CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-506

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; . 50 mg**

Proposed Indications and Doses	Adults (mg/day)
Prophylaxis of *Candida* 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, [redacted] on April 29, 2002. While [redacted] were not approved, 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 2 to 17 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 ± 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	Cmax (µg/mL)	4.1 ± 1.4	8.0 ± 2.4	11.6 ± 3.1
	AUCτ (µg-hr/mL)	35.7 ± 8.9	74.5 ± 18.7	104.3 ± 26.3
	AUC∞ (µg-hr/mL)	53.4 ± 17.8	107.9 ± 30.7	150.6 ± 44.6
	CL (mL/hr/kg)	19.3 ± 5.9	19.8 ± 5.4	20.4 ± 5.5
	Vz (mL/kg)	401 ± 124	388 ± 114	407 ± 103
	t½ (hr)	14.9 ± 4.3	13.8 ± 3.0	14.1 ± 2.6
At Steady State	Cmax (µg/mL)	5.1 ± 1.1	10.1 ± 2.6	16.4 ± 6.5
	AUCτ (µg-hr/mL)	54.3 ± 13.1	115.3 ± 24.9	166.5 ± 40.4
	CL (mL/hr/kg)	18.1 ± 4.2	18.1 ± 4.3	17.5 ± 4.8
	t½ (hr)	15.6 ± 2.8	16.9 ± 4.4	15.2 ± 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	Tmax (hr)	12.6 ± 12.9	6.4 ± 8.1	4.3 ± 6.7
	Cmax (µg/mL)	0.31 ± 0.14	0.62 ± 0.25	0.93 ± 0.34
	AUCτ (µg-hr/mL)	6.0 ± 2.1	12.1 ± 4.0	18.1 ± 4.7
	t½ (hr)	64.6 ± 31.8	62.0 ± 30.6	53.5 ± 15.5
M2	Tmax (hr)	22.9 ± 24.7	21.2 ± 22.6	26.2 ± 26.6
	Cmax (µg/mL)	0.08 ± 0.02	0.10 ± 0.03	0.14 ± 0.04
	AUCτ (µg-hr/mL)	0.98 ± 0.69	1.81 ± 0.55	2.57 ± 0.77
	t½ (hr)	NC	NC	NC
M5	Tmax (hr)	5.7 ± 3.3	6.9 ± 3.8	8.4 ± 3.4
	Cmax (µg/mL)	0.41 ± 0.20	0.63 ± 0.21	1.00 ± 0.29
	AUCτ (µg-hr/mL)	7.84 ± 3.52	12.8 ± 4.5	19.8 ± 5.7
	t½ (hr)	22.7 ± 4.5	25.3 ± 5.2	24.5 ± 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 AUCτ 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 Cmax or AUC following the first and steady-state doses presented in Table 1 were > 0.99. Micafungin accumulation ratios (ratio of micafungin AUCτ at steady state to AUCτ 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 (t½) 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 ^{14}C-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 μg/mL to 100 μg/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 1.5 mg/kg infused over 30 minutes to premature infants (Study 99-0-063).

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

Body Weight (g)	Dose (mg/kg)	N	Cmax (µg/mL)	$AUC_{0\text{-}24hr}$ (µg-hr/mL)	CL (mL/hr/kg)	$t_{1/2}$ (hr)	Vss (mL/kg)
500 - 1000	0.75	4	1.31 ± 0.31	8.8 ± 1.4	79.3 ± 12.5	5.7 ± 0.6	693 ± 129
>1000	0.75	6	2.54 ± 0.92	16.5 ± 9.0	58.0 ± 49.1	8.1 ± 1.7	641 ± 605
	1.5	5	4.15 ± 1.13	34.5 ± 5.6	38.6 ± 8.9	8.3 ± 2.2	440 ± 57
	3.0	6	9.28 ± 5.31	59.5 ± 29.0	71.1 ± 79.1	8.5 ± 1.8	735 ± 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 t½ of micafungin were faster and shorter in premature infants. The $AUC_{0\text{-}24hr}$ 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 Cmax 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 t½ 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 ± 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)
Cmax (µg/mL)	24.7 ± 6.3	18.8 ± 3.0	1.31 (p = 0.002)
AUC_τ (µg-hr/mL)	285 ± 54	232 ± 35	1.23 (p < 0.001)
CLss (mL/min/kg)	0.147 ± 0.023	0.147 ± 0.021	1.00 (p = 0.91)
t½ (hr)	14.2 ± 1.6	15.7 ± 2.5	1.5 hr* (p = 0.91)

* difference

The gender difference in the Cmax 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 Cmax/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 Cmax 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 Cmax and AUC in Japanese subjects appear to be due to smaller body weight. The mean values for weight-adjusted CL and terminal t½ 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***
Cmax (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#, ^**
t½ (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 Cmax 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 $AUC_{0\text{-}72hr}$ 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 Cmax 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

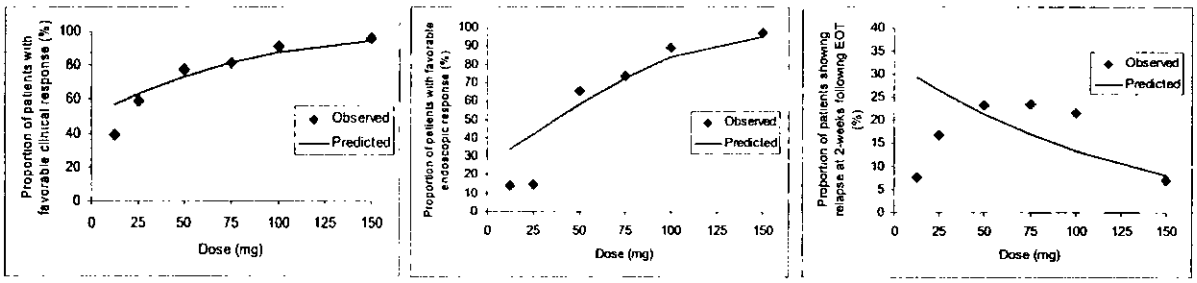
endpoint was clinical response, which was determined by resolution of disease symptoms. Most fungal infections are known to relapse in a certain proportion of patients and hence relapse was also a response endpoint and this was determined by endoscopic assessment 2 and 4-weeks after EOT.

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.

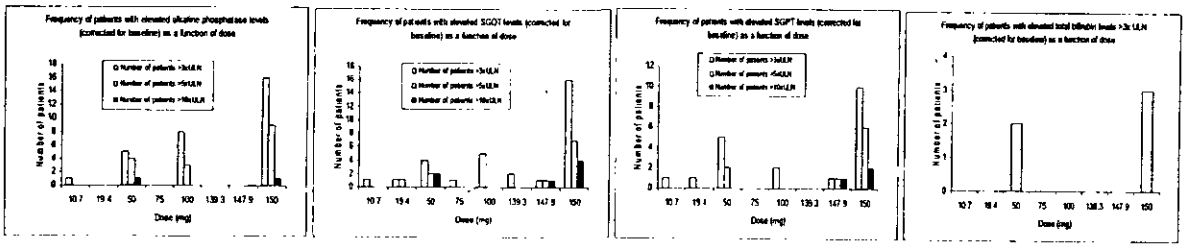
Figure 1: Plot of the dose-response relationship of micafungin for the primary endpoint of endoscopic cure (grade 0 at EOT) and secondary endpoint of clinical cure. Also plotted is the relationship of dose and relapse rate.



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×ULN), >5×ULN, >10×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.



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 (Cmax), 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 ± 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	Cmax (µg/mL)	4.1 ± 1.4	8.0 ± 2.4	11.6 ± 3.1
	AUCτ (µg-hr/mL)	35.7 ± 8.9	74.5 ± 18.7	104.3 ± 26.3
	AUC∞ (µg-hr/mL)	53.4 ± 17.8	107.9 ± 30.7	150.6 ± 44.6
	CL (mL/hr/kg)	19.3 ± 5.9	19.8 ± 5.4	20.4 ± 5.5
	Vz (mL/kg)	401 ± 124	388 ± 114	407 ± 103
	t½ (hr)	14.9 ± 4.3	13.8 ± 3.0	14.1 ± 2.6
At Steady State*	Cmax (µg/mL)	5.1 ± 1.1	10.1 ± 2.6	16.4 ± 6.5
	AUCτ (µg-hr/mL)	54.3 ± 13.1	115.3 ± 24.9	166.5 ± 40.4
	CL (mL/hr/kg)	18.1 ± 4.2	18.1 ± 4.3	17.5 ± 4.8
	t½ (hr	15.6 ± 2.8	16.9 ± 4.4	15.2 ± 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 t½ of M1 was longer than the t½ 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 t½ 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 ± 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	Tmax (hr)	12.6 ± 12.9	6.4 ± 8.1	4.3 ± 6.7
	Cmax (µg/mL)	0.31 ± 0.14	0.62 ± 0.25	0.93 ± 0.34
	AUCτ (µg-hr/mL)	6.0 ± 2.1	12.1 ± 4.0	18.1 ± 4.7
	t½ (hr)	64.6 ± 31.8	62.0 ± 30.6	53.5 ± 15.5
M2	Tmax (hr)	22.9 ± 24.7	21.2 ± 22.6	26.2 ± 26.6
	Cmax (µg/mL)	0.08 ± 0.02	0.10 ± 0.03	0.14 ± 0.04
	AUCτ (µg-hr/mL)	0.98 ± 0.69	1.81 ± 0.55	2.57 ± 0.77
	t½ (hr)	NC	NC	NC
M5	Tmax (hr)	5.7 ± 3.3	6.9 ± 3.8	8.4 ± 3.4
	Cmax (µg/mL)	0.41 ± 0.20	0.63 ± 0.21	1.00 ± 0.29
	AUCτ (µg-hr/mL)	7.84 ± 3.52	12.8 ± 4.5	19.8 ± 5.7
	t½ (hr)	22.7 ± 4.5	25.3 ± 5.2	24.5 ± 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 AUCτ 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 AUCτ 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 AUCτ 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 Cmax 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
Cmax (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
AUCτ (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 Cmax or AUC at Day 1 and at steady state displayed in Table 7 were > 0.99. Micafungin accumulation ratios (ratio of micafungin AUCτ at steady state to AUCτ 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 t½ 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 AUCτ 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 ± 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 (µg/mL)	M1 (µg/mL)	M2 (µg/mL)	M5 (µg/mL)
50 (n = 20)	1	0.78 ± 0.27	< 0.05	< 0.05	0.17 ± 0.07
	3	1.18 ± 0.81	0.09 ± 0.02	< 0.05	0.24 ± 0.10
	7	1.10 ± 0.33	0.19 ± 0.05	< 0.05	0.30 ± 0.12
	14	1.06 ± 0.28	0.22 ± 0.04	< 0.05	0.30 ± 0.16
100 (n = 20)	1	1.65 ± 0.73	0.07*	< 0.05	0.31 ± 0.11
	3	2.84 ± 1.58	0.18 ± 0.05	< 0.05	0.47 ± 0.18
	7	3.84 ± 4.18	0.42 ± 0.13	< 0.05	0.63 ± 0.40
	14	2.51 ± 0.57	0.48 ± 0.12	0.07 ± 0.02	0.62 ± 0.30
150 (n = 14)	1	2.21 ± 0.64	0.11*	< 0.05	0.51 ± 0.17
	3	3.97 ± 3.22	0.27 ± 0.06	< 0.05	0.81 ± 0.43
	7	4.53 ± 3.51	0.65 ± 0.18	0.05 ± 0.04	0.84 ± 0.49
	14	3.53 ± 2.27	0.46 ± 0.40	0.07 ± 0.06	0.83 ± 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 Cmax 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 t½ 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 µg-eq/mL (range, 0.60 - 1.04 µg-eq/mL) and further decreased to 0.45 µg-eq/mL (range, 0.34 - 0.63 µg/mL) by 72 hours post dose. By 28 days post dose, the mean concentration decreased to 0.11 µg-eq/mL (range,0.07 - 0.16 µg 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 ^{14}C-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, ´ ⟶ mL/min) and matched healthy controls (CrCL range ⟶ 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 [redacted] 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 1.5 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	Cmax (µg/mL)	$AUC_{0\text{-}24hr}$ (µg-hr/mL)	CL (mL/hr/kg)	t½ (hr)	Vss (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 Cmax and $AUC_{0\text{-}24hr}$ 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 Cmax for the two groups was significant (p = 0.036), but the differences in $AUC_{0\text{-}24hr}$ 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-conceptional 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 t½ of micafungin were faster (approx. 8 *versus* 14 hour) and shorter (approx. 50 *versus* 20 mL/hr/kg) in premature infants. The $AUC_{0\text{-}24hr}$ 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 Cmax and AUCτ 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 t½ 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 Cmax 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)
Cmax (µg/mL)	24.7 ± 6.3	18.8 ± 3.0	1.31 (p = 0.002)
AUCτ (µg-hr/mL)	285 ± 54	232 ± 35	1.23 (p < 0.001)
CLss (mL/min/kg)	0.147 ± 0.023	0.147 ± 0.021	1.00 (p = 0.91)
t½ (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 Vss, and terminal t½ 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 Cmax 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)
Cmax (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)
t½ (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)
Vss (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 Cmax/Dose, AUC/Dose, and CL for males and females were comparable (Table 17).

Table 17: Micafungin pharmacokinetics (mean ± 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	Cmax/Dose (μg/mL)/(mg/kg)	AUC_{24hr}/Dose (μg·hr/mL)/(mg/kg)	CL (mL/hr)/kg
Day 1	Male	27	4.2 ± 1.3	36.8 ± 8.7	20.6 ± 5.9
	Female	27	4.1 ± 1.0	38.1 ± 9.3	19.8 ± 5.1
Day 14 or 21	Male	27	5.3 ± 1.2	58.6 ± 13.2	18.0 ± 4.4
	Female	27	5.4 ± 1.3	59.3 ± 15.5	17.9 ± 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 Cmax compared to all other racial groups by 19%, and greater mean value in dose-adjusted AUC_∞ by 26% and in weight-adjusted Vss by 19% compared to blacks. The greater mean values in the Cmax and AUC in Japanese subjects appear to be due to smaller body weight: the mean values for weight-adjusted CL and terminal t½ were not different. The reason for the greater Vss in Japanese compared to black subjects is not known.

Table 18: Comparison of micafungin pharmacokinetic parameters (mean ± 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 ± 13.0	85.2 ± 8.0	72.8 ± 10.4	**59.7 ± 7.7***
Cmax (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#, ^**
t½ (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
Vss (L/kg)	0.207 ± 0.024	**0.197 ± 0.026#**	0.212 ± 0.023	**0.234 ± 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 Cmax, AUCτ, terminal t½, 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 Cmax/Dose, AUC/Dose, and CL for Caucasians, blacks, and Mulattos were comparable (Table 19).

Table 19: Effect of race on micafungin pharmacokinetics (mean ± 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	Cmax/Dose (μg/mL)/(mg/kg)	AUC_{24hr}/Dose (μg·hr/mL)/(mg/kg)	CL (mL/hr)/kg
Day 1	Caucasian	18	4.1 ± 1.1	37.1 ± 9.4	20.8 ± 6.9
	Black	30	4.1 ± 1.2	37.2 ± 9.0	20.1 ± 4.8
	Mulatto	5	5.1 ± 1.0	42.2 ± 6.0	17.7 ± 3.1
Day 14 or 21	Caucasian	18	5.3 ± 1.3	60.4 ± 14.0	17.5 ± 4.6
	Black	30	5.3 ± 1.3	58.5 ± 14.2	17.9 ± 3.9
	Mulatto	5	5.6 ± 1.1	60.4 ± 14.0	17.7 ± 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 Cmax 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 (%)
Tmax* (hr)	1.5 (—	0.7 —	0.8^	
Cmax (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
Vz/F (L)	495 ± 219	605 ± 537	102.7	82.7 - **127.6**
t½ (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 Cmax and $AUC_{0\text{-}24hr}$ of micafungin were within the range of 80% to 125% (Table 21). The mean Cmax 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 (%)
Cmax (ng/mL)	21.4 ± 4.9	21.7 ± 4.9	101.4	98.9 - 104.0
$AUC_{0\text{-}24hr}$ (ng-hr/mL)	253 ± 50	250 ± 48	98.7	97.6 - 99.9
t½ (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 $AUC_{0\text{-}72hr}$ of sirolimus was increased by 21% (GMR, 121.1%; 90% CI, 112.1% - 130.9%; Table 22). However, the Cmax 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 (,)	1.5 ( )		
Cmax (ng/mL)	17.4 ± 4.9	17.8 ± 5.3	101.6	92.5 - 111.5
$AUC_{0\text{-}72hr}$ (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
t½ (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 $AUC_{0\text{-}24hr}$ 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
$AUC_{0\text{-}24hr}$ (ng-hr/mL)	223 ± 37	224 ± 37	100.2	98.9 - 101.6
t½ (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 $AUC_{0\text{-}72hr}$ 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 Cmax and $AUC_{0\text{-}24hr}$ of micafungin were within the range of 80% to 125% (Table 25). The mean Cmax 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	Tmax* (hr)	1.0 (⌣)	0.67 (⌢ J)		
	Cmax (µg/mL)	36.3 ± 14.0	37.7 ± 17.7	101.3	84.5 - 121.5
	$AUC_{0\text{-}72hr}$ (µg-hr/mL)	86.8 ± 25.0	87.5 ± 22.9	101.0	94.4 - 108.1
	t½ (hr)	13.4 ± 6.0	14.8 ± 7.3		
MPAG	Tmax* (hr)	2.0 (1.0 - 4.0)	1.5 (1.0 - 10.0)		
	Cmax (µg/mL)	83.9 ± 14.1	80.8 ± 24.6	92.9	84.4 - 102.2
	$AUC_{0\text{-}72hr}$ (µg-hr/mL)	678 ± 146	681 ± 171	99.9	93.2 - 107.0
	t½ (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 (%)
Cmax (ng/mL)	23.0 ± 5.8	23.4 ± 5.6	101.8	97.4 - 106.4
$AUC_{0\text{-}24hr}$ (ng-hr/mL)	268 ± 47	281 ± 49	104.9	103.0 - 106.9
t½ (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 Cmax and $AUC_{0\text{-}72hr}$ 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 Cmax and $AUC_{0\text{-}24hr}$ of micafungin were within the range of 80% to 125% (Table 27). The mean Cmax 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 [illegible]	3.0 [illegible]		
Cmax (ng/mL)	4.5 ± 0.58	4.5 ± 0.7	98.8	94.5 - 103.4
$AUC_{0\text{-}72hr}$ (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
$AUC_{0\text{-}24hr}$ (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 6β-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 Cmax and AUCs 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 (%)
Cmax (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
t½ (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.

