to 125% (Table 24).

A single oral dose of MMF 1.5 g did not affect micafungin pharmacokinetics following a steady-state intravenous dose of micafungin 150 mg. The 90% CIs for the GMR of Day 22 (micafungin

+ MMF) to Day 21 (micafungin alone) with respect to the C_{max} and AUC_{0-24hr} of micafungin were within the range of 80% to 125% (Table 25). The mean C_{max} and AUC values for micafungin metabolites were similar when administered alone and coadministered with MMF.

Table 24: Effect of a steady-state intravenous dose of micafungin 150 mg on MPA and MPAG pharmacokinetics (mean ± SD) following a single oral dose of MMF 1500 mg (Study 03-0-176, n = 27).

Pharmacokinetic Parameter		MMF Alone (Day 1)	In Combination with Micafungin (Day 22)	Day 22 / Day 1	
				GMR (%)	90% CI (%)
MPA	T _{max} * (hr)	1.0 (0.3 - 3.0)	0.67 (0.3 to 3.0)		
	C _{max} (µg/mL)	36.3 ± 14.0	37.7 ± 17.7	101.3	84.5 - 121.5
	AUC _{0-72hr} (µg-hr/mL)	86.8 ± 25.0	87.5 ± 22.9	101.0	94.4 - 108.1
	t _{1/2} (hr)	13.4 ± 6.0	14.8 ± 7.3		
MPAG	T _{max} * (hr)	2.0 (1.0 - 4.0)	1.5 (1.0 - 10.0)		
	C _{max} (µg/mL)	83.9 ± 14.1	80.8 ± 24.6	92.9	84.4 - 102.2
	AUC _{0-72hr} (µg-hr/mL)	678 ± 146	681 ± 171	99.9	93.2 - 107.0
	t _{1/2} (hr)	13.5 ± 4.2	10.7 ± 3.5		

* median (range); GMR, geometric mean ratio; CI, confidence interval

Table 25: Effect of a single oral dose of MMF 1500 mg on micafungin pharmacokinetics (mean ± SD) following an intravenous dose of micafungin 150 mg at steady state (Study 03-0-176, n = 27).

Pharmacokinetic Parameter	Micafungin Alone (Day 21)	In Combination with MMF (Day 22)	Day 22 / Day 21	
			GMR (%)	90% CI (%)
C _{max} (ng/mL)	23.0 ± 5.8	23.4 ± 5.6	101.8	97.4 - 106.4
AUC _{0-24hr} (ng-hr/mL)	268 ± 47	281 ± 49	104.9	103.0 - 106.9
t _{1/2} (hr)	15.4 ± 3.6	17.7 ± 9.1		

* median (range); ^ mean difference; GMR, geometric mean ratio; CI, confidence interval

Fluconazole-Micafungin Interaction

A steady-state intravenous dose of micafungin did not affect fluconazole exposure. In a fixed-sequence drug interaction study (03-0-177) conducted in 28 healthy subjects, a single oral dose of fluconazole 200 mg was administered on Day 1, followed by a 1-week washout period. A daily dose of micafungin 150 mg was administered on 15 successive days (Days 8 through 22) as 1-hour intravenous infusion. A second single dose of fluconazole 200 mg was administered concomitantly with the 15th dose of micafungin on Day 22. The 90% CIs for the GMR of Day 22 (fluconazole + micafungin) to Day 1 (fluconazole alone) with respect to the C_{max} and AUC_{0-72hr} of fluconazole were within the range of 80% to 125% (Table 26).

A single oral dose of fluconazole 200 mg did not affect micafungin pharmacokinetics following a steady-state intravenous dose of micafungin 150 mg. The 90% CIs for the GMR of Day 22 (micafungin + fluconazole) to Day 21 (micafungin alone) with respect to the C_{max} and AUC_{0-24hr} of micafungin were within the range of 80% to 125% (Table 27). The mean C_{max} and AUC values for micafungin metabolites were similar when administered alone and coadministered with fluconazole

Table 26: Effect of a steady-state intravenous dose of micafungin 150 mg on fluconazole pharmacokinetics (mean ± SD) following a single oral dose of fluconazole 200 mg (Study 03-0-177, n = 28).

Pharmacokinetic Parameter	Fluconazole Alone (Day 1)	In Combination with Micafungin (Day 22)	Day 22 / Day 1	
			GMR (%)	90% CI (%)
Tmax* (hr)	3.0 (1.5 to 14.0)	3.0 (0.5 to 14.0)		
Cmax (ng/mL)	4.5 ± 0.58	4.5 ± 0.7	98.8	94.5 - 103.4
AUC _{0-72hr} (ng-hr/mL)	159 ± 24	164 ± 31	102.3	98.8 - 105.9
t½ (hr)	35.2 ± 7.2	37.0 ± 10.9		

* median (range); GMR, geometric mean ratio; CI, confidence interval

Table 27: Effect of a single oral dose of fluconazole 200 mg on micafungin pharmacokinetics (mean ± SD) following intravenous administration of micafungin 150 mg at steady state (Study 03-0-177, n = 28).

Pharmacokinetic Parameter	Micafungin Alone (Day 21)	In Combination with Fluconazole (Day 22)	Day 22 / Day 21	
			GMR (%)	90% CI (%)
Cmax (ng/mL)	19.1 ± 2.9	19.4 ± 3.0	101.7	99.7 - 103.7
AUC _{0-24hr} (ng-hr/mL)	238 ± 41	240 ± 38	101.1	100.1 - 102.1
t½ (hr)	15.3 ± 1.5	16.1 ± 2.6		

GMR, geometric mean ratio; CI, confidence interval

Effect of Ritonavir on Micafungin Pharmacokinetics

Multiple oral doses of ritonavir did not affect micafungin exposure. In a fixed-sequence drug interaction study (FG-463-21-15) conducted in 24 healthy male subjects, a single intravenous dose of micafungin 200 mg was infused over an hour on Day 1, followed by a washout period of 5 days. Subjects received oral doses of ritonavir 300 mg twice daily on Days 6 to 17, with a second dose of micafungin 200 mg coadministered with the morning dose of ritonavir on Day 10. The overall exposure and the disposition kinetics of micafungin were similar when administered alone and administered in combination ritonavir. The geometric mean values for Cmax and AUCs of micafungin were comparable on Days 1 and 10 and the mean ratios close to unity (Table 28).

Table 28: Pharmacokinetic parameters of micafungin following a single intravenous dose of micafungin 200 mg on Days 1 (micafungin alone) and 10 (micafungin + ritonavir 300 mg for 5 days, Study FG-463-21-15).

PK Parameter	Day 1 (N = 24)		Day 10 (N = 24)		Day 10 to Day 1	
	Mean	CV (%)	Mean	CV (%)	GMR (%)	90% CI (%)
Cmax (µg/mL)	15.7	16.6	16.2	13.6	104	100 - 107
AUC _∞ (µg-hr/mL)	241	19.7	247	15.4	102	99 - 105
t½ (hr)	15.1	7.0	14.9	7.8		

Mean, geometric mean; CV, coefficient of variation; GMR, geometric mean ratio; CI, confidence interval

Effect of Rifampin on Micafungin Pharmacokinetics

Multiple oral doses of rifampin did not affect micafungin exposure. In a fixed-sequence drug interaction study (FG-463-21-16), 24 healthy male subjects received a single intravenous dose of micafungin 200 mg infused over an hour on Day 1, followed by a washout period of 4 days. Subjects received oral doses of rifampin 600 mg once daily on Days 5 to 15 and a second dose of micafungin 200 mg coadministered with rifampin on Day 12. There was a 3.3-fold (range, 1.3 - 5.3) increase in the mean urinary 6 β -hydroxycortisol to cortisol ratio following the administration of rifampin for 8 days (Day 12) compared to pre rifampin treatment (Day 1). However, the overall exposure and the disposition kinetics of micafungin were similar when administered alone and administered in combination with rifampin. The geometric mean values for C_{max} and AUC_∞ of micafungin were comparable on Days 1 and 12, and the mean ratios close to unity (Table 29).