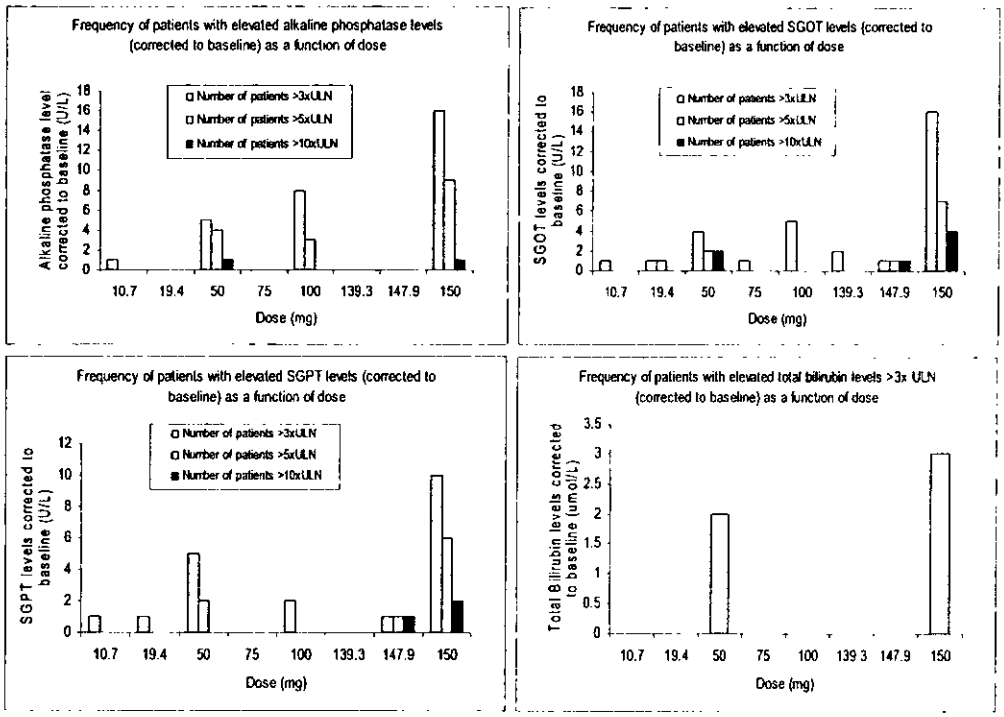
3. ***Based upon what is known about exposure-response relationships and their variability, what dosage regimen adjustments do you recommend for each of these factors?***

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×ULN), >5×ULN, >10×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 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 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, [ ] in 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

micafungin and its metabolites. The respective ranges of retention time for micafungin, M1, M2, and FR195743 were , minutes.

Micafungin, M1 and M2 in Urine: The analytical method used to measure the concentrations of micafungin and its metabolites in urine samples was very similar to the method used to measure the concentrations in plasma samples. The procedure for analyte preparation varied slightly; Tween 20 (1% to urine volume) was added to all urine samples to prevent drug adsorption to plastic surface, and the samples were diluted . HPLC system.

Micafungin, M1 and M2 in Ultrafiltrate: The analytical method used to measure micafungin concentrations in ultrafiltrate samples for protein binding studies was also similar to the method used to measure the concentrations in plasma. Unltrafiltrate samples were diluted with 3% Tween 20 in 20 mM potassium dihydrogenphosphate and with dilute phosphoric acid in acetonitrile. Then the samples were injected onto an HPLC system.

^{14}C-Micafungin: The amount of radioactivity in plasma, urine, and feces following the administration of ^{14}C-micafungin was measured using a liquid scintillation counting method. Fecal samples were dried and oxidized prior to counting. All samples were counted in duplicate with 10 mL of liquid scintillation cocktail for 20 minutes.

Cyclosporine: The whole blood concentrations of cyclosporine were measured using a HPLC method with mass spectrometric detection (LC-MS). Cyclosporin U was used as an internal standard. In principle, analytes were extracted from whole blood samples with methyl-tert-butyl-ether. Extracts were reconstituted in acetonitrile/water (65/35, v/v) and injected (5 µL) onto an LC-MS system.

Tacrolimus: The whole blood concentrations of tacrolimus were measured using a liquid chromatographic method FR900520, a tacrolimus analog, was used as an internal standard. In principle, analytes were extracted from whole blood samples by

Prednisolone: The plasma concentrations of prednisolone were measured using an LC-MS method. Dexamethasone was used as an internal standard. In principle, analytes were extracted from plasma samples by solid phase extraction using a

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 µg/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

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 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 ng/mL with a calibrated linear range of ng/mL (r^2 = Inter-assay accuracy using quality control samples at fluconazole concentrations of ranged between %. The corresponding precision ranged

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 (µg/mL)	Accuracy (mean bias %)	Precision (CV %)	Calibration Range (µg/mL)	LOQ (µg/mL)
99-0-063		Micafungin					
		M1					
		M2					
03-3-175 03-3-176 03-3-177 03-3-178		Micafungi					
		M1					
		M2					
		M5					
FG-463-21-09		Micafunc					
		M1					
		M2					
		M5					
FG-463-21-15 FG-463-21-16		Micafungi					

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 — g/mL (r^2 = —. Inter-assay accuracy using quality control samples at nifedipine concentrations of — µg/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 —. Sirolimus and internal standard (desmethoxyrapamycin) were extracted from whole blood samples using — followed by — extraction. — — — .. Detection was done with — The peak area ratio of sirolimus and the internal standard *versus* concentration data of the standards were fitted by inversely weighted ($1/x^2$) linear regression. The LOQ for sirolimus was — ng/mL with a calibrated linear range of to — ng/mL (r > —. Inter-assay accuracy (mean bias %) using quality control samples at sirolimus concentrations of — ng/mL ranged between —

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____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

IV. APPENDICES

A. Package Insert (proposed and annotated)

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

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, randomized, 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

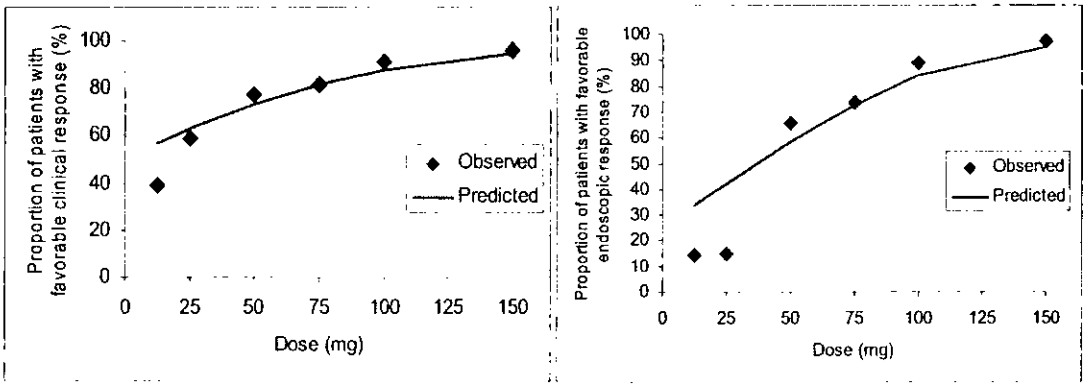
The relationship between dose and effectiveness was modeled by the FDA reviewer using multiple endpoints using data from 2 Phase 2 studies and 1 Phase 3 study. The primary effectiveness endpoint in this study was endoscopic response rate, defined as the proportion of patients with a mucosal grade=0 or 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.

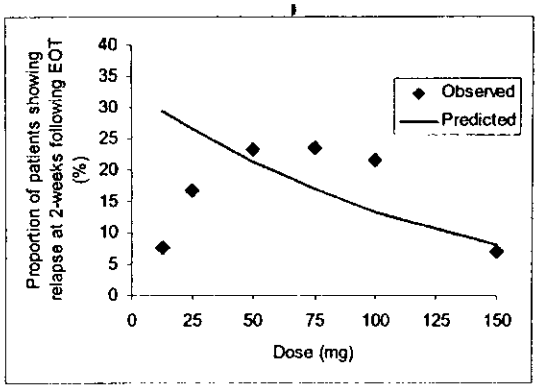
Question Based Review for Pharmacometrics

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

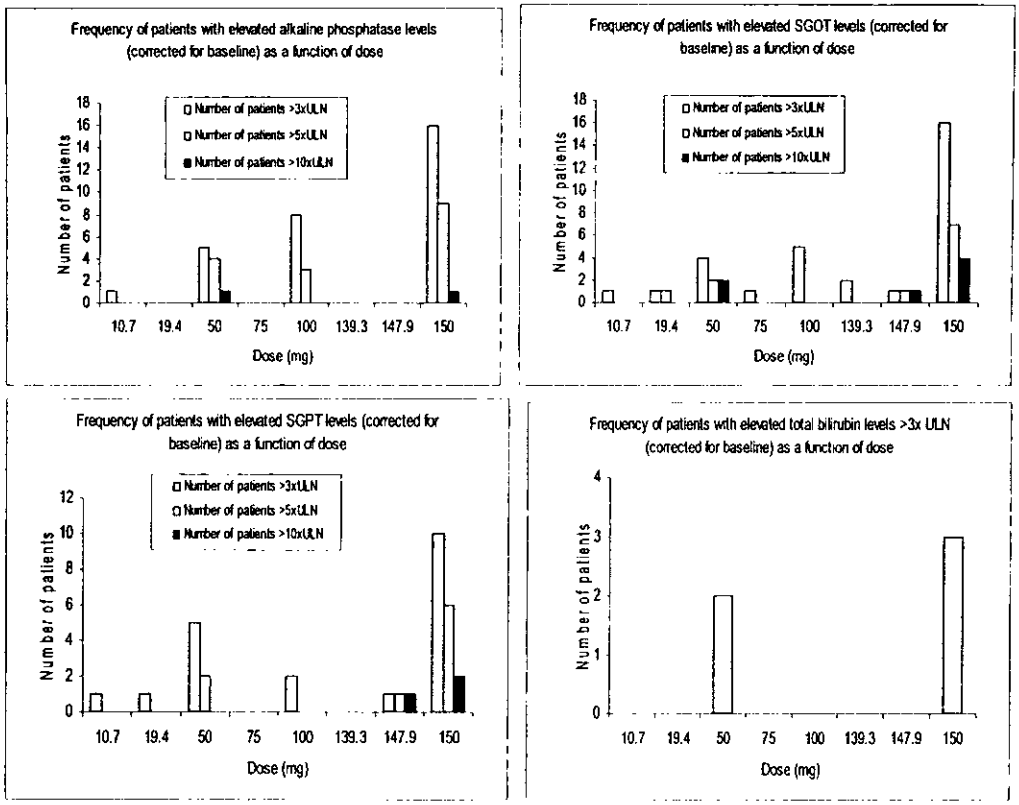




The effect of covariates such as dose on the elevations in liver enzyme levels normalized to baseline levels was studied. Also, an effect of time of enzyme level measurement subsequent to drug administration was studied on the elevation of the enzyme levels. The results of the analysis indicated that 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×ULN), >5×ULN, >10×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 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.

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 AUC_{24} 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 AUC_{24} 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 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?

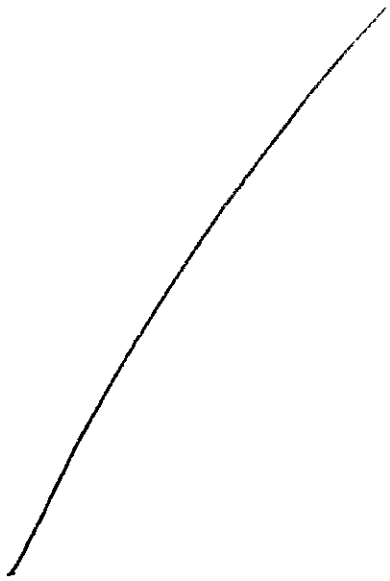
The dose-response analysis performed by the reviewer and the exposure response analysis conducted by the applicant indicate that the 100 mg and 150 mg doses provide comparable rate of cure. However, the 150 mg dose group is associated with a lower rate (15%) of relapse compared to the 100 mg dose group. 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:



Date: _____

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.
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Division of Pharmaceutical Evaluation III
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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

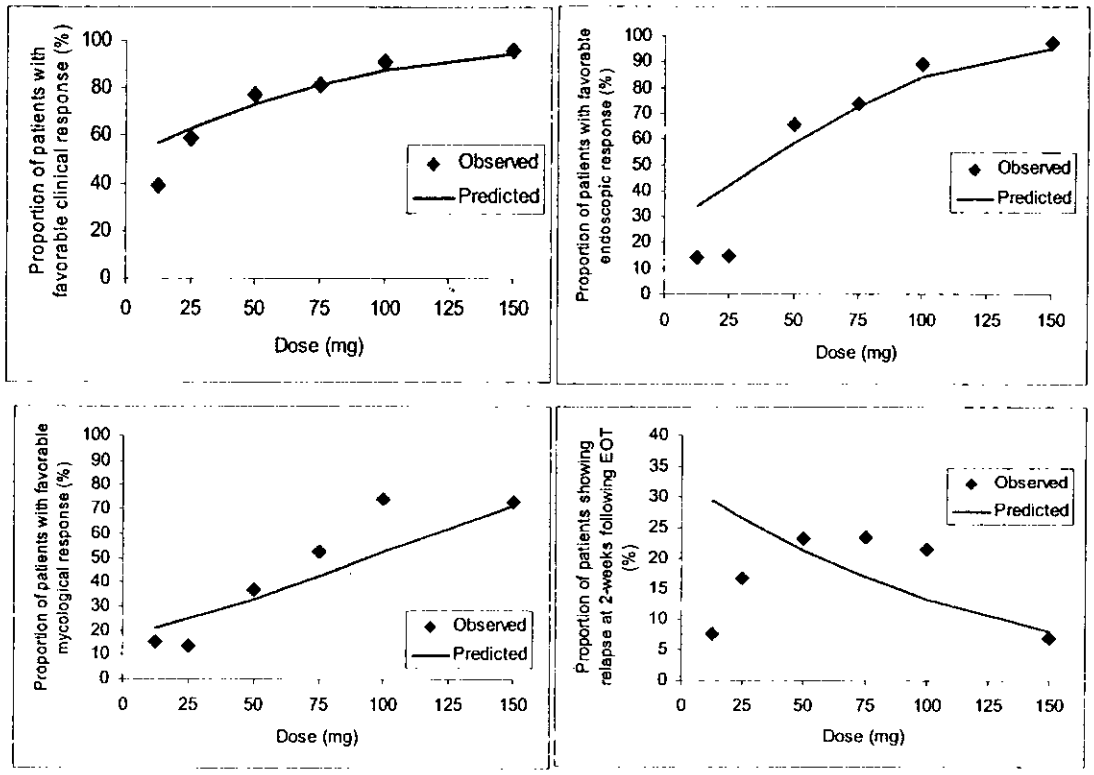
All available datasets were formatted for each study individually and then combined into one data set. Dose-toxicity analysis were performed using NONMEM version V, level 1.1, NM-TRAN version III, level 1.0 and PREDPP version IV, level 1.0. The models were run using Compaq Digital Fortran compiler version 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.



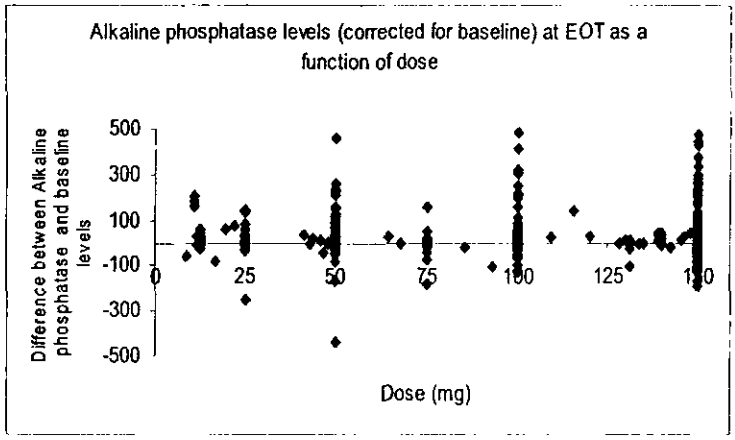
Baseline endoscopic grade did not influence the effect of micafungin on the treatment of esophageal candidiasis.

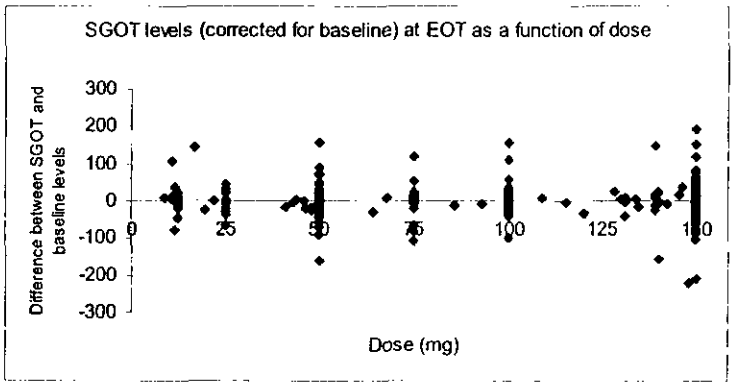
Dose-toxicity of micafungin

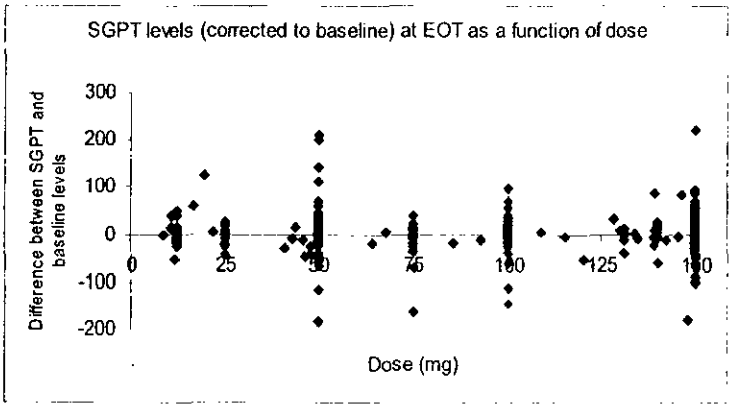
Micafungin was found to cause elevations in liver enzymes, SGOT, SGPT, alkaline phosphatase and bilirubin. Preclinical studies showed that micafungin caused dose dependent elevations in liver enzymes, in addition to more serious hepatic toxicity problems at higher doses (compared to the human doses). 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.

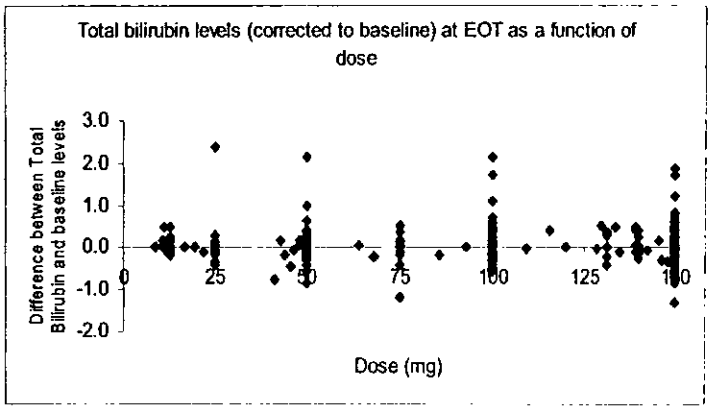
As seen below in Figure 5, the scatter-plot of the liver enzymes at EOT indicated that there is no relationship between dose and elevations in the liver enzymes. The number of patients who received 50, 100 and 150 mg doses were higher in number and hence more data points are seen for those 3 doses.

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



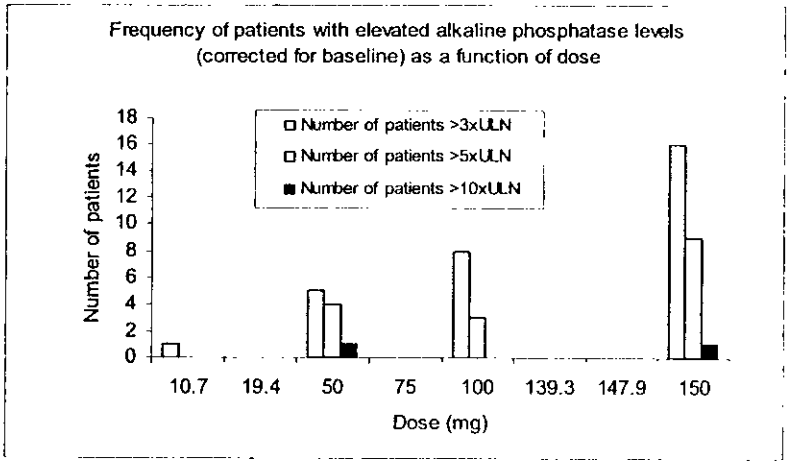


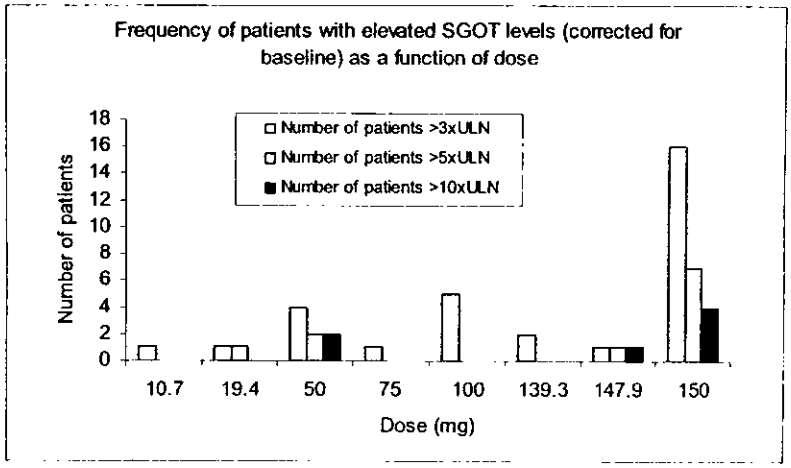


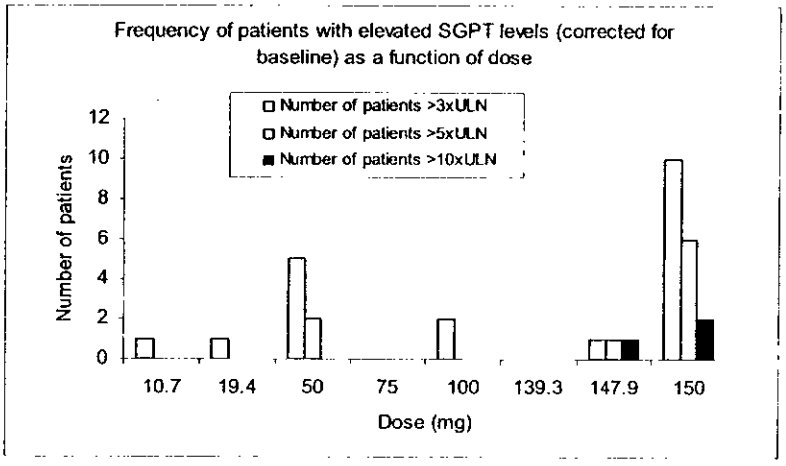


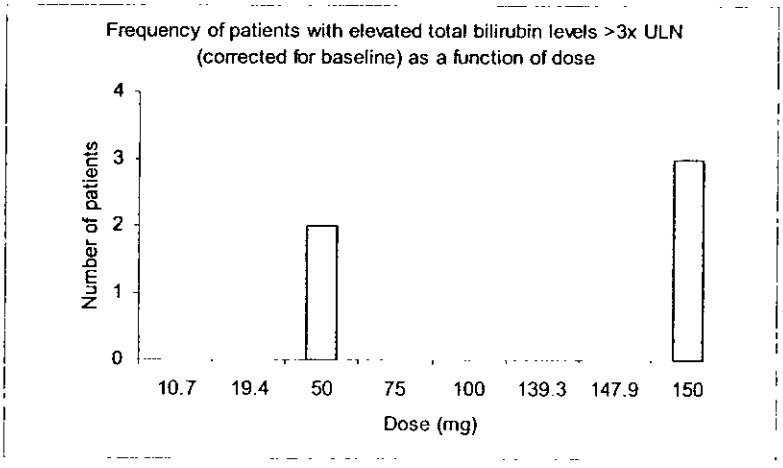
A detailed analysis using SAS was performed on the dataset with specific emphasis on patients whose values were >3×upper limit of normal (ULN), >5×ULN, >10×ULN. The relationship of dose versus these high enzyme values was performed using logistic regression in SAS. These results indicated a lack of statistically 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 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 6: A frequency plot of patients with elevated enzyme levels as a function of dose.




Frequency of patients with elevated SGOT levels (corrected for baseline) as a function of dose
Number of patients >3xULN
Number of patients >5xULN
Number of patients >10xULN
Number of patients
18
16
14
12
10
8
6
4
2
0
10.7
19.4
50
75
100
139.3
147.9
150
Dose (mg)


Frequency of patients with elevated SGPT levels (corrected for baseline) as a function of dose
Number of patients >3xULN
Number of patients >5xULN
Number of patients >10xULN
Number of patients
12
10
8
6
4
2
0
10.7
19.4
50
75
100
139.3
147.9
150
Dose (mg)


Frequency of patients with elevated total bilirubin levels >3x ULN (corrected for baseline) as a function of dose
Number of patients
4
3
2
1
0
10.7
19.4
50
75
100
139.3
147.9
150
Dose (mg)

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×ULN were 2-fold greater than patients who were dosed with 100 mg dose.

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/s/

Jang-Ik Lee
3/3/05 01:43:43 PM
BIOPHARMACEUTICS

Phil Colangelo
3/4/05 03:07:38 PM
BIOPHARMACEUTICS

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: **21-506,** —	Submission Date(s): **4/29, 8/28, 9/4, 9/6, 9/13, 11/4/02**
Brand Name	**Mycamine for Injection (tentative)**
Generic Name	**Micafungin sodium (formerly FK463) for injection**
Reviewer	**Jang-Ik Lee, Pharm.D., Ph.D.**
Team Leader	**Barbara Davit, 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, priority review; 1P**
Formulation; Strength(s)	**Lyophilized product for IV infusion; — 50 mg**

Proposed Indications and Doses	Adults (mg/day)	—
Prophylaxis of — s in patients undergoing hematopoietic stem cell transplant	50	—

1. EXECUTIVE SUMMARY

Micafungin is a semisynthetic cyclic lipopeptide. Micafungin belongs to an echinocandidin class of antifungal agent and is structurally and pharmacologically similar to caspofungin (Cancidas®). The Agency approved Cancidas® (N21-227) for the treatment of invasive Aspergillosis in 2001. N21-506 is an original application for micafungin sodium for injection under 6-month priority review under the consideration of therapeutic gain for the prophylaxis — The review period was extended to 9 months because the sponsor submitted an unusual amount of clinical pharmacology information as a part of the 120-day safety update — and — for treatment indications are under standard 10-month review cycle.

These applications contain 16 human pharmacokinetic studies (Table 1 in 3. SUMMARY OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS), 1 retrospective pharmacokinetic analysis, and 12 *in vitro* studies in the section of Human Pharmacokinetics and Bioavailability. Among them, three human pharmacokinetic studies and one retrospective analysis (Table 1)

were not reviewed because they (1) were conducted using lower micafungin doses than proposed clinical doses; or (2) did not allow adequate micafungin pharmacokinetic profiling. Many study reports in this application were poorly written with inadequate data analysis and poorly organized with missing essential subparts. This reviewer is the primary reviewer and had assistance from Dr. Seong Jang, who reviewed a clinical pharmacology study in patients with moderate hepatic dysfunction.

Deficiencies were found in the clinical part and data analysis of a pivotal pharmacokinetic study conducted in adult patients and a pharmacokinetic study conducted in pediatric patients. This reviewer asked the sponsor to correct the deficiencies, at least in part, by reanalyzing the data in the two studies; the sponsor did not provide us the reanalysis by the date it promised (12/20/02) and even by the completion of this review (1/17/02). However, the deficiencies are not likely to be major issues influencing the overall decision to approve these applications. According to the HFD-590 medical review team, these applications may not be approved as submitted because of insufficient clinical data to support the efficacy of micafungin for the proposed indications.

1.1. Recommendation

The information in the section of Human Pharmacology and Bioavailability in these applications is not complete from a Clinical Pharmacology and Biopharmaceutics (CPB) standpoint. The pharmacokinetics of micafungin were not adequately studied in the targeted patient populations at proposed clinical doses.

The sponsor conducted a pivotal pharmacokinetic study (97-0-041) in adult patients undergoing bone marrow or peripheral stem cell transplantation at the micafungin dose range of 12.5 - 200 mg/day and a pharmacokinetic study (98-0-043) in pediatric patients with febrile neutropenia at the range of 0.5 - 4 mg/kg body weight. The clinical part of these studies appears to be poorly controlled. There are a number of missed blood samplings and unexplained outliers in micafungin concentration-time data (up to 20 times larger than mean values). These problems are not seen in other pharmacokinetic studies such as Study FG463-21-03 that was conducted in a similar adult patient population of interest using larger micafungin doses (3 - 8 mg/kg body weight). It is suspected that many blood samples were collected from the micafungin infusion port and, therefore, the samples were contaminated by residual micafungin in the port. The number of samples collected from the port and the extent of contamination in each sample are largely unknown. Other pharmacokinetic studies that were conducted in patients of interest used micafungin doses other than proposed clinical doses or did not determine complete pharmacokinetic profiles. Pharmacokinetic studies that were conducted in healthy subjects at the proposed clinical doses performed following a single micafungin dose only or in non-Caucasian populations only. Therefore, we do not have reliable data on micafungin pharmacokinetics at the proposed clinical doses in the patient population of interest in the United States.

In addition, we do not have adequate pharmacokinetic data for micafungin metabolites. Some studies such as FG463-21-03 demonstrated that metabolites M1 and M2 kept accumulating at the end of study period. However, no study was conducted to determine the pharmacokinetics of micafungin metabolites at the steady state of metabolite disposition. No study was conducted to determine the elimination half-life of any metabolite. The protein binding characteristics of

micafungin were not quantitatively determined at the proposed clinical doses in the patient population of interest.

The CPB review team recommends that the applicant be asked to conduct adequate and well-controlled studies to characterize micafungin pharmacokinetics over the full range of possible clinical doses in human adult and pediatric subjects. Ideally, the studies should be conducted in the patient populations of interest. The studies should also determine the degree of protein binding and the pharmacokinetic profile of the most abundant metabolite (M5) in addition to the profile of the parent drug and active metabolites (M1 and M2). The effects of age, gender, and race on micafungin pharmacokinetics should be reanalyzed retrospectively based on the new study results if no separate studies are conducted for these purposes.

1.2. Phase IV Commitments

Not applicable

_____ Date: _____

Jang-Ik Lee, Pharm.D., Ph.D.
Clinical Pharmacology and Biopharmaceutics Reviewer
Division of Pharmaceutical Evaluation III

_____ Date: _____

Barbara Davit, Ph.D.
Clinical Pharmacology and Biopharmaceutics Team Leader
Division of Pharmaceutical Evaluation III

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3. SUMMARY OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS

Micafungin is a semisynthetic cyclic lipopeptide that structurally belongs to echinocandidin class. Micafungin inhibits 1,3-beta-D-glucan synthase, an enzyme for the synthesis of an essential glucose polymer in susceptible fungal cell wall. Micafungin sodium for Injection is a sterile, non-pyrogenic lyophilized drug product for intravenous infusion containing — 50 mg of micafungin sodium.

The sponsor reported the pharmacokinetic parameter values of micafungin determined in a pivotal pharmacokinetic study (97-0-041) conducted in adult patients undergoing bone marrow or peripheral stem cell transplantation. The mean ± SD plasma clearance (CL) of micafungin was 0.210 ± 0.052 mL/min/kg following intravenous doses of 50 mg/day infused over an hour for 7 days. The CL value is approximately 1.8% of the plasma flow rate through the liver (11.4 mL/min/kg). The mean volume of distribution of micafungin at steady state (Vss, 0.224 ± 0.055 L/kg) was four to five times larger than the mean plasma volume of adults. The mean terminal half-life ($t_{1/2}$) of micafungin was 12.8 ± 2.67 hours; steady state can be reached in approximately 3 days after repeated daily infusions. The maximum concentration (Cmax) and area under the concentration-time curve within a dosing interval (AUC_{0-24}) at steady state was 4.69 ± 1.16 μg/mL and 53.4 ± 22.7 μg-hr/mL, respectively. However, these pharmacokinetic values are not reliable because the clinical part of the study was poorly controlled.