Table 29: Pharmacokinetic parameters of micafungin following a single intravenous dose of micafungin 200 mg on Days 1 (micafungin alone) and 12 (micafungin + rifampin 600 mg for 8 days, Study FG-463-21-16).

PK Parameter	Day 1 (N = 24)		Day 12 (N = 24)		Day 12 to Day 1	
	Mean	CV (%)	Mean	CV (%)	GMR (%)	90% CI (%)
C _{max} (µg/mL)	17.2	11.5	16.7	11.2	97	95 - 100
AUC _∞ (µg-hr/mL)	253	12.1	257	12.1	102	98 - 106
t _{1/2} (hr)	14.6	6.9	14.3	7.0		

Mean, geometric mean; CV, coefficient of variation; GMR, geometric mean ratio; CI, confidence interval

2. What issues related to dose, dosing regimens, or administration are unresolved, and represent significant omissions?

It is not clearly known whether a loading dose is required in micafungin regimens for the proposed indications. The Sponsor did not propose a loading dose. Ideally, the decision on loading dose should be made based on efficacy outcomes in the comparison of micafungin regimens with and without a loading dose, which were not explored.

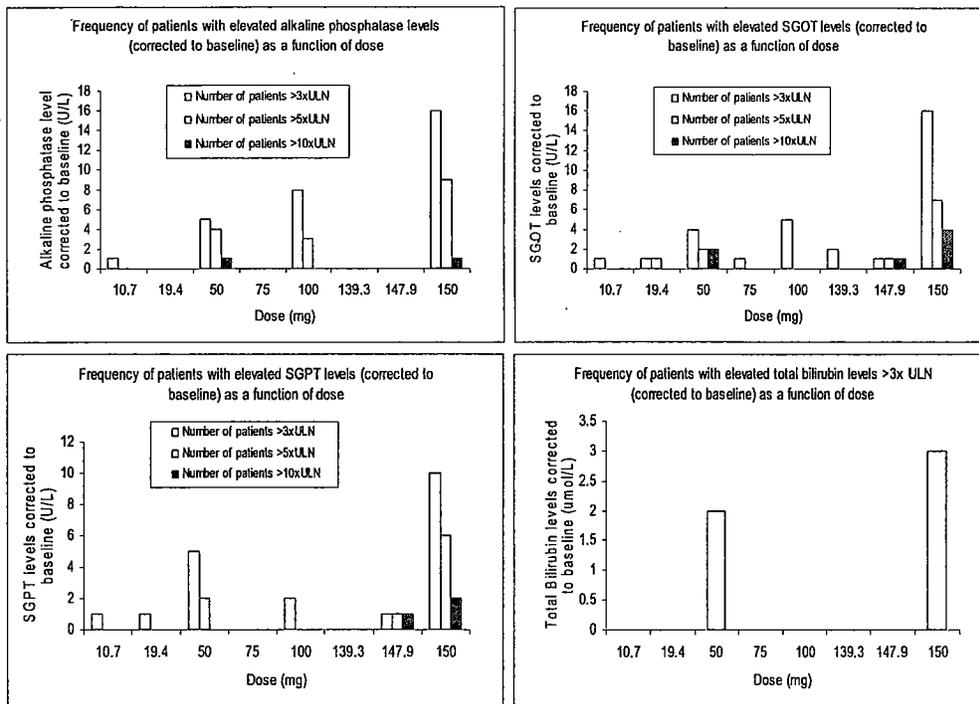
3. Based upon what is known about exposure-response relationships and their variability, what dosage regimen adjustments do you recommend for each of these factors?

The dose-response analysis performed by the pharmacometrics reviewer and the exposure response analysis conducted by the applicant indicate that the 100 mg and 150 mg doses provide comparable rate of cure. However, the 150 mg dose group is associated with a lower rate (15%) of relapse compared to the 100 mg dose group. In view of these findings, the applicant's proposed dosage regimen of 150 mg/day is appropriate and no dosage regimen adjustments are recommended based on the dose-response analysis.

The effect of covariates such as dose on the elevations in liver enzyme levels normalized to baseline levels was studied. Also, an effect of time of enzyme level measurement subsequent to drug administration was studied on the elevation of the enzyme levels. The results of the analysis indicated that the enzyme levels relative to the baseline levels are not related to the dose of micafungin or the time of enzyme level measurement (duration of exposure). A detailed analysis

was performed with specific emphasis on patients whose values were greater than 3 times the upper limit of normal ($3\times\text{ULN}$), $>5\times\text{ULN}$, $>10\times\text{ULN}$. The relationship of dose versus these high enzyme values was performed using logistic regression in SAS. These results indicated a lack of statistically significant dose effect on the elevations in enzyme values. However, as seen below in Figure 3, a frequency plot of patients with elevated enzyme values as a function of dose indicates that a higher number of patients receiving 150 mg dose had elevated enzyme levels. This effect appears more pronounced with alkaline phosphatase, SGOT and SGPT and can be readily seen that for the clinical dose of 150 mg micafungin is associated with a higher number of elevations in liver enzymes. For bilirubin, none of patients had enzyme values $>5x$ ULN and there does not seem to be a dose-related elevations of bilirubin.

Figure 3: A frequency plot of patients with elevated enzyme levels as a function of dose.



E. General Biopharmaceutics

Please refer to the CPB review for original submissions of N21-506 DFS as of January 23, 2003.

F. Analytical

1. What bioanalytical methods are used to assess drug concentrations?

Determination of Micafungin and Metabolite Concentrations in Human Plasma

The plasma concentrations of micafungin and its metabolites M1, M2, and M5 in plasma were measured using high performance liquid chromatographic (HPLC) method with fluorescence detection. FR195743 was used as an internal standard. The method was initially developed and

validated at Fujisawa Pharmaceutical Co., Ltd., Osaka, Japan, and transferred and validated at other laboratories. Interlaboratory modifications of the original method were not permitted throughout drug development.

In principle, plasma samples were separated from whole blood and acidified with 1% diluted phosphoric acid. Acetonitrile was used for the extraction of micafungin, M1, M2, and M5 from plasma matrix. The samples were centrifuged and the supernatant was mixed with 20 mM potassium dihydrogenphosphate. This solution was injected onto the HPLC system.

Fluorescence detection with excitation wavelength of _____ and emission wavelength of _____ was used to detect micafungin and its metabolites. A weighted ($1/x^2$) linear regression was used to determine the slopes, intercepts, and correlation coefficients. The limit of quantitation (LOQ) was _____ $\mu\text{g/mL}$ using _____ mL plasma samples. The in-process performance of the HPLC method is summarized in Table 30.

Determination of Micafungin and Metabolite Concentrations in Human Urine

The same chromatographic conditions were used for the measurements of micafungin and metabolite concentrations in human urine as those for human plasma. The extraction procedure varied slightly from that for plasma. Tween 20 was added to the human urine, and the drug was extracted using the mobile phase.

Determination of Radioactivity Derived from ^{14}C -Micafungin

Total radioactivity in biological samples after administration of ^{14}C -radiolabeled micafungin administrations was measured by a liquid scintillation counting method; the LOQ was twice the background radioactivity.

Determination of Fluconazole Concentrations in Human Plasma

Fluconazole plasma concentrations were measured using a validated HPLC method with tandem mass spectrometric detection (LC/MS/MS). Fluconazole and internal standard (ritonavir) were extracted from plasma samples with methyl-tert butyl ether in a 96 well format.

The residue was reconstituted and the sample was introduced onto an HPLC system. The peak area ratio of fluconazole and the internal standard *versus* concentration data of the standards were fitted by inversely weighted ($1/x^2$) linear regression.

The LOQ for fluconazole was _____ $\mu\text{g/mL}$ with a calibrated linear range of _____ ng/mL ($r^2 =$

_____ Inter-assay accuracy using quality control samples at fluconazole concentrations of 1.5, _____ ng/mL ranged between _____ The corresponding precision ranged

between _____

Table 30: In-process performance of the analytical method used to measure the plasma concentrations of micafungin and its metabolites.

Study No.	Assay Site	Analyte	QC ($\mu\text{g/mL}$)	Accuracy (mean bias %)	Precision (CV %)	Calibration Range ($\mu\text{g/mL}$)	LOQ ($\mu\text{g/mL}$)
99-0-063		Micafungin					
		M1					
		M2					
03-3-175 03-3-176 03-3-177 03-3-178		Micafungin					
		M1					
		M2					
		M5					
FG-463-21-09		Micafungin					
		M1					
		M2					
		M5					
FG-463-21-15 FG-463-21-16		Micafungin					

Determination of Nifedipine Concentrations in Human Plasma

Nifedipine plasma concentrations were measured using a validated gas chromatographic method with _____ detection. Nifedipine and the nifedipine internal standard (nitrendipine) were extracted from plasma samples using toluene. The peak height ratio of nifedipine and the

internal standard *versus* concentration data of the standards were fitted by inversely weighted (1/x) linear regression. The LOQ for nifedipine was _____ ng/mL with a calibrated linear range of _____ ng/mL ($r^2 =$ _____). Inter-assay accuracy using quality control samples at nifedipine concentrations of _____ μ g/mL ranged between _____ and _____. The corresponding precision ranged between _____ and _____.

Determination of Sirolimus Concentrations in Human Blood

Sirolimus concentrations in whole blood were determined using a validated HPLC method with tandem mass spectroscopic detection (LC/MS/MS). Sirolimus and internal standard (desmethoxyrapamycin) were extracted from whole blood samples using _____

_____. Detection was done with _____ MS/MS. The peak area ratio of sirolimus and the internal standard *versus* concentration data of the standards were fitted by inversely weighted (1/x²) linear regression. The LOQ for sirolimus was _____ μ g/mL with a calibrated linear range of _____ to _____ ($r >$ _____). Inter-assay accuracy (mean bias %) using quality control samples at sirolimus concentrations of _____ μ g/mL ranged between _____

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ON ORIGINAL**

4 Page(s) Withheld

 Trade Secret / Confidential

✓ Draft Labeling

 Deliberative Process

IV. APPENDICES

A. Package Insert (proposed and annotated)

Please refer to \\Cdsesub1\N21506\N_000\2004-08-24\LABELING\PROPOSED.pdf.

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B. Individual Study Review

Study Code	Objectives	Design	Subject No. (M/F), Race, Age	Dosage Form, Dose, Route, Duration	Remarks
Basic Pharmacokinetic Study					
FG-463-21-09	To determine the pharmacokinetics of micafungin at various dose levels in HIV positive patients with an endoscopically confirmed diagnosis of esophageal candidiasis	multicenter, randomize d, parallel- group	74 (43/31) HIV positive patients with esophageal candidiasis 21W, 45B, 7O 19 - 68 years old	Micafungin: 50, 100, 150 mg IV QD for 14 - 21 days	Adequate micafungin pharmacokinetic results in 54 patients
Mass Balance Study					
FG-463-21-14	To obtain the pharmacokinetics of [¹⁴ C]-micafungin, metabolites and total radioactivity To determine the route of elimination and rates excretion of micafungin and total radioactivity To obtain a mass balance estimate.	open-label, single dose	6 (6/0) healthy subjects 5W, 1A 30 - 50 years old	[¹⁴ C]-micafungin: 25 mg IV x 1	
Special Population (Pediatrics)					
99-0-063	To evaluate the pharmacokinetics, safety, and tolerance of three dose levels of micafungin in premature infants.	multi-center, open-label, sequential	23 (14/9) premature infants 14W, 9B 24 - 34 weeks old	Micafungin 0.75, 1.5, and 3.0 mg/kg x 1 over 0.5-hr infusion	Reviewed by pediatrics review team in DPEIII
Drug Interaction Studies					
03-0-175	To characterize the pharmacokinetic effect of micafungin as a daily infusion for 15 days on the single-dose pharmacokinetics of sirolimus To characterize the pharmacokinetic effect of a single dose of sirolimus on the steady-state pharmacokinetics of micafungin	Open label, repeated dose, fixed sequence	26 (22/4) healthy subjects 19W, 6B, 1O 19 - 46 years old	Micafungin: 150 mg IV QD on Days 8 through 22 Sirolimus: 6 mg PO QD on Days 1 and 22	Increase in sirolimus Cmax by 21%

Study Code	Objectives	Design	Subject No. (M/F), Race, Age	Dosage Form, Dose, Route, Duration	Remarks
03-0-176	To characterize the pharmacokinetic effect of micafungin as a daily infusion for 15 days on the single-dose pharmacokinetics of mycophenolic acid To characterize the pharmacokinetic effect of a single dose of mycophenolic acid on the steady-state pharmacokinetics of micafungin	Open label, repeated dose, fixed sequence	27 (16/11) healthy subjects 24W, 3B 18 - 50 years old	Micafungin: 150 mg IV QD on Days 8 through 22 Mycophenolate mofetil: 1.5 g PO QD on Days 1 and 22	No interaction
03-0-177	To characterize the pharmacokinetic effect of micafungin as a 150 mg daily infusion for 15 days on the single-dose pharmacokinetics of fluconazole To characterize the pharmacokinetic effect of a single dose of fluconazole on the steady-state pharmacokinetics of micafungin	Open label, repeated dose, fixed sequence	28 (25/3) healthy subjects 28W 18 - 47 years old	Micafungin: 150 mg IV QD on Days 8 through 22 Fluconazole: 200 mg PO QD on Days 1 and 22	No interaction
03-0-178	To characterize the pharmacokinetic effect of micafungin as a daily infusion for 15 days on the single-dose pharmacokinetics of nifedipine To characterize the pharmacokinetic effect of a single dose of nifedipine 10 mg on the steady-state pharmacokinetics of micafungin	Open label, repeated dose, fixed sequence	26 (17/9) healthy subjects 19W, 7B 18 - 50 years old	Micafungin: 150 mg IV QD on Days 8 through 22 Nifedipine: 100 mg PO QD on Days 1 and 22	Increase in nifedipine Cmax and AUC by 24% and 18%, respectively
FG-463-21-15	To characterize the pharmacokinetic effect of micafungin as a daily infusion for 15 days on the single-dose pharmacokinetics of ritonavir To characterize the pharmacokinetic effect of a single dose of ritonavir on the steady-state pharmacokinetics of micafungin	Open label, repeated dose, fixed sequence	24 (24/0) healthy subjects 24W 19 - 51 years old	Micafungin: 200 mg IV QD on Days 1 and 10 Ritonavir: 300 mg PO QD on Days 6 through 17	No interaction
FG-463-21-16	To determine the effect of multiple oral doses of rifampin on the single intravenous dose pharmacokinetics of micafungin	Open label, repeated dose, fixed sequence	24 (24/0) healthy subjects 24W 19 - 55 years old	Micafungin: 200 mg IV QD on Days 1 and 12 Rifampin: 600 mg PO QD on Days 5 through 15	No interaction

W, white; B, black; A, Asian; O, other
IV, intravenous; PO, per oral; QD, once daily

C. Consult Review

PHARMACOMETRICS REVIEW

NDA:	21-754
Submission date:	April 26, 2004
Product:	150 mg injection
Brand name:	Mycamine
Generic name:	Micafungin
Sponsor:	Fujisawa Inc.
Type of submission:	New NDA for Treatment of Esophageal Candidiasis
Pharmacometrics Reviewer:	Dakshina Chilukuri, Ph.D.
Primary reviewer:	Jang-Ik Lee, Pharm.D., Ph.D.
PM Team Leader:	Jogarao Gobburu, Ph.D.
OCPB Team Leader:	Philip Colangelo, Pharm D., Ph.D.

Introduction and Background

Fujisawa submitted NDA 21-754 for micafungin for the treatment of esophageal candidiasis. Micafungin is formulated as an IV infusion. Micafungin sodium is a semisynthetic lipopeptide (echinocandin) synthesized by a chemical modification of a fermentation product of *Coleophoma empetri* F-11899. Micafungin sodium inhibits the synthesis of 1, 3- β -D-glucan, an integral component of the cell wall of susceptible fungi. The proposed dose of micafungin is 150 mg given once a day for 14-21 days for the treatment of esophageal candidiasis.