Micafungin pharmacokinetics was linear over a single dose range of 25 - 150 mg when determined in Japanese healthy volunteers. The CL, Vss, and $t_{1/2}$ of micafungin were comparable between single dose levels of 25, 50, 75, and 150 mg infused over 0.5 hour. The Cmax and $AUC_{0-\infty}$ of micafungin increased in proportion to the dose administered ($r^2 > 0.99$). The pharmacokinetic parameters were not changed following repeated 0.5-hr infusions of 75 mg for 7 days. Micafungin is highly bound to plasma proteins (99.82 ± 0.01 %); primarily to albumin. The protein binding was comparable on Day 1 and Day 7. The dose-linearity and time-dependency in micafungin pharmacokinetics were not adequately determined in the patient populations of interest at the range of proposed clinical doses.

The metabolic pathways of micafungin are not fully understood. Micafungin is metabolized to metabolite M1 (catechol form) by aryl sulfatase. M1 is metabolized to secondary metabolite M2 (methoxy form) by catechol-O-methyl transferase (COMT). M1 and M2 have comparable *in vitro* antifungal activity to the parent compound. Micafungin is also metabolized by cytochrome P450 (CYP) isozymes. According to *in vitro* studies, CYP1A2, 2B6, 2C, and 3A4 were the major enzymes involved in the formation of the inactive M5 metabolite (side chain hydroxylated form), while CYP1A1, 1A2, and 3A4 played a major role in the formation of the inactive M13 metabolite (unidentified structure). In a mass balance study conducted in six healthy Caucasian male volunteers given a radioactive dose equivalent to micafungin 28.3 mg, M1, M2, M3 (cleavage form), M5, and M11 (unidentified structure) accounted for 0.4%, 0.3%, 1.8%, 3.7%, and 1.8%, respectively, of the total radioactivity recovered (52.9% of the dose). The major metabolite found in plasma was M5, which accounted for up to 8.3 ± 1.2 % of the total radioactivity measured in plasma until 47 hours post infusion. The relative amount of M1 in plasma gradually increased to 2.0 ± 0.5 % at 47 hours post infusion. M2 was not detectable in plasma. The major metabolite found in urine was also M5, which accounted for 48.9 ± 7.3 % of

the total urinary radioactivity recovered, while the composition of other metabolites was 1% or less. In feces, respective M3 and M11 accounted for 3.9 ± 1.0 % and 3.9 ± 2.2 % of the total fecal radioactivity recovered, while the compositions of other metabolites was less than 1%. Pharmacokinetic profiles for micafungin metabolites following proposed clinical doses were not adequately studied in the patient populations of interest.

Biotransformation in the liver followed by excretion via feces appears to be the predominant route of micafungin elimination. In the mass balance study mentioned above, the non-renal clearance of ^{14}C-micafungin-derivered radioactivity (0.050 ± 0.005 mL/min/kg) was approximately 88 % of its total body clearance (CLt, 0.057 ± 0.004 mL/min/kg). The recovery of the radioactivity in feces was 43.8 ± 6.0 % out of the total recovery of 52.9 ± 4.8 % as collected for up to 167 hours post dose, which also suggests that fecal elimination is the major route of micafungin elimination. Urinary excretion plays a minor role in the overall elimination of micafungin; the renal clearance of the radioactivity (0.006 ± 0.001 mL/min/kg) was approximately 12 % of the CLt. The urinary recovery of the radioactivity was 7.4 ± 1.4 % as collected for up to 167 hours post dose. The amount of the radioactivity in plasma was estimated to be 1.8 ± 0.3 % at 167 hours post dose. Unchanged micafungin accounted for 26.4 ± 6.0 % of the total fecal radioactivity and for 9.7 ± 2.0 % of the total urinary radioactivity as collected up to 167 hours post dose.

A single dose of micafungin had no effect on the pharmacokinetics of cyclosporine or tacrolimus following a single or multiple (steady state) oral dose(s) and *vice versa*. Steady state doses of micafungin also had no effect on the pharmacokinetics of a single oral dose of cyclosporine or tacrolimus. A single dose of micafungin increased the Cmax of prednisolone by 19% without affecting the AUC following multiple oral doses at steady state. This appears to be a food effect on prednisolone pharmacokinetics rather than a true drug-drug interaction caused by micafungin coadministration. Multiple oral doses of prednisolone did not affect the single dose pharmacokinetics of micafungin. The effect of micafungin on the disposition of fluconazole and *vice versa* could not be reliably determined. Based on *in vitro* studies, micafungin at clinically relevant concentrations is not likely to affect the activity of major CYP enzymes and P-glycoprotein, nor to have clinically significant drug-drug interactions due to protein binding displacement of drugs such as warfarin, diazepam, and salicylic acid.

The pharmacokinetic parameter values of micafungin estimated from healthy elderly subjects were not significantly different from the values estimated from non-elderly controls. The plasma protein binding of micafungin also showed no significant difference between elderly and non-elderly groups. Micafungin pharmacokinetics were not adequately determined in pediatric patients of interest.

The pharmacokinetic parameter values of micafungin in patients with severe renal dysfunction (GFR range at screening, 15.0 - 29.2 mL/min) were comparable to the values estimated from matched control subjects with normal renal function (GFR range at screening, 75.1 -123.7 mL/min). Renal failure did not alter the extent of micafungin binding to plasma proteins. Micafungin exposure, based on dose-normalized (mg/kg body weight) Cmax and AUC, in patients with moderate hepatic dysfunction (Child-Pugh score 7 - 9) was lower by approximately 10% than the exposure observed in healthy controls. The reasons for this reduction are not

known but the reduction is not likely to produce efficacy concerns. Moderate hepatic failure did not alter the extent of micafungin binding to plasma proteins.

The plasma and urinary concentrations of micafungin, M1, and M2 were measured using a validated — high performance liquid chromatographic (HPLC) method with fluorescence detection. The results of initial validations and in-process quality controls met the criteria in the Agency's Guidance for Bioanalytical Method Validation.

Table 1 shows a summary of all clinical pharmacology studies and retrospective analysis for micafungin conducted in humans. Three studies (FJ-463-0001 — , and FJ-463-0002,) were not reviewed because lower micafungin doses than proposed clinical doses were administered or because full pharmacokinetic profiles for micafungin were not determined. The study (FG-463-21-03) conducted in a patient population of interest was reviewed but not considered for CPB recommendation because the study used much larger doses than proposed clinical doses. The pharmacokinetic data obtained from Studies 97-0-041 and 98-0-043 are not acceptable because the clinical part of the studies was inadequate. A retrospective analysis to determine the effect of age, gender, and race on micafungin pharmacokinetics was not reviewed because the analysis was based on the two inadequate studies mentioned above.

Table I: Pharmacokinetic Studies for Micafungin in Humans

Study No. (Country)	Objective	Subjects, No. (M/F), Age (yr)	Dose	Remarks
Studies in Healthy Volunteers				
FJ-463-0001 (Japan)	To determine micafungin pharmacokineticsfollowing single infusion in healthy male subjects	Healthy volunteers 27 (27/0), 27 - 56	2.5 - 50 mg IV single dose	Lower doses than highest clinical doses proposed -> **Not reviewed**
97-0-040 (US)	To determine the distribution, metabolism, elimination, and mass balance of micafungin following a single dose of ^{14}C-micafungin	Healthy volunteers 6 (6/0), 22 - 54	Equivalent to 28.3 mg IV single dose	Mass balance study
FJ-463-0002 (Japan)	To determine micafungin pharmacokinetics following repeated doses in healthy male subjects	Healthy volunteers 6 (6/0), 20 - 29	Lower than clinical doses proposed	Lower doses than proposed clinical doses -> **Not reviewed**
FJ-463-0005 (Japan)	To determine micafungin pharmacokinetics following single and repeated doses in healthy male subjects	Healthy volunteers 29 (29/0), 20 - 31	25 - 150 mg IV x 1 or 75 mg/d IV x 7 days	

Studies in Patients of Interest				
97-0-041 (US)	To determine micafungin pharmacokinetics following administration in combination with fluconazole in patients To determine fluconazole pharmacokinetics following administered in combination with micafungin at steady-state	Patients undergoing bone marrow or peripheral stem cell transplant 62 (20/42), 19 - 65	12.5 - 200 mg/d IV x 7+ days	**Not acceptable because of poor study control** Only one control patient in the determination of fluconazole pharmacokinetics
FG463-21-03 (UK)	To determine the pharmacokinetics of micafungin and its metabolites following repeated doses in patients of interest	Patients undergoing bone marrow or peripheral stem cell transplant 34 (22/12), 19 - 62	3 - 8 mg/kg/d IV x 7+ days	Higher doses (225 - 600 mg/day) than proposed clinical doses -> **Not considered in CPB recommendation**
(Japan)	To determine micafungin pharmacokinetics in patients of interest	66 (53/13), 26 - 77	12.5 - 150 mg/d IV x 5+ days	Measured peak, mid, and trough levels only -> Not reviewed
Studies in Subjects with Intrinsic Factors of Interest				
98-0-043 (US)	To determine micafungin pharmacokinetics in pediatric patients	Pediatric patients with febrile neutropenia 72 (42/30), 2 - 17	0.5 - 4 mg/kg/d IV x 7 days	**Not acceptable because of poor study control and data analysis**
FJ-463-0004 (Japan)	To compare micafungin pharmacokinetics between healthy elderly and non-elderly subjects	Healthy volunteers 10 (10/0), 66 - 78	50 mg IV single dose	10 subjects in non-elderly control group (20 - 24 yo)
01-0-110 (US)	To determine the effect of severe renal impairment on micafungin pharmacokinetics	Subjects with severe renal impairment 9 (5/4), 33 - 75	100 mg IV single dose	In comparison with 9 healthy subject controls Submitted in 120-day safety update
01-0-111 (US)	To determine the effect of moderate hepatic dysfunction on micafungin pharmacokinetics	Subjects with moderate hepatic dysfunction 8 (2/6), 43 - 69	100 mg IV x 1	In comparison with 8 healthy subject controls Submitted in 120-day safety update Dr. Seong Jang reviewed

Studies of Drug-Drug Interactions				
01-0-104 (US)	To evaluate the effect of single or multiple dose micafungin on the single dose pharmacokinetics of cyclosporine and single dose cyclosporine on the single dose pharmacokinetics of micafungin	Healthy volunteers 27 (20/7), 19 - 50	micafungin 100 mg IV single/multiple doses, cyclosporine 5 mg/kg PO single dose	
FG-463-21-05 (UK)	To evaluate the effect of single or multiple dose cyclosporine on the single dose pharmacokinetics of micafungin and single dose micafungin on the multiple dose pharmacokinetics of cyclosporine	Healthy volunteers 24 (24/0), 18 - 50	micafungin 200 mg IV single dose, cyclosporine 50 mg PO single/multiple doses	Submitted in 120-day safety update
01-0-105 (US)	To evaluate the effect of single or multiple dose micafungin on the single dose pharmacokinetics of tacrolimus and single dose tacrolimus on the single dose pharmacokinetics of micafungin	Healthy volunteers 26 (18/8), 19 - 50	micafungin 100 mg IV single/multiple doses,, tacrolimus 5 mg PO single dose	
FG-463-21-04 (UK)	To evaluate the effect of single or multiple dose tacrolimus on the single dose pharmacokinetics of micafungin and single dose micafungin on the multiple dose pharmacokinetics of tacrolimus	Healthy volunteers 24 (24/0), 18 - 50	micafungin 200 mg IV single dose, tacrolimus 2 mg PO single/multiple doses	Submitted in 120-day safety update
FG-463-21-06 (UK)	To determine the effect of single dose micafungin on the multiple dose pharmacokinetics of prednisolone and *vice versa*	Healthy volunteers 24 (24/0), 18 - 50	micafungin 200 mg IV single dose, predisolone 20 mg PO multiple dose	Submitted in 120-day safety update
Retrospective Analysis				
Report 2002001040	To determine the effect of intrinsic factors (gender, race, age) on the pharmacokinetics of micafungin	Same as Studies 97-0-041 and 98-0-043	Same as Studies 97-0-041 and 98-0-043	**Based on unacceptable studies -> Not reviewed**

4. QUESTION-BASED REVIEW

4.1. General Attributes

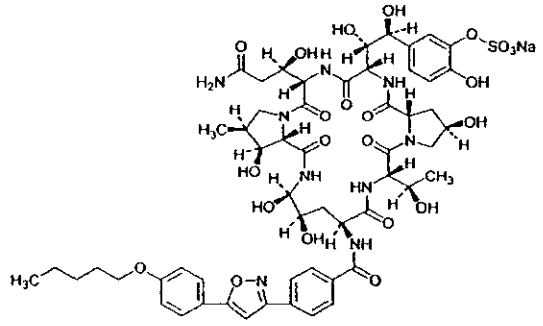
What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product? What is the proposed mechanism of drug action and therapeutic indications? What is the proposed dosage and route of administration?

Micafungin, code name FK463, is a semisynthetic cyclic lipopeptide synthesized by a chemical modification of a fermentation product of the F-11899 — *Coleophoma empetri.* Structurally, micafungin belongs to echinocandidin class and is similar to caspofungin.

Chemical Name (IUPAC):

Sodium 5-[(1S,2S)-2-[(3S,6S,9S,11R,15S,18S,20R,21R,24S,25S,26S)-3-[(R)-2-carbamoyl-1-hydroxyethyl]-11,20,21,25-tetrahydroxy-15-[(R)-1-hydroxyethyl]-26-methyl-2,5,8,14,17,23-hexaoxo-18-[4-[5-(4-pentyloxyphenyl)isoxazol-3-yl]benzoylamino]-1,4,7,13,16,22-hexaazatricyclo[22.3.0.$0^{9,13}$] heptacos-6-yl]-1,2-dihydroxyethyl]-2-hydroxyphenyl sulfate

Structure:



Molecular Weight:

1292.26 as sodium salt ($C_{56}H_{70}N_9NaO_{23}S$)
1270.27 as free acid ($C_{56}H_{71}N_9O_{23}S$)

Physicochemical Properties:

A white — powder, —, hygroscopic, freely soluble in water, pH of 10% aqueous solution = — pKa = 9.15, partition coefficient (log P) = - 0.39 at pH 7.0

Formulation:

Mycafungin sodium for Injection is a sterile, non-pyrogenic lyophilized drug product for intravenous infusion. Each vial contains micafungin sodium — 50 mg, lactose 200mg (NF), citric acid and/or sodium hydroxide used for pH adjustment. Following reconstitution with 0.9% Sodium Chloride for Injection (USP), the pH of the solution is between 5.0 - 7.0.

Mechanism of Action:

Micafungin inhibits 1,3-β-D-glucan synthase, an enzyme required for the synthesis of an essential glucose polymer that provides rigidity and osmotic/structural integrity to the cell wall of susceptible fungi. This mechanism of action is unique to the 1,3-β-D-glucan synthesis inhibitor class of antifungal agents such as caspofungin; other antifungal therapies such as polyenes and azoles affect the synthesis or integrity of the fungal cell membrane. Morphologically, the treatment of *Candida* or *Aspergillus* organisms with micafungin results in thin walls, abnormal septal formation, inhibition of germination and hyphal extension, swelling and abnormal extension of hyphal tips, and lysis. Mechanism-based toxicity with 1,3-β-D-glucan synthesis inhibitors is unlikely because 1,3-β-D-glucan is present in fungal cell walls but not in mammalian cells. Micafungin has broad-spectrum activity against *Candida* and *Aspergillus* species, clinically important pathogens that cause systemic fungal infections.

Proposed Indications:

N21-506: Prophylaxis of — in patients undergoing hematopoietic stem cell transplantation

Proposed Dosage and Route of Administration:

Mycafungin sodium for Injection is reconstituted and diluted using 0.9% Sodium Chloride for Injection (USP) or 5% Dextrose Injection (USP) and infused intravenously over an hour. Proposed micafungin doses are listed in Table 2.

Table 2. Proposed micafungin doses

Indications	Adult Patients (mg per day)	Pediatric Patients* (mg/kg per day)
Prophylaxis of — in patients undergoing hematopoietic stem cell transplantation	50	—

The micafungin doses were initially determined based on a dose-response study (97-7-003) performed in 84 HIV positive adult patients with esophageal candidiasis. In this study, a positive clinical response (clearing or improvement in clinical signs and symptoms such as dysphagia, odynophagia, and retrosternal pain) was observed in all patients who received daily micafungin doses of 50, 75, and 100 mg for 7 - 23 days (Table 3). The study showed a dose-response trend for clinical response from 12.5 mg/day (presumed minimal effective dose) to 100 mg/day. Daily doses of 75 or 100 mg were more effective than lower doses in clearing mucosal lesions and eradicating a *Candida* infection. No other dose-response studies were performed to determine an optimal micafungin dose based on efficacy. In subsequent clinical studies (97-0-041 and 98-0-043) conducted to determine the safety of micafungin, no dose-limiting toxicity (maximum tolerated dose) was observed at a daily dose up to 4 mg/kg body weight for pediatric patients (not to exceed 200 mg/day) or 8 mg/kg for adult patients (600 mg/day for patients weighing 75 kg).