Executive Summary

Based on the dose-effectiveness analysis, it was determined that the effectiveness of micafungin increases as dose is increased and maximum effectiveness is seen at both 100 and 150 mg dose. For the purpose of analysis, multiple endpoints of effectiveness were used, which were endoscopic grade of 0 at end of therapy (EOT), clinical response at EOT, mycological response at EOT, proportion of patients showing no relapse at 2-weeks following EOT. Baseline severity of the disease was not found to affect the outcome of the treatment. The dose-toxicity analysis showed no statistically significant relationship between dose and liver enzyme elevations measured at various time points, day 7, day 14, EOT and end of study (EOS), which were 2-weeks after EOT.

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

Objectives of the analysis

- To determine the appropriate dose of micafungin for the treatment of esophageal candidiasis by evaluating the dose-efficacy and dose-safety relationships

Dose-Response analysis

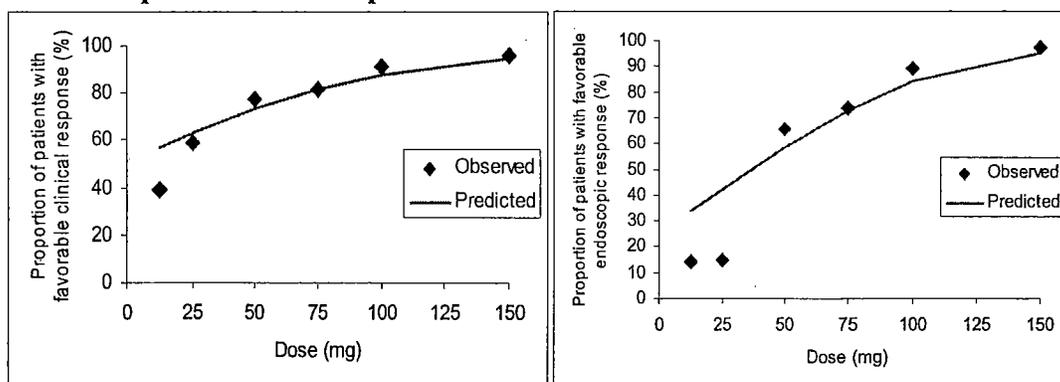
The relationship between dose and effectiveness was modeled by the FDA reviewer using multiple endpoints using data from 2 Phase 2 studies and 1 Phase 3 study. The primary effectiveness endpoint in this study was endoscopic response rate, defined as the proportion of patients with a mucosal grade=0 or cleared at the end of therapy. The endoscopic response rate is studied by assessing the intensity of the lesions in the affected area and graded based on a scale from 0 (cured, no evidence of esophageal candidiasis- associated lesions) to 4 (confluent plaques combined with ulceration). Secondary effectiveness assessments included clinical response at end of therapy, which is based on evaluation of clinical symptoms whether the patient has complete resolution of the symptoms (clinical response grade = 0). Relapse at 2 weeks post treatment was defined as patients with endoscopy grade=0 and clinical response of 0 at end of therapy who had recurrence of esophageal candidiasis as assessed by clinical symptoms or received antifungal medication during the follow-up phase. The dose-toxicity relationship was modeled using elevations in liver enzymes such as alkaline phosphates, serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT) and total bilirubin as the endpoints.

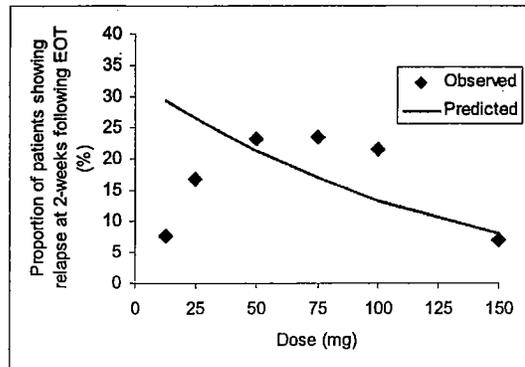
Question Based Review for Pharmacometrics

1. *The sponsor studied various doses between 12.5 and 150 mg. What doses should be approved for the treatment of esophageal candidiasis?*

Based on the reviewer's analysis of the available effectiveness data for the range of doses 12.5-150 mg, the most appropriate dose of micafungin for the treatment of esophageal candidiasis is 150 mg. The reviewer found a sigmoid relationship between dose and the effectiveness endpoints as shown in Figure 1. As seen in Figure 1, there were increases in the proportion of patients with favorable clinical and endoscopic responses as the dose was increased from 12.5 to 150 mg and comparable responses between 100 and 150 mg. The dose-relapse rate relationship indicated that the relapse rate for the 100 mg dose is 15% higher than the 150 mg dose. This indicated that while the comparable effectiveness based on the primary and secondary endpoints were seen for the 100 and 150 mg doses, the higher relapse rate seen in the 100 mg dose group is indicative of the 150 mg dose being more appropriate for the treatment of esophageal candidiasis.

Figure 1: Plot of the dose-response relationship of micafungin for the primary endpoint of endoscopic cure (grade 0 at EOT) and secondary endpoint of clinical cure. Also plotted is the relationship of dose and relapse rate

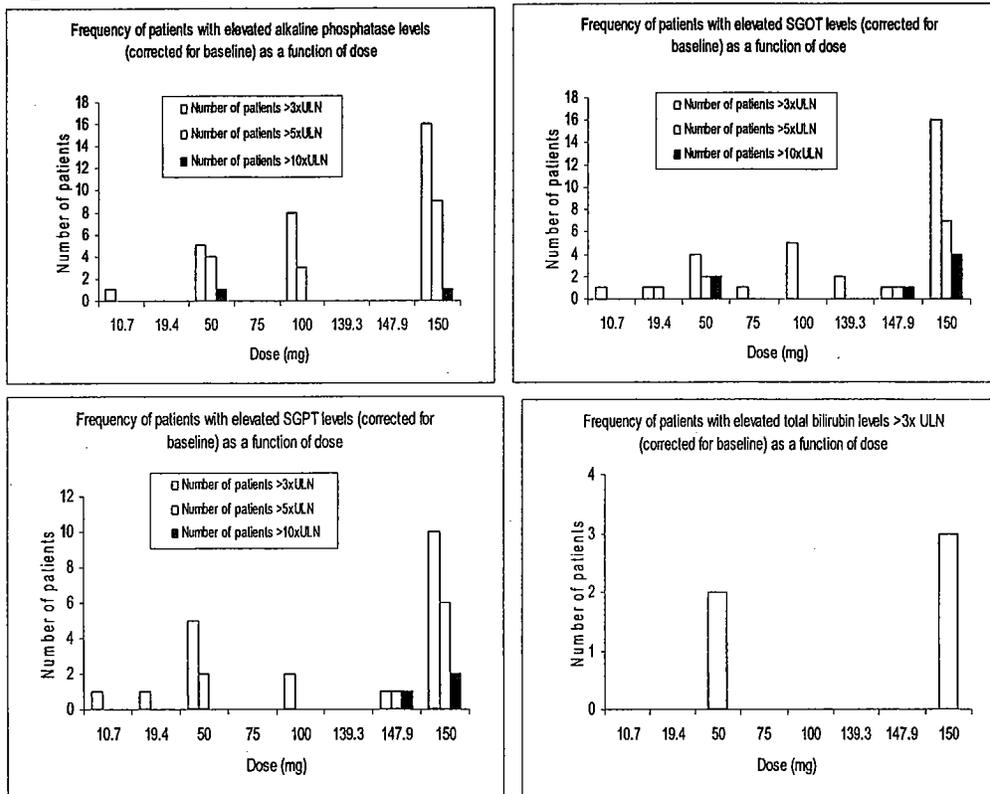




The effect of covariates such as dose on the elevations in liver enzyme levels normalized to baseline levels was studied. Also, an effect of time of enzyme level measurement subsequent to drug administration was studied on the elevation of the enzyme levels. The results of the analysis indicated that the enzyme levels relative to the baseline levels are not related to the dose of micafungin or the time of enzyme level measurement (duration of exposure). A detailed analysis was performed with specific emphasis on patients whose values were greater than 3 times the upper limit of normal ($3 \times \text{ULN}$), $>5 \times \text{ULN}$, $>10 \times \text{ULN}$. The relationship of dose versus these high enzyme values was performed using logistic regression in SAS. These results indicated a lack of statistically significant dose effect on the elevations in enzyme values. However, as seen below in Figure 3, a frequency plot of patients with elevated enzyme values as a function of dose indicates that a higher number of patients receiving 150 mg dose had elevated enzyme levels. This effect appears more pronounced with alkaline phosphatase, SGOT and SGPT and can be readily seen that for the clinical dose of 150 mg micafungin is associated with a higher number of elevations in liver enzymes. For bilirubin, none of patients had enzyme values $>5 \times \text{ULN}$ and there does not seem to be a dose-related elevations of bilirubin.