Table 3. Overall clinical response observed at the end of therapy (7 - 23 days) in a dose-response study performed in 84 HIV positive adult patients with esophageal candidiasis

	Micafungin Dose Level (mg/day)					Total (n=84)
	12.5 (n=18)	25 (n=13)	50 (n=15)	75 (n=19)	100 (n=19)	
Positive Clinical Response	12 66.7%	12 92.3%	14 93.3%	19 100.0%	19 100.0%	76 90.5%
Cleared	6 33.3%	7 53.8%	13 86.7%	16 84.2%	18 94.7%	60 71.4%
Improved	6 33.3%	5 38.5%	1 6.7%	3 15.8%	1 5.3%	16 19.0%
Unchanged or Worse	6 33.3%	1 7.7%	0 0.0%	0 0.0%	0 0.0%	7 8.3%

In a pivotal clinical trial (98-0-047), micafungin was initiated from 50 mg/day for the treatment of *Candida albicans* infection (1.0 mg/kg/day for patients weighing < 40 kg) or from 100 mg/day for the treatment of non-*Candida albicans* infection (2.0 mg/kg/day). Based on the physician's judgment, dose increases were allowed by 50 mg/day (1.0 mg/kg/day) up to 200 mg/day (4 mg/kg/day). Therefore, the clinical use of micafungin for adult and pediatric patients of interest is likely to follow this dosing paradigm.

What efficacy and safety information contribute to the assessment of clinical pharmacology and biopharmaceutics study data?

As stated in the previous question, the micafungin doses were initially determined based on a dose-response study (97-7-003) that showed a dose-response trend for clinical response from 12.5 mg/day to 100 mg/day. In subsequent clinical studies (97-0-041 and 98-0-043) conducted to determine the safety of micafungin, no dose-limiting toxicity (maximum tolerated dose) was observed at a daily dose of 3 - 8 mg/kg body weight (adult patients, 600 mg/day for patients weighing 75 kg) or 0.5 - 4 mg/kg body weight (pediatric patients, not to exceed 200 mg/day). The pharmacokinetic studies conducted in patients of interest cover such dose ranges.

4.2. General Clinical Pharmacology

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

The efficacy endpoint was not measured in clinical pharmacology studies. In clinical studies, the primary efficacy endpoint used was treatment success, defined (as per regulatory guidance) as the absence of a proven, probable, or suspected systemic fungal infection through the end of therapy and the absence of a proven or probable systemic fungal infection through the end of the 4-week post-treatment period. Both criteria had to be met in order for the patient to be considered a treatment success. Suspected fungal infection was defined as a requirement for empirical systemic antifungal therapy for fever and neutropenia despite 96 hours of broad-spectrum antibacterial therapy.

Are the active moieties in the plasma or other biological fluid appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Yes. Refer to 4.6. Analytical Section

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

The characteristics were not clearly determined; as shown in *Dosage and Route of Administration*, only a limited dose-response study (97-7-003) was conducted.

Degree of Linearity in Dose-Concentration Relationship and Time Dependency in Pharmacokinetics:

Micafungin pharmacokinetics were linear over a single intravenous dose range of 25 - 150 mg when determined in healthy Japanese volunteers. Micafungin pharmacokinetics were independent of time; pharmacokinetic parameter values following the first dose (Day 1) were comparable to the values following multiple doses at steady state (Days 4 and 7). Dose linearity and time dependency at the range of proposed clinical doses were not adequately determined in patients of interest.

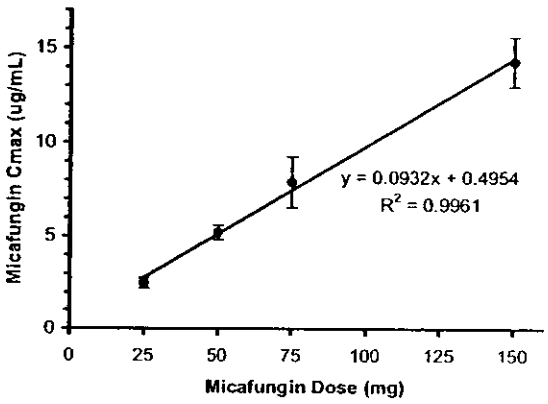
In a Japanese pharmacokinetic study (FJ-463-0005) conducted in 23 healthy male volunteers, the total body clearance (CLt), volume of distribution at steady state (Vss), and terminal half-life ($t_{1/2}$) of micafungin were comparable between single dose levels of 25, 50, 75, and 150 mg infused over 0.5 hour (Table 4). The maximun concentration (Cmax) and area under the concentration-time curve ($AUC_{0-\infty}$) of micafungin increased in proportion to the dose administered (Figure 1).

Table 4. Pharmacokinetic parameters (mean ± SD) of micafungin determined after a single intravenous infusion over 0.5 hour

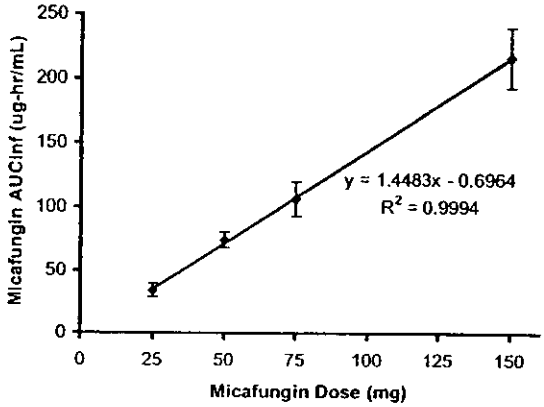
Dose (mg)	N	Cmax (μg/mL)	$AUC_{0-\infty}$ (μg·hr/mL)	$t_{1/2}$ (hr)	Vss (L/kg)	Vβ (L/kg)	CL (mL/min/kg)
25	6	2.52 ± 0.28	34.3 ± 5.8	14.0 ± 1.2	0.232 ± 0.017	0.240 ± 0.018	0.199 ± 0.027
50	6	5.23 ± 0.38	74.3 ± 6.2	14.2 ± 1.2	0.226 ± 0.017	0.233 ± 0.018	0.190 ± 0.014
75	6	7.90 ± 1.35	106.5 ± 13.4	13.3 ± 0.7	0.225 ± 0.020	0.233 ± 0.022	0.203 ± 0.015
150	5	14.3 ± 1.31	216.6 ± 23.1	14.0 ± 0.9	0.229 ± 0.012	0.237 ± 0.012	0.196 ± 0.013
25-150	23	-	-	13.9 ± 1.0	0.228 ± 0.016	0.236 ± 0.017	0.197 ± 0.018

Figure 1. Relationship between micafungin Cmax or $AUC_{0-\infty}$, and dose infused over 0.5 hour to healthy Japanese subjects (N = 23)

A. Cmax (mean ± SD)



B. $AUC_{0-\infty}$ (mean ± SD)

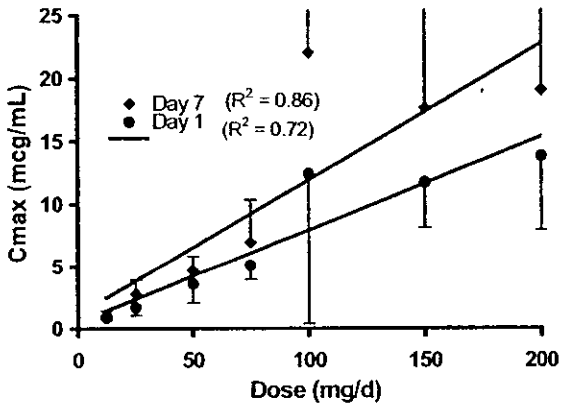


Micafungin pharmacokinetic parameters were independent of time following repeated daily infusions of 75 mg for 7 days in the Japanese pharmacokinetic study mentioned above. The values of CL, Vss, and $t_{1/2}$ of micafungin estimated on Day 1 were comparable to the values on Day 4 or Day 7 (Table 5). The difference (approx. 10%) between the AUC_{0-24} determined on Day 7 and the $AUC_{0-\infty}$ on Day 1 was statistically significant ($p = 0.002$) but does not appear to be clinically meaningful. The Cmax and trough concentration (Cmin) of micafungin reached steady state by Day 4. The accumulation ratios of Day 4 to Day 1 values were 1.34, 1.60, and 1.55 based on the Cmax, Cmin, and AUC_{0-24} of micafungin, respectively. The micafungin binding to plasma proteins was 99.82 ± 0.01 % on Day 7, which was comparable to that of 99.83 ± 0.01 % on Day 1.

Table 5. Pharmacokinetic parameters of micafungin (mean ± SD) determined following repeated 0.5-hr infusion at the dose of 75 mg daily for 7 days (N = 6)

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Cmax (μg/mL) [Accumulation Ratio]	7.64 ± 0.93			10.21 ± 1.38 [1.34 ± 0.04]			10.87 ± 1.53 [1.42 ± 0.06]
Cmin (μg/mL) [Accumulation Ratio]		1.52 ± 0.17 [1.37 ± 0.03]	2.08 ± 0.24 [1.52 ± 0.07]	2.31 ± 0.28 [1.60 ± 0.07]	2.43 ± 0.30 [1.62 ± 0.07]	2.47 ± 0.40 [1.52 ± 0.12]	2.48 ± 0.31 [1.63 ± 0.05]
$AUC_{0\text{-}24}$ (μg·hr/mL) [Accumulation Ratio]	69.9 ± 7.2			108.3 ± 13.6 [1.55 ± 0.05]			111.3 ± 14.1 [1.59 ± 0.07]
$AUC_{0\text{-}\infty}$ (μg·hr/mL)	101.3 ± 11.1						
$t_{1/2}$ (hr)	14.3 ± 0.8			15.2 ± 1.0			14.0 ± 0.7
Vβ (L/kg)	0.237 ± 0.023			0.238 ± 0.037			0.212 ± 0.026
CL (mL/min/kg)	0.193 ± 0.021			0.181 ± 0.022			0.176 ± 0.022

Figure 2. Relationship between micafungin Cmax (mean ± SD) and dose infused over an hour to adult patients of interest



The applicant conducted pivotal pharmacokinetic studies in 62 adult patients undergoing bone marrow transplantation (97-0-041) and 72 pediatric patients with febrile neutropenia (98-0-043). The clinical part of the two studies appears to be poorly controlled. There are a number of missed blood samplings and unexplained outliers in micafungin concentration-time data (up to 20 times larger than mean values). It is suspected that many blood samples were collected from micafungin infusion port and, therefore, the samples were contaminated by residual micafungin in the port. The number of samples collected from the port and the extent of contamination in each sample are largely unknown. Because of these problems, the dose linearity and time dependency in micafungin pharmacokinetics determined in an adult (Figure 2) or pediatric patient population of interest at the range of proposed clinical doses are not acceptable.

Onset or Offset of Pharmacological Response: Not applicable

Dose with Respect to Relationship in Dose-Concentration-Response:

Micafungin dosing is not based on the relationship in dose-concentration-response.

How does the pharmacokinetics of the drug and its major active metabolites in healthy volunteers compare to that in patients?

The pharmacokinetic parameter values of micafungin estimated from pharmacokinetic studies in healthy subjects cannot be directly compared with the values from studies conducted in patients of interest. The reasons are: (1) most pharmacokinetic studies with healthy subjects were conducted in a Japanese population, whereas most studies with patients of interest were conducted in a Caucasian-dominant population (Table 1), (2) pivotal pharmacokinetic studies

conducted in a patient population of interest at the range of proposed clinical doses are not acceptable because of the problems mentioned in the pervious question.

Basic Pharmacokinetic Parameters:

Figure 3 shows a representative micafungin concentration-time profile determined following 1-hr intravenous infusion of a proposed clinical dose (50 mg) to an adult patient undergoing bone marrow transplantation (Study 97-0-041, Patient No. 050-304). The pharmacokinetic parameter values reported in pharmacokinetic studies with healthy volunteers and adult patients of interest are shown in Table 6. In a study (97-041) conducted in adult patients undergoing bone marrow or peripheral stem cell transplantation, the mean ± SD CL of micafungin at steady state was 0.210 ± 0.052 mL/min/kg (N = 8). The mean Vss (0.224 ± 0.055 L/kg) were four to five times larger than the mean plasma volume of adults. The mean $t_{1/2}$ of micafungin was 12.8 ± 2.67 hours; steady state can be reached approximately 3 days after repeated daily infusions. The Cmax and AUC_{0-24} following 50 mg dose was 4.69 ± 1.16 μg/mL and 53.4 ± 22.7 μg-hr/mL, respectively. The AUC_{0-24} following 100 mg dose was 53.4 ± 22.7 μg-hr/mL, while the mean Cmax value was not adequately determined. These values are not reliable because there were critical problems in the clinical part of the study as mentioned in the previous question. The pharmacokinetics of M1 and M2 could not be determined in the study because a large number of plasma concentrations of M1 and M2 were near or lower the limit of quantitation (LOQ). The pharmacokinetic parameter values estimated in the Study FG-463-21-03 cannot be used as representative values for micafungin pharmacokinetics because larger doses than the proposed clinical doses were administered.

Figure 3. Micafungin concentration-time profile determined following 1-hr intravenous infusion of 50 mg to an adult patient of interest (Study 97-0-041, Patient No. 050-304) on Day 1 (first dose) and Day 7 (steady state)

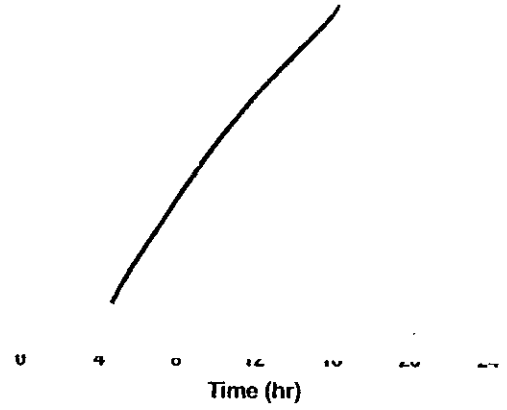


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Table 6. Pharmacokinetic parameter values (mean ± SD) of micafungin estimated from various populations at steady state

Study No. (Population)	Dose (mg/d)	N	Cmax (µg /mL)	AUC_{0-24} (µg-hr/mL)	$t_{1/2}$ (hr)	Vss (L/kg)	CL (mL/min/kg)
FJ-463-0005#	75	6	10.9 ± 1.5	111.3 ± 14.1	14.0 ± 0.7	ND	0.176 ± 0.022
97-0-041 (US) Adult BMT/PSCT Patients (Day 7)	12.5	6	1.1 ± 0.4	11.5 ± 4.5	10.6 ± 2.7*	0.233 ± 0.068	0.290 ± 0.086
	25	8	2.8 ± 1.1	22.8 ± 7.5	11.9 ± 1.6	0.208 ± 0.030	0.216 ± 0.036
	50	8	4.7 ± 1.2	53.4 ± 21.7	12.8 ± 2.6***	0.224 ± 0.055	0.210 ± 0.052
	75	8	7.0 ± 3.4	63.0 ± 20.1	13.2 ± 4.9	0.273 ± 0.107	0.296 ± 0.229
	100	8	22.0 ± 21.1	104.0 ± 31.8	12.6 ± 2.9	0.198 ± 0.060	0.216 ± 0.046
	150	8	17.6 ± 8.4	170.2 ± 45.8	12.6 ± 2.2	0.203 ± 0.042	0.202 ± 0.053
	200	7	19.1 ± 9.3**	211.2 ± 69.7	14.4 ± 3.7	0.235 ± 0.056	0.194 ± 0.028
FG-463-21-03 (UK) Adult BMT/PSCT Patients (Day 7)	3 (225)^	8	21.1 ± 2.8	234 ± 34	14.0 ± 1.4	0.243 ± 0.020	0.214 ± 0.030
	4 (300)^	10	29.2 ± 6.2	339 ± 72	14.2 ± 3.2	0.240 ± 0.047	0.204 ± 0.036
	6 (450)^	8	38.4 ± 6.9	479 ± 157	14.9 ± 2.6	0.278 ± 0.062	0.224 ± 0.064
	8 (600)^	8	60.8 ± 26.9	663 ± 212	17.2 ± 2.3	0.307 ± 0.114	0.223 ± 0.081

* N = 7, ** N = 8, *** N = 9
\# Day 7 values determined in healthy Japanese subjects
^ Dose as mg/day per kg body weight (equivalent dose as mg/day when given a patient weighing 75kg)
ND Not determined

In a study (FJ-463-0005) with healthy subjects using ultrafiltration technique, micafungin binding to plasma proteins was 99.82 ± 0.01 % following first 75 mg dose and unchanged following repeated doses at steady state. In an *in vitro* ultrafiltration study (CRR970244), the percentage of bound micafungin in human serum was 99.84 ± 0.00%. Human serum albumin was the major carrier and α1-acid glycoprotein could also contribute to the overall protein binding of micafungin; the binding to albumin and α1-acid glycoprotein was 99.60 ± 0.03% and 72.49 ± 0.91%, respectively. The findings in a protein binding study (97-0-041) conducted in patients of interest following proposed clinical doses was not quantitatively adequate but qualitatively the same as the findings in the healthy subject and *in vitro* studies.