In summary, both the 100 and 150 mg doses of micafungin resulted in comparable cure rates based on endoscopic and clinical response rates. However, patients who received the 150 mg dose had a lower rate of relapse compared to the 100 mg dose. Also a higher number of patients receiving 150 mg micafungin showed elevated liver enzyme levels (except bilirubin) compared to the patients receiving 100 mg dose. Thus, while the 150 mg dose results in better effectiveness, based on clinical and endoscopic endpoints and relapse, it also results in a higher number of patients with elevated liver enzyme elevations. In view of the higher relapse in 100 mg dose seen as a safety issue, the 150 mg micafungin dose is recommended for approval for the treatment of esophageal candidiasis. A statement in the package insert will be added indicating the potential of liver toxicity of micafungin.

Figure 3: A frequency plot of patients with elevated enzyme levels as a function of dose.



2. *What is the basis for selecting the response endpoints and how are they measured in clinical pharmacology and clinical studies?*

The primary response endpoint is endoscopic cure (endoscopic grade=0) and this is measured by endoscopic assessment of the lesions in the affected area. This was studied at EOT and 2-weeks after EOT for most clinical studies and 4-weeks after EOT in the Phase 3 study. The secondary endpoint was clinical response, which was determined by resolution of disease symptoms. Most fungal infections are known to relapse in a certain proportion of patients and hence relapse was also a response endpoint and this was determined by endoscopic assessment 2 and 4-weeks after EOT.

3. *What is the effect of baseline condition of the disease on the effectiveness of various doses of micafungin?*

The analysis conducted by the FDA reviewer indicated that patients with baseline severity characterized by endoscopic grade '4' did not respond to micafungin differently than patients with baseline severity '1'. Hence it was concluded that there is no effect of the baseline condition of the disease on the effectiveness of micafungin.

4. *What are the characteristics of the exposure-response relationships for efficacy and safety?*

If relevant, indicate the time to onset of the pharmacological response or clinical endpoint?

The applicant conducted an exposure-response study using data generated in a phase 2 study. The study was a phase 2, multicentre, prospectively randomized, reference therapy controlled, double-blind, and parallel-group study. Eligible patients were randomized 1:1:1:1 to 50, 100 or 150 mg/day micafungin or 200 mg/day fluconazole. The planned treatment period was 14 days, but was allowed to extend to 21 days for patients who did not achieve endoscopic clearance by Day 14. Pharmacokinetic profiles (assessed on Day 1 and the last day of treatment) were estimated and trough concentrations (Days 3, 7 and 14) were determined. In general, the pharmacokinetics observed in this patient population were similar to those obtained in earlier studies in adults. Micafungin exhibited linear pharmacokinetics over the dose range investigated (50 - 150 mg/day).

No differences in pharmacokinetic parameters were observed as a function of gender or race (Caucasian, Black and Mulatto). There was a difference in mean exposure between patients in whom endoscopic clearance was observed and those in whom infection persisted. On Day 1, the respective mean AUC₂₄ values were 74 vs. 38 µg.hr/mL for the patients in whom endoscopic clearance was observed and those in whom infection persisted. The mean AUC₂₄ in the 50 mg micafungin treatment group (36 µg×hr/mL) was similar to that of the non-responders. In comparison, the corresponding values in the 100 and 150 mg treatment groups were 75 and 104 µg×hr/mL respectively. These data suggest that a daily dose of between 100 and 150 mg would appear necessary to achieve the optimal exposure associated with a therapeutic response against esophageal candidiasis in this patient population. The dose response findings based on the full analysis set of 185 patients treated with micafungin in the clinical study indicated greater effectiveness with 100 mg/day and 150 mg/day micafungin compared to 50 mg/day micafungin.

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Table 1. Mean Values Of Pharmacokinetic Parameters Correlated With Effectiveness As Measured By Endoscopic Grade At End Of Therapy

Parameter	Units	Mean value in patients with endoscopic grade =0 (n=43)	Mean value in patients with endoscopic grade >0 (n=9)	p value*
Profile 1				
AUC ₂₄	µg*hr/mL	74.13	38.23	0.0026
C _{max}	µg/mL	8.07	4.76	0.0158
Profile 2				
AUC ₇₂	µg*hr/mL	171.55	82.49	0.0017
C _{max}	µg/mL	10.80	5.20	0.0071

* Student's t-Test: Two-Sample Assuming Equal Variances

5. Based upon what is known about exposure-response relationships and their variability, what dosage regimen adjustments do you recommend for each of these factors?

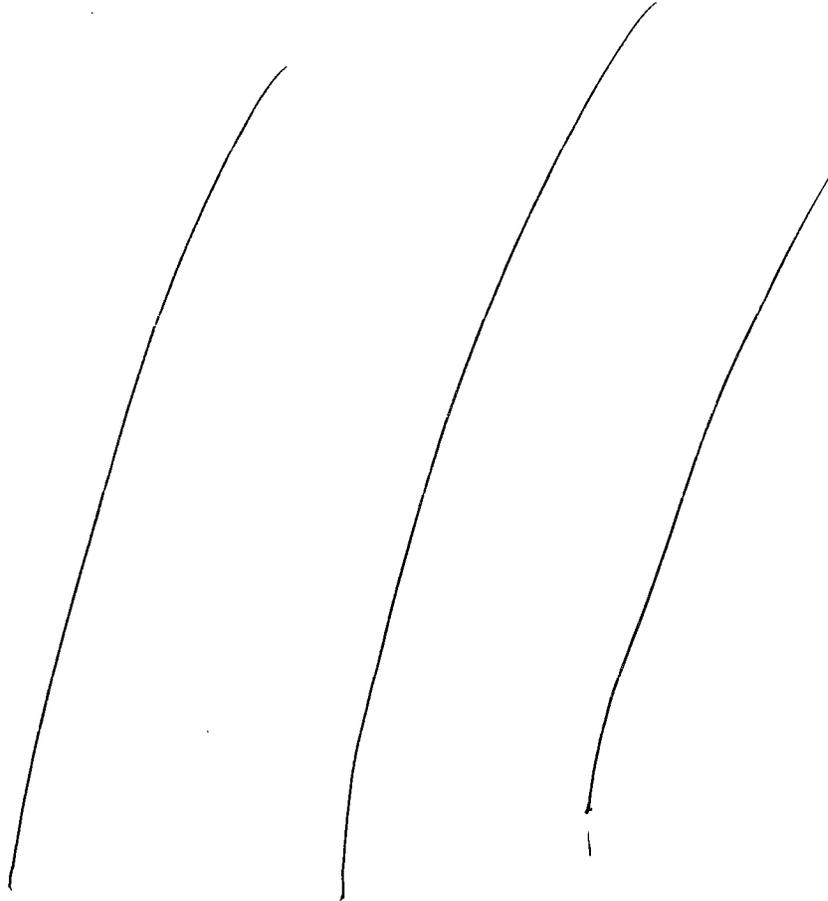
The dose-response analysis performed by the reviewer and the exposure response analysis conducted by the applicant indicate that the 100 mg and 150 mg doses provide comparable rate of cure. However, the 150 mg dose group is associated with a lower rate (15%) of relapse compared to the 100 mg dose group. In view of these findings, the applicant's proposed dosage regimen of 150 mg/day is appropriate and no dosage regimen adjustments are recommended based on the dose-response analysis.

Overall Conclusions

1. The 150 mg dose displayed the maximum response for the primary endpoint for esophageal candidiasis (endoscopic cure or grade 0) and both 100 and 150 mg doses resulted in comparable responses for the secondary endpoint (clinical response). Lower doses (12.5, 25, 50 and 75 mg) resulted in lower cure rate (20-75% cure rate) for all endpoints studied.
2. A lower proportion (15%) of patients showed relapse at 2-weeks following EOT in the 150 mg dose group compared to the other dose groups, including those treated with 100 mg.
3. Liver enzyme elevations are statistically dose-independent and time-independent across all dosing regimens studied (12.5 – 150 mg) in the clinical studies for 14-21 days of administration, followed by a 2-week follow-up evaluation. However, the number of patients dosed with 150 mg with LFT elevations >3×ULN were 2-fold greater than patients who were dosed with 100 mg dose.
4. The results of the population PK analysis confirm the dosage recommendations made based on the Phase I PK studies. No dosage adjustments are needed in patients with renal and hepatic impairment, and no dosage adjustments are needed based on age, body weight and gender of the patients.

Recommendations:

1. Based on the dose response analysis of micafungin, a dose of 150 mg is recommended for approval for the treatment of esophageal candidiasis.
2. Following are the labeling recommendations, based on the pharmacometrics analysis:



Dakshina Chilukuri, Ph.D.
Clinical Pharmacology and Biopharmaceutics Reviewer
Division of Pharmaceutical Evaluation III
Office of Clinical Pharmacology and Biopharmaceutics

Date: _____

Philip Colangelo, Pharm.D., Ph.D.
Clinical Pharmacology and Biopharmaceutics Team Leader
Division of Pharmaceutical Evaluation III
Office of Clinical Pharmacology and Biopharmaceutics

Date: _____

Dose-response analysis of micafungin

Background

The applicant (Fujisawa) has developed an antifungal, micafungin for the treatment of esophageal candidiasis. Micafungin (FK463) is a member of a new class of cyclic lipopeptides, 1,3-beta-D-glucan synthesis inhibitors that act by inhibiting 1,3-beta-D-glucan synthase, an enzyme essential for the synthesis of fungal cell walls. The applicant has provided data in support of micafungin in the treatment of esophageal candidiasis.

Data

Data from 3 effectiveness studies were submitted to the NDA.

- Study FG-463-21-09 was a multi-center, prospectively randomized, double-blind, active-controlled, parallel-group study. Patients were randomized 1:1:1:1 to receive a 1-hour daily infusion of micafungin (50, 100, or 150 mg) or fluconazole (200 mg) for 14 to 21 days. The primary effectiveness endpoint in this study was endoscopic response rate, defined as the proportion of patients with a mucosal grade=0 or cleared at the end of therapy. Secondary effectiveness assessments included the proportion of patients with an endoscopy grade of 0 on day 14, clinical response at end of therapy, mycological response (including findings from histology, cytology, and fungal culture), clinical assessment (clinical symptoms over time), overall therapeutic success (clearing or improvement in clinical signs and symptoms and endoscopy), and relapse (patients with endoscopy grade=0 and clinical response of 0 at end of therapy who have recurrence of esophageal candidiasis as assessed by clinical symptoms or receive antifungal medication during the follow-up phase) at 2 weeks post treatment. Safety was analyzed by incidence of adverse events, and results/findings from laboratory measurements and vital signs. Additionally, blood samples were obtained in a subset of patients to determine the PK of micafungin.
- Study 97-7-003 was a phase 2, open-label, dose de-escalation study conducted in South Africa. Patients were administered a 1-hour infusion of 12.5 mg, 25.0 mg, 50.0 mg, 75.0 mg or 100.0 mg of micafungin once daily for 14 to 21 days. Effectiveness endpoints included the primary endpoint of clinical response at the end of therapy (success was defined as cleared or improved clinical signs and symptoms [dysphagia, odynophagia, and retrosternal pain]), and the following secondary endpoints performed at the end of therapy: improvement in esophageal mucosal lesions based on endoscopic examination, mycological response, changes in the quantitative clinical assessment of esophagitis, clinical response of oropharyngeal candidiasis (fissures, mouth pain, inflammation, and plaques; if present at baseline), and overall therapeutic success or failure (an overall success was defined as a patient who experienced improvement in both clinical and endoscopic grades and did not discontinue due to a study drug related adverse event or lack of effectiveness). For patients who had cleared or improved clinical response at the end of therapy, the incidence of relapse of esophageal candidiasis was assessed at 2 weeks post treatment.

- Study 03-7-005 was a multicenter, multinational, randomized (1:1), double-blind, parallel group, non-inferiority study in patients aged 16 years and older with esophageal candidiasis. Either micafungin 150 mg or fluconazole 200 mg was administered IV once daily for a minimum of 14 days or for 7 days after resolution of all clinical symptoms of esophageal candidiasis. The maximum permitted duration of study drug treatment was 42 days. The primary effectiveness endpoint was treatment success (endoscopic cure rate), which was defined as an esophageal mucosal grade of 0 (zero) at the end of therapy. The secondary endpoints included: (1) clinical response at the end of therapy; (2) mucosal response at the end of therapy; (3) overall therapeutic response at the end of therapy; (4) incidence of relapse at 2 weeks and 4 weeks post treatment; (5) changes in mucosal grade at the end of therapy compared to baseline; (6) changes in clinical symptoms of esophageal candidiasis at the end of therapy compared to baseline; (7) changes in clinical signs and symptoms of oropharyngeal candidiasis at the end of therapy compared to baseline; and (8) mycological response at the end of therapy.

Methods

Dose-effectiveness

In order to explore the dose-relationship of micafungin, all the available effectiveness data were collated. Using dose as a continuous variable and the following endpoints as categorical variables, the dose-response relationship was studied. The endpoints are:

- Clinical response at the end of therapy (EOT) and 2-weeks following EOT
- Endoscopic response at end of therapy and 2-weeks following EOT
- Mycological response at EOT
- Relapse at 2-weeks following EOT

Further, the baseline endoscopic grade was used as a covariate to see if there is an effect of the baseline grade on the effectiveness as a function of dose.

Dose-toxicity

The relationship between adverse events such as liver function tests, namely, alanine transaminase (ALT), aspartate transaminase (AST), bilirubin and alkaline phosphatase and dose was studied. For this purpose, lab data containing values of the 4 enzymes was collated across 3 studies as mentioned above. The data comprised of lab measurements with enzyme levels in each patient at baseline, day 7, day 14, end of therapy and end of study (usually 2-weeks after EOT). Using this data, the difference between the lab values at each time point and the baseline were obtained. For the purpose of modeling, this data was used. Further, a relationship of liver enzyme elevations and the time of measurement were also performed to see if there was a trend in enzyme elevations at various doses.