In an *in vitro* study (CRR970245) using human whole blood, the blood to plasma ratio was 0.82 - 0.85 and was independent of micafungin concentrations over the range of 0.1 - 10 µg/mL. The percent transfer into human red blood cells was 33.2 - 35.1%. An *in vitro* study (CRD980083) showed that 65.4 - 66.6% of micafungin-derived radioactivity was covalently bound to human plasma proteins at the micafungin concentration of 0.4 - 10 µg/mL. The binding ratios of ^{14}C-micafungin to human albumin, human α1-acid glycoprotein, and human globulin were 20.4%, 26.6%, and 48.4%, respectively. In a mass balance study (97-0-040) with 6 healthy subjects following a ^{14}C-micafungin dose equivalent to 28.3 mg, approximately 3% of radioactivity was covalently bound to plasma proteins at the end of infusion.

Extraction Ratio:

Based on the Study 97-0-041, the CL value of micafungin at 50 mg dose (0.210 ± 0.052 mL/min/kg) was approximately 1.8% of the mean plasma flow rate through the liver (11.4 mL/min/kg). The low CL also appears to be related to high protein binding.

Route of Elimination (Mass Balance):

Biotransformation in the liver followed by excretion via feces appears to be the predominant route of micafungin elimination. In a mass balance study (97-0-040) conducted in 6 healthy Caucasian male volunteers who received a 1-hr intravenous infusion of radioactivity equivalent to micafungin 28.3 mg, the non-renal clearance of ^{14}C-micafungin-derivered radioactivity (0.050 ± 0.005 mL/min/kg) was approximately 88 % of its CLt (0.057 ± 0.004 mL/min/kg). The recovery of the radioactivity also suggests that fecal elimination is the major route of micafungin elimination. When collected up to 167 hours post dose, the recovery of the radioactivity in feces was 43.8 ± 6.0 % out of the total recovery of 52.9 ± 4.8 %. Urinary excretion played a minor role in the overall elimination of micafungin; the renal clearance of the radioactivity (0.006 ± 0.001 mL/min/kg) was approximately 12 % of the CLt, and the urinary recovery of the radioactivity was 7.4 ± 1.4 % upon completion of the clinical portion of the study. The amount of radioactivity in plasma was estimated to be 1.8 ± 0.3 % at 47 hours post dose.

The contribution of unchanged micafungin, M1 (catechol form), M2 (methoxy form), M3 (cleavage form), M5 (ω-1 hydroxy form), and M11 (unknown structure) to the total recovery of the radioactivity (52.9%) for up to 167 hours post dose was estimated to be 12.3%, 0.4%, 0.3%, 1.8%, 3.7%, and 1.8%, respectively. In plasma, the composition of unchanged micafungin decreased from 66.4 ± 4.4 % (at end of infusion) to 19.3 ± 1.6 % (47 hours post infusion) of the total plasma radioactivity. The most abundant metabolite found in plasma was M5, which accounted for up to 8.3 ± 1.2 % of the total plasma radioactivity. The composition of M1 in plasma approached 2.0 ± 0.5 % at 47 hours post infusion. M2 was not detectable in plasma. In urine, unchanged micafungin accounted for 9.7 ± 2.0 % of the total urinary radioactivity in samples collected up to 167 hours post dose. The most abundant metabolite found in urine was also M5, which accounted for 48.9 ± 7.3 % of the total urinary radioactivity. Other metabolites were less than 1% of total urinary radioactivity. In feces, unchanged micafungin accounted for 26.4 ± 6.0 % of the total fecal radioactivity in samples collected for up to 167 hours post dose. M3 and M11 accounted for 3.9 ± 1.0 % and 3.9 ± 2.2 %, respectively. Other metabolites comprised less than 1% of the total fecal radioactivity.

The result of the mass balance study should be interpreted with caution. The determination of mass balance was incomplete at the end of clinical part of the study (167 hours post dose); the total recovery of the radioactivity was only 52.9%. This is most likely due to the long elimination half-life of ^{14}C-micafungin-derived radioactivity (92.8 ± 7.1 hours). Radioactivity (approx. 9% of maximum concentration of ^{14}C-micafungin-derived radioactivity) was still detectable in plasma at 167 hours post dose. The fecal excretion profile was incomplete indicating that the elimination process was still ongoing. In addition, the micafungin dose administered in this study (82.4 μCi equivalent to 28.3 mg of micafungin) was lower than the proposed clinical dose of 50 or

What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

The inter-subject variability of the pharmacokinetic parameters of micafungin observed in healthy subjects was relatively small; the largest coefficients of variation (CV) of the pharmacokinetic parameters were 14% ($t_{1/2}$ in Study FJ-463-0005 in Table 6). In contrast, the inter-subject variability observed in patients of interest were much greater; the CV for micafungin Cmax at 100 mg doses approaches 96% (Study 97-0-041 in Table 6). The greater inter-subject variability in micafungin pharmacokinetic parameters in patients of interest appears to be due to the poor control of the study and the clinical instability of the patients after bone marrow or stem cell transplantation rather than the true variability in micafungin disposition. Data were not sufficient to determine the intra-subject variability of micafungin pharmacokinetics.

4.3. Intrinsic Factors

What intrinsic factors influence exposure and/or response and what is the impact of any differences in exposure on the pharmacodynamics?

Age (Elderly Patients):

In a Japanese pharmacokinetic study in healthy elderly male volunteers (66 - 78 years old) compared with non-elderly controls (20 - 24 years old), each subject received a single dose of micafungin 50 mg by 1-hr intravenous infusion. There were no significant differences ($p > 0.05$) in the micafungin pharmacokinetic parameter estimates between the elderly and non-elderly groups (Table 7). No significant difference was found in the percentage of micafungin binding to plasma protein between the elderly (99.85 ± 0.01%) and young subjects (99.85 ± 0.02%).

Table 7. Pharmacokinetic parameters (mean ± SD) of micafungin determined after a single intravenous infusion of 50 mg to elderly and non-elderly subjects

	N	Cmax (μg/mL)	$AUC_{0-\infty}$ (μg·hr/mL)	$t_{1/2}$ (hr)	Vss (L/kg)	Vβ (L/kg)	CL (mL/min/kg)
Elderly	10	4.97 ± 0.60	71.5 ± 9.0	14.9 ± 1.0	0.239 ± 0.027	0.257 ± 0.028	0.200 ± 0.028
Young	10	4.95 ± 0.56	76.6 ± 9.4	15.2 ± 0.9	0.228 ± 0.016	0.243 ± 0.017	0.185 ± 0.019

Age (Pediatric Patients):

The sponsor did not adequately define the relationship between patient's age and pharmacokinetic parameter estimates of micafungin in pediatric patients. Based on a pharmacokinetic study (98-0-043) conducted in 72 pediatric patients with febrile neutropenia, the dose-normalized AUC of micafungin appears to be positively correlated with patient's age, while the weight-normalized CL appears to be inversely correlated with age. The values of weight-normalized Vss and dose-normalized Cmax does not seem to be changed with respect to age. However, these findings are not reliable because no adequate statistical tests were conducted and because there were critical problems in the clinical part of the study as mentioned in the previous section (4.2. **General Clinical Pharmacology**).

Gender and Race:

There is no reliable information on the effect of gender or racial difference on micafungin pharmacokinetics in this submission. The effect was determined in a retrospective analysis (Report 2002001040) of two pharmacokinetic studies conducted in adult patients undergoing bone marrow or peripheral stem cell transplantation (Study 97-0-041) and pediatric patients with febrile neutropenia (Study 98-0-043). Both studies demonstrated neither gender nor effect but had critical problems in the clinical part as described in the previous section (4.2. **General Clinical Pharmacology**).

Renal Impairment:

The pharmacokinetic parameter values of micafungin estimated in patients with severe renal dysfunction were comparable to the values estimated in matched control subjects with normal renal function. A regression analysis demonstrated no correlation between creatinine clearance and any pharmacokinetic parameters of micafungin. Renal failure did not alter the extent of micafungin binding to plasma proteins.

A clinical pharmacology study (01-0-110) was conducted in nine patients with severe renal dysfunction (GFR range at screening, 15.0 - 29.2 mL/min) but otherwise healthy, and in nine age-, weight-, and sex-matched healthy subjects with normal renal function (GFR range at screening, 75.1 -123.7 mL/min). Each patient or subject received micafungin 100 mg infused over an hour. The differences in geometric mean values of the Cmax, AUC_{0-48}, and $AUC_{0-\infty}$ between renally impaired patients and healthy controls were no larger than 7% although corresponding 90% CIs were not completely contained in the range of 80 - 125% (Table 8). The mean values of the weight-adjusted CL and Vss, and $t_{1/2}$ of micafungin estimated from patients with severe renal dysfunction were comparable to the values estimated from healthy controls

Table 8. Comparison of the pharmacokinetic parameter values of micafungin between patients with severe renal dysfunction (GFR range, 15.0 - 29.2 mL/min) and subjects with normal renal function (GFR range, 75.1 -123.7 mL/min) following a single intravenous dose of 100 mg

Pharmacokinetic Parameter	Severe Dysfunction (Mean ± SD)	Normal Function (Mean ± SD)	Geometric Mean Ratio (%)	90% Confidence Interval (%)
Cmax (μg/mL)	8.68 ± 2.85	8.17 ± 1.39	102.5	**81.9 – 128.3**
AUC_{0-48} (μg-hr/mL)	107.8 ± 30.0	111.4 ± 14.9	94.2	**78.4 – 113.1**
$AUC_{0-\infty}$ (μg-hr/mL)	118.9 ± 33.4	123.9 ± 17.0	93.3	**77.6 – 112.3**
CL (mL/min/kg)	0.180 ± 0.029	0.163 ± 0.027	110.7	96.5 - 124.9
Vss (L/kg)	0.202 ± 0.024	0.190 ± 0.030	106.2	94.3 - 118.1
$t_{1/2}$	14.3 ± 1.6	14.9 ± 1.8		

A regression analysis showed no significant relationships between creatinine clearance and micafungin pharmacokinetic parameters (Table 9). All p-values in statistical tests for the regression between creatinine clearance and the $AUC_{0-\infty}$, CL, or Vss of micafungin exceeded 0.05. The extent of micafungin binding to plasma proteins in renally impaired patients was

similar to the extent in matched healthy controls, at both one (end of infusion) and eight hours (terminal phase) after start of infusion (Table 10).

Table 9. Relationship between creatinine clearance and micafungin pharmacokinetic parameters observed following a single intravenous dose of 100 mg to renally impaired patients (GFR range, 15.0 - 29.2 mL/min) and matched healthy controls (GFR range, 75.1 -123.7 mL/min) (N = 18)

Pharmacokinetic Parameter	Slope	Intercept	Coefficient (R^2)	P-value
$AUC_{0-\infty}$ (µg-hr/mL)	0.22729	106.128	0.137	0.1586
CL (mL/min/kg)	-0.00009	0.179	0.014	0.6614
Vss (L/kg)	-0.00001	0.198	0.000	0.9517

Table 10. Comparison of the plasma protein binding parameters of micafungin between renally impaired patients (GFR range, 15.0 - 29.2 mL/min) and matched healthy controls (GFR range, 75.1 -123.7 mL/min) at 1 and 8 hours after start of infusion of 100 mg (N = 9 each)

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
	Ultrafiltrate (ng/mL)	18.03 ± 3.57	17.64 ± 3.93	2.2	102
	% Bound	99.77 ± 0.04	99.77 ± 0.07	0.0	100
	% Unbound	0.24 ± 0.04	0.23 ± 0.07	4.0	104
8	Plasma (µg/mL)	3.66 ± 1.01	3.75 ± 0.47	-23	98
	Ultrafiltrate (ng/mL)	8.26 ± 1.38	7.83 ± 1.42	5.4	105
	% Bound	99.76 ± 0.06	99.79 ± 0.05	0.0	100
	% Unbound	0.24 ± 0.06	0.21 ± 0.05	11.8	112

Hepatic Impairment:

Micafungin exposure, based on dose-normalized (mg/kg body weight) Cmax and AUC, in patients with moderate hepatic dysfunction was lower by approximately 10% than the exposure observed in healthy subjects. The reason for this reduction is not known but the reduction is not likely to produce efficacy concerns at proposed clinical doses; in a dose-response study, the minimum effective dose was considered to be 12.5 mg (a quarter of the lowest proposed clinical dose, 50 mg). The applicant reported a statistically significant linear regression between Child-Pugh score and the $AUC_{0-\infty}$ of micafungin, but this appears to be meaningless because the correlation coefficient was low ($r^2 = 0.26$). Hepatic impairment did not alter the extent of micafungin binding to plasma proteins.

In a clinical pharmacology study conducted in eight patients with moderate hepatic dysfunction (Child-Pugh score 7 - 9) but otherwise healthy and eight healthy control subjects, each patient or subject received micafungin 100 mg infused over an hour. The patients were well-matched with control subjects in age (53 ± 9 *vs* 52 ± 10 years old, respectively) and sex (2 female and 6 males in both groups) but not in body weight (84.4 ± 9.4 *vs* 98.2 ± 18.8 kg, respectively). The micafungin Cmax, AUC_{0-48}, and $AUC_{0-\infty}$ values estimated from the patients with moderate hepatic dysfunction were lower by 21.0%, 21.1%, and 21.9% than the respective values

estimated from the healthy controls (Table 11). When normalized by micafungin dose (mg/kg body weight), however, these differences were reduced to approximately 10%. Whereas the weight-normalized CL value of micafungin were larger by 12 %, the $t_{1/2}$ and weight-normalized Vss values estimated from the patients with moderate hepatic dysfunction were not different from the values estimated from healthy controls (Table 11).

Table 11. Comparison of the pharmacokinetic parameter values of micafungin between subjects with moderate hepatic dysfunction (Child-Pugh score 7 - 9) and normal function following a single intravenous dose of micafungin 100 mg

Pharmacokinetic Parameters	Moderate Dysfunction (Mean ± SD)	Normal Function (Mean ± SD)	Geometric Mean Ratio (%)	90% Confidence Interval (%)
C_{max} (µg/mL)	6.94 ± 1.86	8.79 ± 1.80	**79.0**	**60.7 – 97.3**
C_{max}/Dose* [(µg/mL)/(mg/kg)]	6.64 ± 1.46	7.33 ± 1.27	90.4	**73.8 – 109**
AUC_{0-48} (µg·hr/mL)	88.7 ± 17.1	113.8 ± 23.5	**77.9**	**62.0 – 93.8**
AUC_{0-inf} (µg·hr/mL)	98.2 ± 19.3	127.5 ± 26.5	**77.1**	**61.0 – 93.1**
AUC_{0-inf}/Dose* [(µg·hr/mL)/(mg/kg)]	94.4 ± 15.2	106 ± 17.9	88.8	**76.9 – 103**
Vss (L/kg)	0.208 ± 0.036	0.194 ± 0.027	107.1	92.7 – 121.5
CL (mL/min/kg)	0.180 ± 0.028	0.161 ± 0.029	112.1	**96.5 – 127.7**
$t_{1/2}$ (hr)	14.3 ± 1.5	14.8 ± 3.0	96.9	82.9 – 110.8

* Re-calculated by Dr. Seong Jang, Clinical Pharmacology Reviewer

A regression analysis showed a significant relationship between Child-Pugh score and micafungin $AUC_{0-\infty}$ ($p = 0.044$, Table 12); however, the regression coefficient (r^2) was only 0.26. Other regression analyses between Child-Pugh score and micafungin pharmacokinetic parameters showed no statistical significance. This result indicates that moderate hepatic dysfunction does not meaningfully affect micafungin disposition. The extent of micafungin binding to plasma proteins was comparable between hepatically impaired patients and healthy controls when determined at one (end of infusion) and eight hours (terminal phase) after start of infusion (Table 13).

Table 12. Relationship between Child-Pugh score and pharmacokinetic parameter values of micafungin observed following a single intravenous dose of 100 mg to subjects with normal liver function and moderate hepatic dysfunction (N = 16)

Pharmacokinetic Parameter	Slope	Intercept	Coefficient (R^2)	P-value
$AUC_{0-\infty}$ (µg·hr/mL)	-5.6412	142.815	0.260	0.0437
CL (mL/min/kg)	0.0044	0.147	0.135	0.1617
Vss (L/kg)	0.0038	0.181	0.088	0.2634

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)

Time (hr)	Protein Binding Parameter	Moderate Dysfunction (Mean ± SD)	Normal Function (Mean ± SD)	Difference (%)	Mean Ratio (%)
1	Plasma (µg/mL)	7.061 ± 1.661	8.616 ± 0.889	-1.93	98.1
	Ultrafiltrate (ng/mL)	13.922 ± 2.631	17.319 ± 2.419	2.18	102.2
	% Bound	99.800 ± 0.030	99.799± 0.020	-0.01	100.0
	% Unbound	0.202 ± 0.033	0.201 ± 0.020	3.98	104.0
8	Plasma (µg/mL)	3.159 ± 0.647	3.911 ± 0.561	-2.27	97.7
	Ultrafiltrate (ng/mL)	5.725 ± 1.270	7.365 ± 0.985	5.40	105.4
	% Bound	99.816 ± 0.035	99.810 ± 0.025	-0.03	100.0
	% Unbound	0.184 ± 0.035	0.190 ± 0.025	11.80	111.8

Pregnancy and Lactation:

The sponsor provided no clinical pharmacology information on micafungin obtained from pregnant women or nursing mothers. In animal studies (refer to Pharmacology and Toxicology Review), no evidence of reproductive or developmental toxicity was observed following the administration of a micafungin dose 2.6 times or larger than a proposed human dose adjusted by body surface area. Micafungin was found in the milk of lactating rats. It is not known whether micafungin is excreted in human milk.