Software

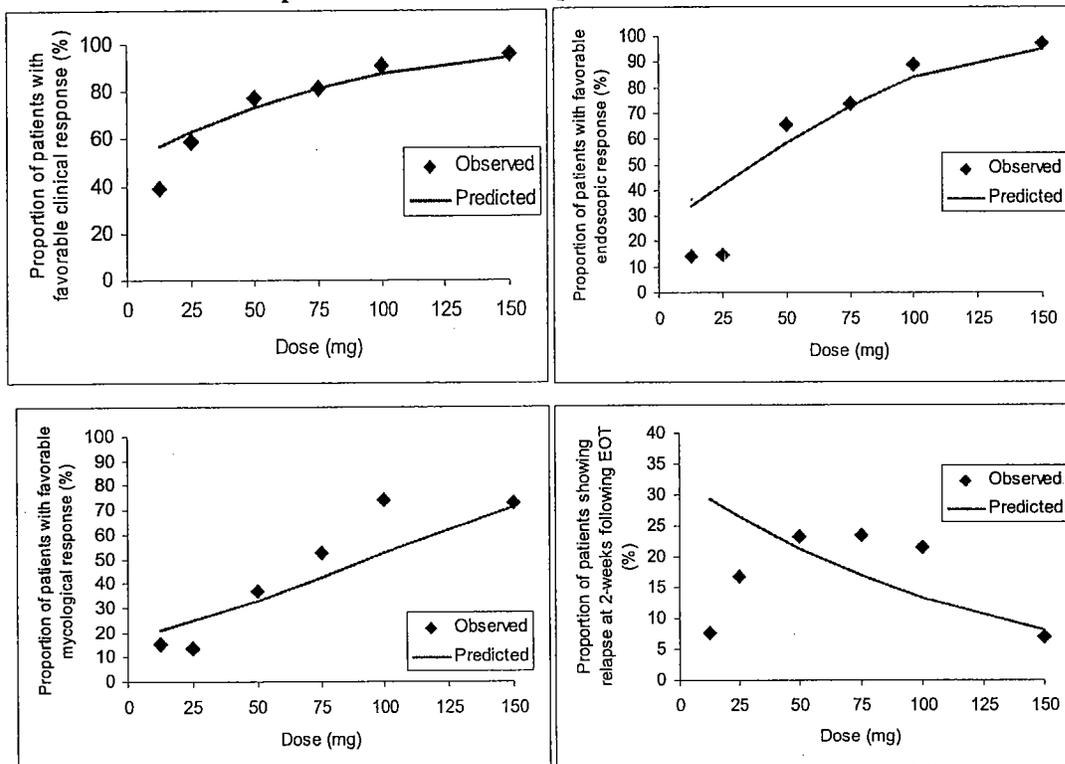
All available datasets were formatted for each study individually and then combined into one data set. Dose-toxicity analysis were performed using NONMEM version V, level 1.1, NM-TRAN version III, level 1.0 and PREDPP version IV, level 1.0. The models were run using Compaq Digital Fortran compiler version 6.6 (update A). The SAS System for Windows (Release 8.02 TS Level 02MO) was used for the dose-effectiveness analyses on a Windows XP operating system.

Results

Dose-effectiveness:

As seen below in Figure 4, a clear dose-response relationship is seen for micafungin for the 4 endpoints. The 100 mg and 150 mg doses were found to be more effective than lower doses and were also found to be similar in effectiveness.

Figure 4. Dose response relationship of micafungin for various endpoints. The observed data is shown as data points and the model predicted data is shown as the solid line.



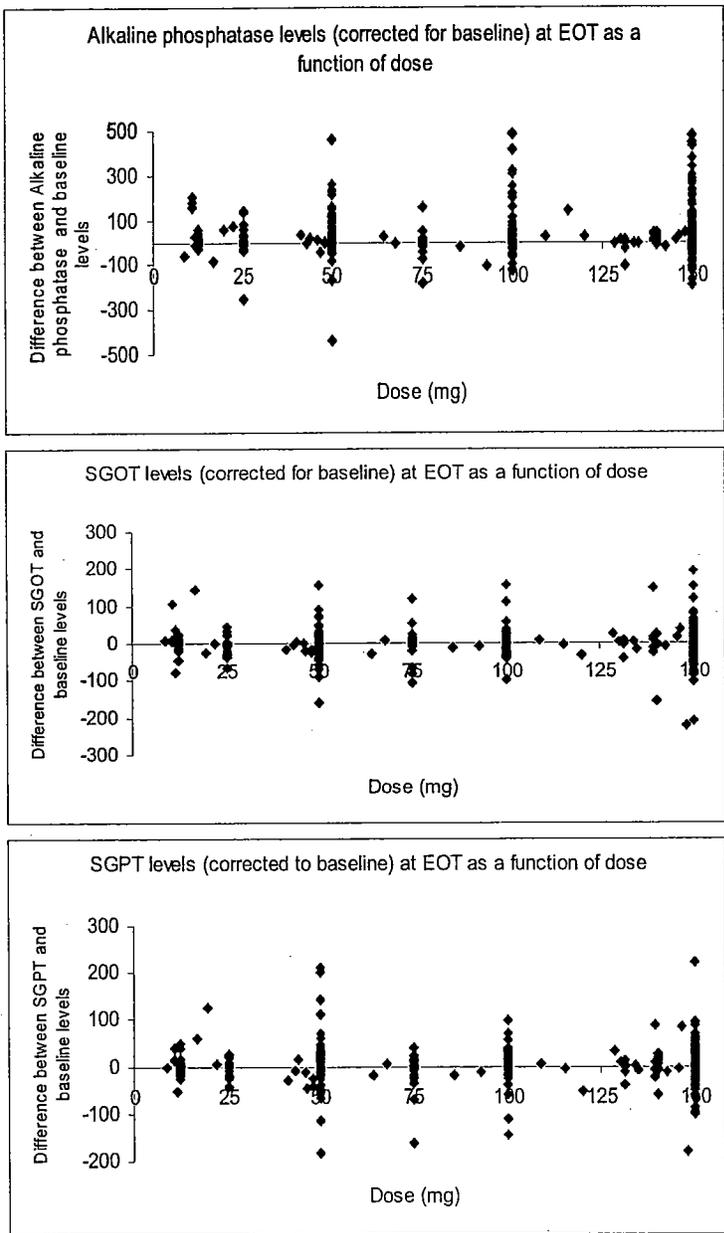
Baseline endoscopic grade did not influence the effect of micafungin on the treatment of esophageal candidiasis.

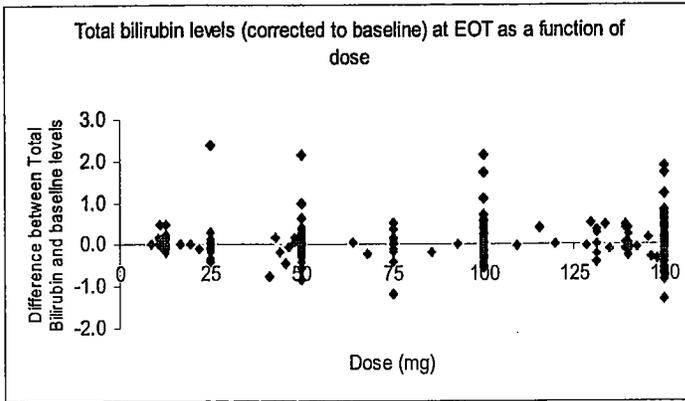
Dose-toxicity of micafungin

Micafungin was found to cause elevations in liver enzymes, SGOT, SGPT, alkaline phosphatase and bilirubin. Preclinical studies showed that micafungin caused dose dependent elevations in liver enzymes, in addition to more serious hepatic toxicity problems at higher doses (compared to the human doses). The objective of this analysis was to see if the elevation of liver enzymes were dose dependent and also if the elevations were dependent on the duration of exposure.

As seen below in Figure 5, the scatter-plot of the liver enzymes at EOT indicated that there is no relationship between dose and elevations in the liver enzymes. The number of patients who received 50, 100 and 150 mg doses were higher in number and hence more data points are seen for those 3 doses.

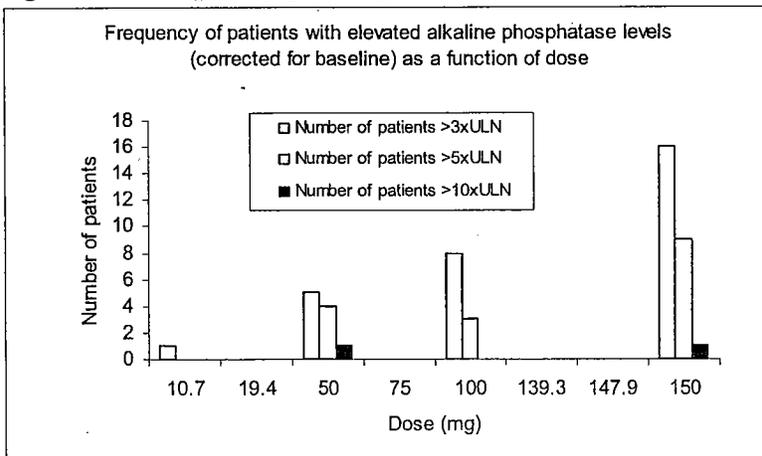
Figure 5. End of therapy enzyme profiles as a function of dose (mg). The enzyme levels shown are corrected for baseline levels.