Weight, Height, Disease, and Genetic Polymorphism:

The sponsor did not provide clinical pharmacology information on the effect of weight, height, disease, or genetic polymorphism on the pharmacokinetics of micafungin. It is not assumed that these factors affect the efficacy or safety of micafungin.

Based upon what is known about exposure-response relationships and their variability, and the groups studied; what dosage regimen adjustments, if any, are recommended for each of these subgroups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.

Elderly, Gender, Race, and Renal and Hepatic Impairment:

The sponsor proposed that all adult patients weighing more than 40 kg be administered a flat dose of micafungin shown in *Dosage and Route of Administration* (50 or 100 mg/day). Adult patients weighing less than 40 kg are to be administered a pediatric dose. No dosage adjustment is recommended for the subgroup(s) of age (elderly), gender, race, renal impairment, and hepatic impairment.

Pediatric Patients:

Pregnancy and Lactation:

The sponsor proposed micafungin as a — , drug and no dosage adjustment for these subpopulations.

4.4. Extrinsic Factors

What extrinsic factors influence exposure and/or response and what is the impact of any differences in exposure on pharmacodynamics?

The drugs (cyclosporine, tacrolimus, and prednisolone) that were orally administered to healthy volunteers in drug-drug interaction studies did not influence the exposure to micafungin administered concurrently through intravenous route, and *vice versa* (see *Drug-Drug Interactions* below). The sponsor conducted no controlled studies to determine the impact of other extrinsic factors such as herbal products, diet, smoking, and alcohol use on the micafungin pharmacokinetics or pharmacodynamics. At this time, it is not assumed that these extrinsic factors produce clinical concerns in the use of micafungin.

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

No dosage adjustment is recommended based on any extrinsic factor.

Drug-Drug Interactions

In Vitro Evidence of Drug-Drug Interaction:

Based on the results of *in vitro* studies that evaluated the effect of micafungin on oxidative metabolism using human liver microsomes, micafungin at clinically relevant concentrations is not likely to affect the metabolic activity of major cytochrome P450 (CYP) enzymes. Similarly, based on *in vitro* studies that evaluated the effect of micafungin on protein binding displacement using human serum, micafungin at clinically relevant concentrations is not likely to have a clinically significant drug-drug interaction with drugs possibly co-administered to the patients of interest.

The effects of micafungin on the metabolic activity of CYP enzymes were determined *in vitro* using human liver microsomes (Reports CRD980042, CRD980078, CRD980079, CRD010207). Micafugin at concentrations below 5 μM (6.4 μg/mL) did not significantly inhibit the metabolic activity of any CYP enzyme. At 50 μM (63.5 μg/mL), micafungin reduced the metabolic activity of CYP3A to 21.4% of control value but scarcely inhibited the activity of CYP2C9, 2C19, 2D6, and 2E1 (79.5%, 80.8%, 85.0%, and 81.2% of control, respectively). The inhibitory effect of micafungin on CYP3A activity was much weaker than the effect of ketoconazole, a CYP3A specific inhibitor (17.9% of control at 1 μM).

With respect to the metabolism of drugs commonly administered to bone marrow transplant patients, micafungin at clinically relevant concentrations produced little or no inhibition *in vitro*. Micafungin produced some inhibition at *in vitro* concentrations 10- to 20-fold greater than expected peak plasma concentrations following proposed clinical doses. Micafungin at 0.5 - 50 μM (0.6 - 63.5 μg/mL) inhibited the oxidative metabolism of tacrolimus (10 μM or 8.2 μg/mL) by 12.8 - 32.4%. The inhibitory effect of micafungin was much weaker than the effect of ketoconazole at a concentration of 5 μM (by 91.4%). At micafungin concentrations of 0.1, 1, 10, and 100 μM, the rate of ^{3}H-cyclosporine metabolism was reduced to 91.8%, 91.2%, 91.9% and 6.0% of control, respectively. At the same concentrations of caspofungin acetate, the rate was 90.7%, 90.0%, 91.2%, and 21.7% of control, respectively. By contrast, at ketoconazole concentrations of 0.1, 1 and 10 μM, the rate was 57.6%, 4.6%, and 0.0% (lower than detection limit) of control, respectively. The concentrations inhibiting ^{3}H-cyclosporine metabolism by 50% (IC_{50}) were 31, 39, and 0.14 μM for micafungin, caspofungin acetate, and ketoconazole, respectively. The inhibition constants (Ki) of micafungin, ketoconazole and fluconazole on nifedipine metabolism were 17.3, 0.012, and 10.71 μM, respectively.

In an *in vitro* study (Report CRD980156) to determine the effect of micafungin on the serum protein binding of highly protein-bound drugs, a solution of micafungin was added to serum spiked with ^{14}C-warfarin, ^{14}C-diazepam, ^{3}H-salicylic acid, or unlabeled methotrexate. Conversely, to determine the effect of highly protein-bound drugs on micafungin binding, a solution of unlabeled warfarin, diazepam, salicylic acid, or methotrexate was added to serum spiked with micafungin. Final concentrations of micafungin, warfarin, diazepam, salicylic acid, and methotrexaete were 10, 3.0, 0.6, 250, and 1.0 μg/mL, respectively. These concentrations are known to be within the range of therapeutic concentrations of respective drugs studied. The serum used in this study was pooled serum obtained from 15 non-fasting healthy male volunteers. The addition of micafungin did not change the percent unbound observed for each drug (Tables 14 and 15).

Table 14. Effect of micafungin on the protein binding of warfarin, diazepam, salicylic acid, and methotrexate using pooled serum from 15 healthy male volunteers (N = 3)

Binding-Problem Drugs		Micafungin Conc. (μg/mL)	% Bound (Mean ± SE)	% Unbound (Mean ± SE)
Name	Conc. (μg/mL)			
^{14}C-Warfarin	3.0	0	98.46 ± 0.01	1.54 ± 0.01
		10	98.73 ± 0.01	1.27 ± 0.01
^{14}C-Diazepam	0.6	0	96.92 ± 0.02	3.08 ± 0.02
		10	97.19 ± 0.02	2.81 ± 0.02
^{3}H-Salicylic Acid	250	0	76.80 ± 0.17	23.20 ± 0.17
		10	78.48 ± 0.11	21.52 ± 0.11
Methotrexate	1.0	0	56.59 ± 0.62	43.41 ± 0.62
		10	59.80 ± 0.17	40.20 ± 0.17

Table 15: Effect of warfarin, diazepam, salicylic acid, and methotrexate on the protein binding of micafungin at a concentration of 10 µg/mL using pooled serum from 15 healthy male volunteers (N = 3)

Binding-Problem Drugs		Micafungin (Mean ± SE)	
Name	Conc. (µg/mL)	% Bound	% Unbound
Control	no addition	99.74 ± 0.01	0.262 ± 0.014
Warfarin	3.0	99.72 ± 0.00	0.284 ± 0.004
Diazepam	0.6	99.67 ± 0.002	0.330 ± 0.020
Salicylic acid	250	99.55 ± 0.09	0.448 ± 0.087
Methotrexate	1.0	99.77 ± 0.03	0.232 ± 0.033

Role of CYP Enzymes on Micafungin Metabolism:

Multiple CYP enzymes appears to be involved in the formation of two inactive micafungin metabolites, M5 and M13 (unidentified structure). Whereas CYP1A2, 2B6, 2C and 3A4 were the major enzymes involved in M5 formation; CYP1A1, 1A2, and 3A4 played a major role in M13 formation.

M5 and M13 were formed when human liver microsomes were incubated aerobically with micafungin and NADPH-generating system (Report CRD010128). Potent substrate inhibition on M5 and M13 formation was observed at the substrate concentration of 500 µM (635 µg/mL) or higher. The formation of M5 was significantly correlated with the activity of coumarin 7-hydroxylase (CYP2A6; $r^2 = 0.40$, $p < 0.05$) and testosterone 6β-hydroxylase (CYP3A4; $r^2 = 0.59$, $p < 0.01$) in microsomes from 14 different human livers. The formation of M13 was significantly correlated with the activity of coumarin 7-hydroxylase (CYP2A6; $r^2 = 0.47$, $p < 0.01$), tolbutamide methyl-hydroxylase (CYP2C9; $r^2 = 0.34$, $p < 0.05$), S-mephenytoin 4'-hydroxylase (CYP2C19; $r^2 = 0.36$, $p < 0.05$), and testosterone 6β-hydroxylase (CYP3A4; $r^2 = 0.836$, $p < 0.001$).

The rates of M5 and M13 formation decreased to 78.8 and 81.5%, 63.6 and 66.4%, 77.9 and 87.4%, 55.1 and 55.7%, and 57.4 and 40.7% of control with furafylline (CYP1A2 inhibitor, 25 µM), coumarin (CYP2A6 substrate, 100 µM), sulfaphenazole (CYP2C9 inhibitor, 100 µM), tranylcypromine (CYP2C19 inhibitor, 50 µM), and ketoconazole (CYP3A4 inhibitor, 2.5 µM), respectively. Therefore, among the compounds tested, tranylcypromine and ketoconazole had the most potent inhibitory effect on micafungin metabolism in human liver microsomes. Whereas monoclonal antibodies of anti-CYP1A2, anti-CYP2B6, anti-CYP2C, and anti-CYP3A4 inhibited M5 formation by 28.7%, 18.8%, 10.6% and 19.2%, respectively; anti-CYP1A1, anti-CYP1A2, and anti-CYP3A4 inhibited M13 formation by 21.4%, 16.0%, and 18.0%, respectively.

Role of P-Glycoprotein:

Micafungin is not considered to be a P-glycoprotein inhibitor. In an animal study (Report CRD010129), micafungin was administered intravenously to male mice (six per group) to determine its potential for P-glycoprotein inhibition. ^{3}H-quinidine was used as a marker for P-glycoprotein activity. Micafungin did not affect the transfer of ^{3}H-quinidine into the brain, testis,

kidney, or liver of the mice; no increase in the ratio of tissue to blood concentration of ^{3}H-quinidine compared with a saline control was observed in the tissue analyzed. However, it is not clear whether micafungin is a P-glycoprotein substrate or not.

Other Metabolic / Transporter Pathways:

The metabolic pathways of micafungin are not completely understood. Micafungin is thought to be converted to metabolite M1 by aryl sulfatase and M1 is converted to a secondary metabolite M2 by catechol-O-methyl transferase (COMT). For the conversion of micafungin to M1 in human liver preparations, similar enzyme activity was detected in microsomal and cytosol fractions (Report CRR970296). The rate of M1 formation reached maximum at the substrate concentration of 100 μM (127 μg/mL). For the conversion of M1 to M2, most of the enzyme activity was limited to the cytosol fraction (S9 fraction of human liver). The rate of M2 formation increased with increasing concentrations of M1 in the reaction mixture.

Effect of Comedications:

A single intravenous dose of micafungin had no effect on the pharmacokinetics of cyclosporine or tacrolimus following a single or multiple (steady state) oral dose(s). Conversely, a single or multiple oral dose(s) of cyclosporine or tacrolimus demonstrated no effect on the pharmacokinetics of micafungin following an intravenous infusion. Multiple (steady state) intravenous doses of micafungin also showed no effect on the pharmacokinetics of cyclosporine or tacrolimus following a single oral dose. A single intravenous dose of micafungin increased the Cmax of prednisolone by 19% without affecting the AUC following multiple oral doses at steady state. This appears to be due to a food effect on the pharmacokinetics of prednisolone rather than a true drug-drug interaction caused by micafungin coadministration. Multiple oral doses of prednisolone did not affect the pharmacokinetics of micafungin following a single intravenous dose. The effect of micafungin on the disposition of fluconazole and *vice versa* could not be reliably determined because all patients studied received fluconazole and because there was only one control patient who received no concomitant micafungin dose.

Micafungin-Cyclosporine Interaction: In a drug-drug interaction study (97-0-041) conducted in 27 healthy adult volunteers, each subject received a micafungin dose of 100 mg by 1-hr intravenous infusion on Days 7, 9, and 11 through 15. Each subject also received an oral dose of cyclosporine (Neoral® capsule, approx. 5 mg/kg body weight) under fasting conditions on Days 1, 9, and 15. The morning doses of cyclosporine on Days 9 and 15 were administered in combination with micafungin infusion. At the doses studied, single or multiple (steady state) administrations of micafungin had no effect on cyclosporine pharmacokinetics (Table 16). The geometric mean ratios of dose-normalized Cmax, C_{12} (trough concentration,12 hour post dose), $AUC_{0\text{-}12}$, and $AUC_{0\text{-}\infty}$ of cyclosporine determined on Day 9 (test in single micafungin dose) or on Day 15 (test in multiple micafungin doses) to the values determined on Day 1 (reference) were contained within the range of 80 - 125%. Most 90% confidence intervals (CI) of the ratios were also contained within the range of 80 - 125%. The 90% CI of the ratio for dose-normalized C_{12} that exceeds the upper limit of the range by 1% is not considered to be clinically meaningful. The mean time to Cmax (Tmax) and $t_{1/2}$ values of cyclosporine following test doses were comparable to the values after reference dose.

Table 16. Effect of single (Day 9) or multiple (Day 15) intravenous doses of micafungin 100 mg on the pharmacokinetic parameters of cyclosporine following a single oral dose of approximately 5 mg/kg body weight (N = 27)

Cyclosporine Pharmacokinetic Parameter	Test (Mean ± SD)		Reference (Mean ± SD)	Geometric Mean Ratio (90% Confidence Interval, %)	
	Day 9	Day 15	Day 1	Day 9 / Day 1	Day 15 / Day 1
Cmax/Dose [(ng/mL)/mg]	5.27 ± 1.00	5.33 ± 0.98	4.73 ± 1.04	114 (106 – 123)	115 (107 – 124)
C_{12}/Dose [(ng/mL)/mg]	0.46 ± 0.12	0.48 ± 0.13	0.44 ± 0.14	110 (100 – 121)	115 (104 – 126)
AUC_{0-12}/Dose [(ng·hr/mL)/mg]	21.9 ± 3.70	22.1 ± 3.69	20.2 ± 5.45	113 (104 – 121)	113 (106 – 123)
$AUC_{0-\infty}$/Dose [(ng·hr/mL)/mg]	27.1 ± 4.8	27.0 ± 4.8	24.8 ± 6.8	114 (106 – 123)	114 (106 – 123)
Tmax (hr)	1.5 ± 0.6	1.6 ± 0.5	1.5 ± 0.5		
$t_{1/2}$ (hr)	7.8 ± 1.6	7.0 ± 1.9	7.2 ± 1.5		

In a drug-drug interaction study (FG-463-21-05) conducted in 24 healthy male volunteers, each subject received 3 intravenous doses of micafungin 200 mg infused over one hour on Days 1, 7, and 16. Each subject also received oral doses of cyclosporine 50 mg (Neoral®) twice daily on Days 7 to 15 and in the morning of Day 16 after at least 2-hr fast. The morning doses of cyclosporine on Days 7 and 16 were administered in combination with micafungin infusion. At the doses studied, the single administration of micafungin had no effect on the steady-state pharmacokinetics of cyclosporine (Table 17). The geometric mean ratios of Cmax, C_{12}, and AUC_{0-12} of cyclosporine determined on Day 16 (test) to the values determined on Day 15 (reference) were contained within the range of 80 - 125%. All corresponding 90% CIs of the ratios were entirely contained within the range of 80 - 125%. The mean Tmax value of cyclosporine following test dose was comparable to the value following reference dose.

Table 17. Effect of single intravenous dose of micafungin 200 mg on the pharmacokinetic parameters of cyclosporine following multiple (steady state) oral doses of 50 mg (N = 23)

Cyclosporine Pharmacokinetic Parameters	Test (Mean ± SD)	Reference (Mean ± SD)	Geometric Mean Ratio (90% Confidence Interval, %)
	Day 16	Day 15	Day 16 / Day 15
Cmax (μg/mL)	329 ± 78	306 ± 78	109 (100 – 118)
C_{12} (μg/mL)*	20.5 ± 6.4	20.3 ± 7.2	101 (95 – 106)
AUC_{0-12} (ng·hr/mL)	905 ± 233	882 ± 231	104 (100 – 109)
Tmax (hr)	1.6 ± 0.5	1.5 ± 0.6	

* N = 21

At the doses administered in the Study FG-463-21-05, a single or multiple (steady state) oral doses of cyclosporine had no effect on micafungin pharmacokinetics (Table 18). The geometric mean ratios of Cmax and $AUC_{0-\infty}$ of micafungin determined on Day 7 (test in single cyclosporine dose) or Day 16 (test in multiple cyclosporine doses) to the values determined on Day 1 (reference) were contained within the range of 80 - 125%. All corresponding 90% CIs of the ratios were entirely contained within the range of 80 - 125%. The mean $t_{1/2}$ values of micafungin following test doses were comparable to the value following reference dose.

Table 18. Effect of single (Day 7) or multiple (Day 16) doses of cyclosporine 50 mg on the pharmacokinetic parameters of micafungin following a single intravenous dose of 200 mg (N = 24)

Micafungin Pharmacokinetic Parameters	Test (Mean ± SD)		Reference (Mean ± SD)	Geometric Mean Ratio (90% Confidence Interval, %)	
	Day 7	Day 16	Day 1	Day 7 / Day 1	Day 16/ Day 1
Cmax (μg/mL)	18.1 ± 3.1	18.0 ± 3.1	16.6 ± 3.2	103 (98 – 107)	102 (98 – 107)
$AUC_{0-\infty}$ (μg·hr/mL)	289 ± 46	279 ± 46	267 ± 48	108 (105 - 112)	104 (102 – 108)
$t_{1/2}$ (hr)	16.2 ± 1.0	15.0 ± 1.1	15.4 ± 1.1		

Micafungin-Tacrolimus Interaction: In a drug-drug interaction study (01-0-105) conducted in 26 healthy adult volunteers, each subject received a daily dose of micafungin 100 mg by 1-hr intravenous infusion on Days 7, 9, and 12 through 16. Each subject also received a single oral dose of tacrolimus 5 mg (Prograf® capsule) under fasting conditions on Days 1, 9, and 16. The morning doses of tacrolimus on Days 9 and 16 were administered in combination with micafungin infusion. At the doses studied, the single or multiple (steady state) doses of micafungin had no effect on tacrolimus pharmacokinetics (Table 19). The geometric mean ratios of Cmax, C_{12}, and $AUC_{0-\infty}$ of tacrolimus determined on Day 9 (test in single micafungin dose) or on Day 16 (test in multiple micafungin doses) to the values determined on Day 1 (reference) were contained within the range of 80 - 125%. All corresponding 90% CI of the ratios were entirely contained within the range of 80 - 125%. The mean Tmax and $t_{1/2}$ values of tacrolimus following test doses were comparable to the value following reference dose.

Table 19. Effect of single (Day 9) or multiple (Day 15) intravenous doses of micafungin 100 mg on the pharmacokinetic parameters of tacrolimus following a single oral dose of 5 mg (N = 26)

Tacrolimus Pharmacokinetic Parameters	Test (Mean ± SD)		Reference (Mean ± SD)	Geometric Mean Ratio (90% Confidence Interval,%)	
	Day 9	Day 16	Day 1	Day 9 / Day 1	Day 16 / Day 1
Cmax (ng/mL)	30.5 ± 10.3	25.7 ± 9.9	27.1 ± 9.4	108.1 (96.2 – 121.4)	89.9 (80.1 – 101.0)
C_{12} (ng/mL)	4.3 ± 1.9	4.0 ± 2.2	4.0 ± 2.0	105.2 (91.7 – 120.8)	95.5 (83.2 – 109.6)
$AUC_{0-\infty}$ (ng·hr/mL)	309 ± 130	287 ± 131	2945 ± 136	102.5 (90.9 – 102.5)	94.5 (83.8 – 106.6)
Tmax (hr)	1.7 ± 0.6	1.5 ± 0.5	1.6 ± 0.5		
$t_{1/2}$ (hr)	34.7 ± 8.7	34.3 ± 6.1	37.9 ± 7.0		

In a drug-drug interaction study (FG-463-21-04) conducted in 24 healthy male volunteers, each subject received 3 intravenous doses of micafungin 200 mg infused over one hour on Days 1, 7, and 16. Each subject also received oral doses of tacrolimus 2 mg (Prograf® capsule) twice daily on Days 7 to 15 and in the morning of Day 16 after at least 2-hr fast. The morning doses of tacrolimus on Days 7 and 16 were administered in combination with micafungin infusion. At the doses studied, the single dose of micafungin had no effect on tacrolimus pharmacokinetics (Table 20). The geometric mean ratios of Cmax, C_{12}, and AUC_{0-12} of tacrolimus determined on Day 16 (test) to the values determined on Day 15 (reference) were contained within the range of 80 - 125%. All corresponding 90% CIs of the ratios were entirely contained within the range of 80 - 125%. The mean Tmax value of tacrolimus following test dose was the same as the value following reference dose.

Table 20. Effect of a single intravenous dose of micafungin 200 mg on the pharmacokinetic parameters of tacrolimus following multiple (steady state) oral doses of 2 mg (N = 24)

Tacrolimus Pharmacokinetic Parameters	Test (Mean ± SD)	Reference (Mean ± SD)	Geometric Mean Ratio (90% Confidence Interval, %)
	Day 16	Day 15	Day 16 / Day 15
Cmax (µg/mL)	15.7 ± 3.9	15.9 ± 4.4	100 (93 – 107)
C_{12} (µg/mL)	5.4 ± 2.1	5.2 ± 2.2	102 (97 – 110)
AUC_{0-12} (ng·hr/mL)	97.1 ± 31.1	98.9 ± 33.6	99 (94 – 104)
Tmax (hr)	1.5 ± 0.5	1.5 ± 0.5	

At the doses administered in the Study FG-463-21-04, single or multiple (steady state) oral doses of tacrolimus had no effects on micafungin pharmacokinetics (Table 21). The geometric mean ratios of Cmax and $AUC_{0-\infty}$ of micafungin determined on Day 7 (test in single tacrolimus dose) or Day 16 (test in multiple tacrolimus dose) to the values determined on Day 1 (reference) were contained within the range of 80 - 125%. All corresponding 90% CIs of the ratios were entirely contained within the range of 80 - 125%. The mean $t_{1/2}$ value of micafungin following test dose was comparable to the value following reference dose.

Table 21. Effect of single (Day 7) or multiple (Day 16) doses of tacrolimus 2 mg on the pharmacokinetic parameters following a single intravenous dose of micafungin 200 mg (N = 24)

Micafungin Pharmacokinetic Parameters	Test (Mean ± SD)		Reference (Mean ± SD)	Geometric Mean Ratio (90% Confidence Interval, %)	
	Day 7	Day 16	Day 1	Day 7 / Day 1	Day 16/ Day 1
Cmax (µg/mL)	17.3 ± 2.8	17.7 ± 2.7	16.0 ± 2.9	108 (105 – 112)	111 (108 – 115)
$AUC_{0-\infty}$ (µg·hr/mL)	262 ± 41	265 ± 37	253 ± 42	104 (102 - 106)	105 (103 – 107)
$t_{1/2}$ (hr)	15.4 ± 1.1	15.3 ± 0.8	15.2 ± 1.1		

Micafungin-Prednisolone Interaction: In a drug-drug interaction study (FG-463-21-06) conducted in 24 healthy male volunteers, each subject received two intravenous doses of micafungin 200 mg infused over an hour on Days 1 and 12. Each subject also received 10 oral doses of prednisolone 20 mg on Days 5 to 14 after a standard breakfast except for a dose given on an empty stomach in combination with micafungin on Day 12. On Day 12 (test) as compared with Day 11 (reference), the mean Cmax value of prednisolone was greater by 19% (90% CI, 110 - 129%; Table 22) but the mean trough concentration (C_{24}) was smaller by 36% (90% CI, 49 - 85%). The mean Tmax and lag time (Tlag) of prednisolone absorption were longer by 1.1 hr (from 3.8 to 4.9 hr) and 0.7 hr (from 1.9 to 2.6 hr), respectively. These differences appear to be due to slower absorption of prednisolone under fed conditions (Day 11) but faster absorption under fasted conditions (Day 12), rather than the effect of micafungin coadministration. The observation of no meaningful differences in the mean AUC_{0-24}, apparent clearance (CL/F), and $t_{1/2}$ of prednisolone supports this speculation. A pronounced outlier (72.7 ng/mL) in C_{24} on Day 11 that deviated from the mean value (7.39 ng/mL) by larger than 3 standard deviations also contributed to the larger mean C_{24} value as compared to the value on Day 12.

Table 22. Effect of single intravenous dose of micafungin 200 mg on the pharmacokinetic parameters of prednisolone following multiple (steady state) oral doses of 20 mg (N = 24)

Prednisolone Pharmacokinetic Parameters	Test (Mean ± SD)	Reference (Mean ± SD)	Geometric Mean Ratio (90% Confidence Interval, %)
	Day 12	Day 11	Day 12 / Day 11
Cmax (ng/mL)	331 ± 57	281 ± 60	**119 (110 – 129)**
C_{24} (ng/mL)*	3.22 ± 1.27	7.39 ± 14.1	**64 (49 – 85)**
$AUC_{0\text{-}24}$ (ng·hr/mL)	1763 ± 282	1858 ± 323	95 (90 – 100)
CL/F (mL/min)	195 ± 38	185 ± 34	
Tmax (hr)	**3.8 ± 0.9**	**4.9 ± 1.8**	
$t_{1/2}$ (hr)	2.9 ± 0.2	2.9 ± 0.3	
Tlag (hr)	**1.9 ± 0.7**	**2.6 ± 1.4**	

At the doses administered in the Study FG-463-21-06, multiple oral doses (steady state) of prednisolone had no effects on micafungin pharmacokinetics. The geometric mean ratios of the Cmax and $AUC_{0\text{-}\infty}$ values of micafungin determined on Day 12 (test) to the values on Day 1 (reference) were contained within the range of 80 - 125% (Table 23). All corresponding 90% CIs of the ratios were entirely contained within the range of 80 - 125%. The mean $t_{1/2}$ value of micafungin following test dose was comparable to the value following reference dose.

Table 23. Effect of multiple (steady state) oral doses of prednisolone 20 mg on the pharmacokinetic parameters of micafungin following single intravenous dose of 200 mg (N = 24)

Micafungin Pharmacokinetic Parameters	Test (Mean ± SD)	Reference (Mean ± SD)	Geometric Mean Ratio (90% Confidence Interval, %)
	Day 12	Day 1	Day 12 / Day 1
Cmax (µg/mL)	16.6 ± 2.7	16.5 ± 2.4	100 (97 – 103)
$AUC_{0\text{-}\infty}$ (µg·hr/mL)	245 ± 38	249 ± 38	101 (97 - 105)
$t_{1/2}$ (hr)	14.2 ± 0.8	15.0 ± 0.8	

Pharmacodynamic Interaction:

There is no known adverse pharmacodynamic drug-drug interaction between micafungin and other drugs that can be used concomitantly for the patient population of interest.

Unresolved Issues in Metabolism, Metabolites, or Protein Binding:

We do not have adequate pharmacokinetic data for micafungin metabolites. While M5 is an inactive but the most abundant metabolite of micafungin in plasma, M1 and M2 are active but relatively less abundant than M5. A mass balance study roughly determined the recovery of M5 in plasma, urine, and feces following a single micafungin dose lower than its proposed clinical doses. Some studies such as FG463-21-03 demonstrated that M1 and M2 kept accumulating at the end of study period. However, no study was conducted to determine the pharmacokinetics of micafungin metabolites at the steady state of metabolite disposition. No study was conducted to determine the elimination half-life of any metabolite.

The characteristics of micafungin in protein binding were not adequately determined in patients of interest at the proposed clinical doses (Study 97-0-041); pooled plasma samples from several patients without regard to sample volume.

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

According the clinical review team, the clinical studies submitted in these applications do not sufficiently support the efficacy of micafungin for the proposed indications. At present, it is not clear if the lack of efficacy is due to an inadequate micafungin dose, the lack of an appropriate control group, or underpowering of the studies. Clinical micafungin doses were proposed based on only a preliminary dose-response study (see *Proposed Dosage and Route of Administration*).

4.5. General Biopharmaceutics

No bioavailability or bioequivalence studies are required for micafungin for injection because the final drug product is a lyophilized form for intravenous infusion that is to be completely reconstituted before administration.

What is the in vivo relationship of the proposed to-be-marketed formulation to the pivotal clinical trial formulation in terms of comparative exposure?

A clinical formulation of micafungin for injection was used only an early portion of Phase I studies conducted in Japan. The to-be-marketed formulation was used for all other clinical studies. The only difference between the clinical and to-be-marketed formulations is the content of lactose (200 mg *vs.* — mg); this difference is not likely to affect the exposure to micafungin following intravenous administration.

4.6. Analytical

How are the active moieties identified and measured in the plasma and urine in the clinical pharmacology and biopharmaceutics studies?

Micafungin, M1 and M2 in Plasma: The plasma concentrations of micafungin, M1, and M2 were measured using a — high performance liquid chromatographic (HPLC) method with fluorescent detection. FR195743, a micafungin analog, was used as an internal standard. In principle, plasma was separated by centrifugation from whole blood and acidified by adding 1% volume of diluted phosphoric acid (distilled water:phosphoric acid, 2:1, v/v) to prevent the degradation of micafungin and metabolites under alkaline conditions. Acetonitrile (50 µL) was added to each plasma sample (50 µL) to precipitate proteins. After a centrifugation, the supernatant (100 µL) was mixed with 20 mM potassium dihydrogenphosphate (200 µL). This solution (40 µL) was injected onto an HPLC system. —

1. Fluorescence detection was used to detect

Which metabolites have been selected for analysis and why?

M1 and M2 were measured because they are active micafungin metabolites. M5 should also have been measured in plasma until M5 reached a steady state following multiple micafungin doses because M5 is most abundant among micafungin metabolites in human plasma and because the degrees of accumulation and toxicity of M5 are not known.

For all moieties measured, is free, bound or total measured? What is the basis for that decision, if any, and is it appropriate?

Only total plasma concentrations of micafungin, M1, and M2 were measured to determine their pharmacokinetic parameters. The measurement of free micafungin concentrations is not likely to give us useful information because micafungin is highly bound to plasma proteins (>99%) and, therefore, the free concentrations following proposed clinical dosing will be lower than the LOQ at most blood collection points. The protein binding characteristics of M1 and M2 are not known at this time.

What bioanalytical methods are used to assess concentrations?

Standard Curve, Limit of Quantitation (LOQ), Accuracy, Precision, Selectivity, Sample Stability, Quality Control:

Micafungin, M1, and, M2 in Plasma: The plasma concentrations of micafungin, M1, and M2 were measured using validated — HPLC methods at four laboratories in Japan, Europe, and the United States (Table 24). Each laboratory followed similar analytical procedures with minor modification from what was initially developed and validated at Fujisawa Pharmaceutical Co., Ltd., Osaka, Japan (Company Report CRD980010). The sample preparation, extraction procedure and chromatographic conditions were kept the same, but the standard and quality control concentrations were slightly different. A weighted (1/concentration) linear regression was used to determine the slope, intercept, and correlation coefficient of a calibration curve. In addition to an initial validation report produced at the time of method transfer, the sponsor provided an analytical report with in-process quality controls for each clinical study conducted in the United States or the United Kingdom. In essence, the results of initial validations and in-process quality controls met the criteria in the Agency's Guidance for Bioanalytical Method Validation. The sponsor did not provide in-process quality control reports for studies conducted in Japan (FJ-463-0004 and FJ-463-0005).

Table 25. Summary of validation for high performance liquid chromatographic methods used to measure the concentrations of micafungin, M1, and M2 in urine and ultrafiltrate samples

Specimen
Analytical Site
Validation Report
Study No. Applied
Calibration
Conncentrations
Micafungin
M1, M2
Limit of Quantitation
Specificity
Quality Controls (per Run)
Precision
Intraday
Micafungin
M1
M2
Interday
Micafungin
M1
M2
Accuracy
Intraday
Micafungin
M1
M2
Interday
Micafungin
M1
M2

* for micafungin only *

^{14}C-Micafungin: The radioactivity in plasma, urine, and feces following the administration of ^{14}C-micafungin was measured at — , using a liquid scintillation counting method. The method was validated for accuracy and reproducibility in sample processing and ^{14}C counting in plasma (—), urine (—) and fecal homogenate (— using quality control samples spiked at three distinct levels of known radioactivity. Results of were corrected for . Analysis of quality control standards in plasma, urine, and feces during the validation gave recoveries that fell between

Stability of Micafungin, M1, and M2 in Assay Samples: Micafungin and its metabolites in whole blood, acidified plasma, and processed samples were stable for — at room temperature (peak height ratio, — , for — at -20°C (—) and for days at -80°C (—), and for — at room temperature (— respectively. The stability was not affected by repeated freezing-thawing up to — cycles (— -

— The stability of micafungin and its metabolites in Tween 20-added urine samples was no worse than the stability in plasma samples.

Cyclosporine, Tacrolimus, and Prednosolone: Cyclosporine assays to support drug-drug interaction studies (FG-463-21-05 and 01-0-104) were conducted at — A weighted (1/concentration^2) linear regression was used to construct a calibration curve. Tacrolimus assays to support drug-drug interaction studies (FG-463-21-05 and 01-0-104) were conducted at — , respectively. A weighted (1/concentration) linear regression was used to construct a calibration curve. Prednisolone assay to support a drug-drug interaction study (FG-463-21-06) was conducted at — A weighted (1/concentration^2) linear regression was used to construct a calibration curve. In-process quality controls for the assays esentially met the criteria in the Agency's Guidance for Bioanalytical Method Validation (Table 26).

Table 26. Performance summary for analytical methods used to measure the concentrations of cyclosporine, tacrolimus, and prednisolone

Drugs	Cyclosporine	Tacrolimus	Prenisolone
Analytical Site			
Study No. Applied			
Assay Method			
Calibration Range			
Limit of Quantitation			
Quality Controls			
Precision (inter-assay coefficient of variation			
Accuracy (inter-assay relative error)			

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5. DETAILED LABELING RECOMMENDATIONS

According to the clinical review team, micafungin will not be approved for any proposed indications. Thus, labeling recommendations are deferred at this time.

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/s/

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1/23/03 12:13:26 PM
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