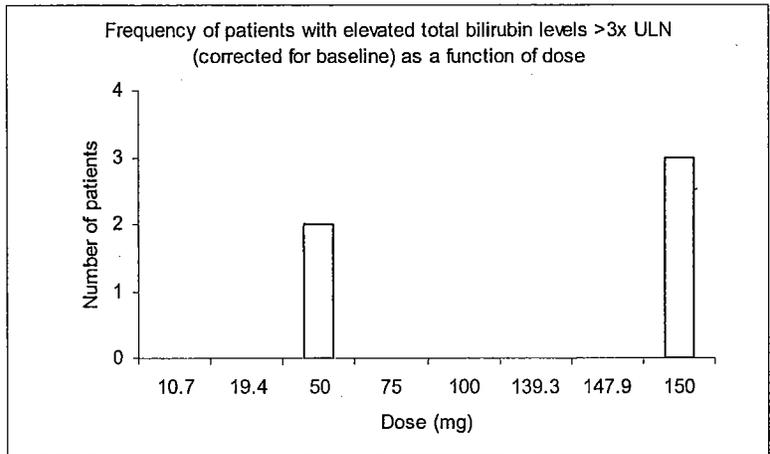
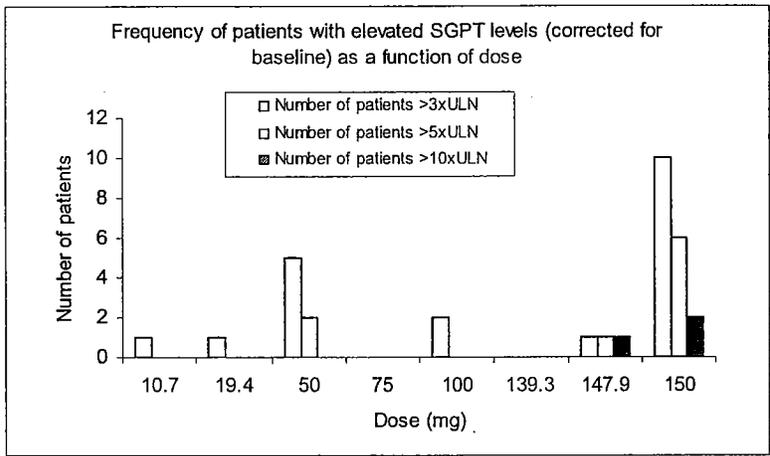
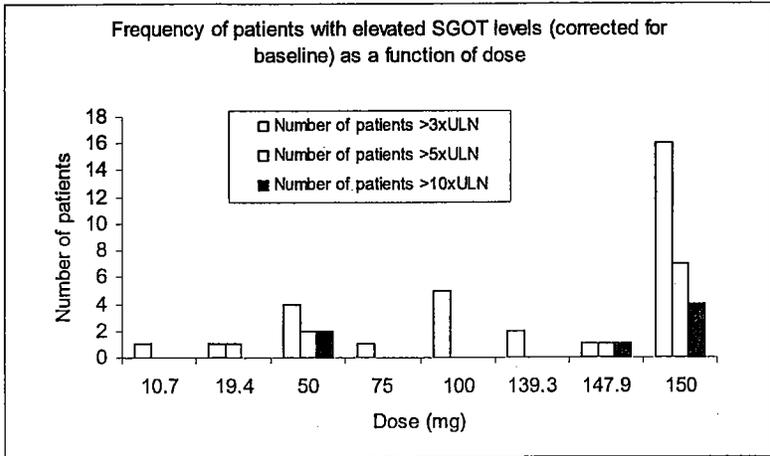




A detailed analysis using SAS was performed on the dataset with specific emphasis on patients whose values were $>3\times$ upper limit of normal (ULN), $>5\times$ ULN, $>10\times$ ULN. The relationship of dose versus these high enzyme values was performed using logistic regression in SAS. These results indicated a lack of statistically significant dose effect on the enzyme values. However, as seen below, a frequency plot of patients with elevated enzyme values as a function of dose indicates that a higher number of patients receiving 150 mg dose had elevated enzyme levels. This effect appears more pronounced with alkaline phosphatase, SGOT and SGPT and can be readily seen that for the clinical dose of 150 mg micafungin is associated with a higher number of elevations in liver enzymes. For bilirubin, none of patients had enzyme values $>5x$ ULN and there does not seem to be a dose-related elevations of bilirubin.

Figure 6: A frequency plot of patients with elevated enzyme levels as a function of dose.





Using NONMEM, the effect of covariates such as dose on the elevations in liver enzyme levels normalized to baseline levels was studied. Also, an effect of time of enzyme level measurement subsequent to drug administration was studied on the elevation of the enzyme levels. Four different linear models were studied as indicated below explain the relationship between dose and time on the enzyme elevations:

1. Model 1: Intercept only model
2. Model 2: Effect of the duration of exposure (time)
3. Model 3: Effect of micafungin dose
4. Model 4: Effect of dose and duration of exposure

The effect of dose and time were studied for models 2, 3 and 4 based on the decrease in the objective function value compared to model 1. If no difference in the objective function value was seen then it was concluded that there is no effect of the covariates and that the elevations in the enzyme levels were not dependent on dose and time.

In model 2 the effect of time on elevations of enzymes was studied by using data from day 7, day 14, EOT (if different from day 14) and EOS (usually 2-weeks after EOT, I.E., day 35). In model 4 the effect of dose on elevations of enzymes was studied by using the actual dose received by the patient in the 3 studies. In model 4 the effect of both dose and extent of exposure (time) was studied.

In table 1 the objective function values for various models for the 4 enzymes are presented. As seen in the table, the objective function values were lowest for Model 1 for each enzyme, compared to other models. Addition of covariates such as time and dose does not result in a reduction in the objective function of the model. These results indicated that the enzyme levels relative to the baseline levels are not related to the dose of micafungin or the time of enzyme level measurement (duration of exposure).

Table 2: Objective function values obtained from NONMEM analysis for various dose-toxicity models.

Model	Objective Function Value
Alkaline Phosphatase Model 1: Intercept	5685
Alkaline Phosphatase Model 2: Time effect	18301
Alkaline Phosphatase Model 3: Dose effect	18301
Alkaline Phosphatase Model 4: Dose and Time effect	18886
SGOT Model 1: Intercept	4938
SGOT Model 2: Time effect	19320
SGOT Model 3: Dose effect	19320
SGOT Model 4: Dose and Time effect	19320
SGPT Model 1: Intercept	4371
SGPT Model 2: Time effect	15754
SGPT Model 3: Dose effect	15754
SGPT Model 4: Dose and Time effect	15754
Total Bilirubin Model 1: Intercept	-617
Total Bilirubin Model 2: Time effect	9703
Total Bilirubin Model 3: Dose effect	9728
Total Bilirubin Model 4: Dose and Time effect	9703

Conclusions from dose-response analysis:

1. The 150 mg dose displayed the maximum response for the primary endpoint (endoscopic cure) and both 100 and 150 mg doses resulted in comparable responses for the secondary endpoint (clinical response). Lower doses (12.5, 50 and 75 mg) resulted in lower cure rate of the disease for all endpoints studied.
2. A lower proportion (15%) of patients showed relapse at 2-weeks following EOT in the 150 mg dose group compared to the other dose groups. This was not due to the difference in the duration of exposure of micafungin among the dose groups.
3. Liver enzyme elevations are statistically dose-independent and time-independent for the dosing regimen studied (12.5 – 150 mg) in the clinical studies for 14-21 days of administration, followed by a 2-week follow-up evaluation. However, the number of patients dosed with 150 mg with LFT elevations $>3 \times \text{ULN}$ were 2-fold greater than patients who were dosed with 100 mg dose.

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