OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA#	21506/S-015 (SDN311)
Date of Original Submission:	September 27, 2012
Brand Name:	Mycamine®
Generic Name:	Micafungin
Strength and Formulation:	IV Infusion
Sponsor:	Astellas
Indication:	Treatment of fungal infections
Submission Type:	Pediatric sNDA
Clinical Pharmacology Review Team:	Dakshina M. Chilukuri, Seong Jang, Yang He, Kimberly Bergman

TABLE OF CONTENTS

EXECUTIVE SUMMARY

Mycamine® (micafungin) was initially approved for the treatment of adult patients with esophageal candidiasis (EC) and for prophylaxis of *Candida* infections in patients undergoing hematopoietic stem cell transplantation (HSCT) in the United States in March, 2005. Later, it was approved for the treatment of adults with candidemia (C), acute disseminated candidiasis (also referred to as invasive candidiasis or IC), *Candida* peritonitis and abscesses in January, 2008. Although some of the studies that supported the adult indications also included pediatric patients, a pediatric written request (PWR) was issued on May 23, 2007 which outlined 5 pediatric studies including 4 pharmacokinetic phase 1 studies (3 of which contain new PK data in pediatric patients) and 1 phase 3 study in neonates and young infants.

The overall micafungin experience during clinical development included a total of 479 pediatric patients. PK, safety and efficacy data were obtained from 11 pediatric trials. The efficacy of micafungin for the treatment of *Candida* infections in pediatric patients was similar to the efficacy seen in adults enrolled in the same study (FG-463-21-08), and similar to the results from a separate adult candidemia/invasive candidiasis study (03-0-192). The efficacy of micafungin for the prevention of *Candida* infections in pediatric patients undergoing HSCT was also similar to that obtained in adults in the same study (98-0-050). In addition, in the phase 3 studies 98-0-050 and FG-463-21-08 the efficacy of micafungin was similar to the comparators used (fluconazole and AmBisome, respectively). The efficacy data for EC in 38 pediatric patients is derived from the phase 1 open-label PK and safety study 9463-CL-2101. Descriptive data from this study shows that the response rate in pediatric patients with EC is similar to that seen in adult EC patients (Study 97-7-005).

In this supplemental NDA, Astellas has submitted new pediatric PK data from 4 completed trials. Of the 4 completed pediatric studies, 3 (Trials 9463-CL-2101, 9463-CL-2102 and 9463-CL-2103) provide new PK and safety data that, combined with pediatric data from legacy safety and efficacy trials, support the use of micafungin in pediatric patients ≥ 4 months through 16 years of age for the currently approved adult indications. The fourth phase 1 PK and safety study (9463-CL-2104) included in this submission contains data in neonates and young infants < 4 months of age. Astellas is not seeking an indication for this age group (b) (4)

Although the efficacy of micafungin in pediatric patients was evaluated in earlier studies for each of the indications, the number of pediatric patients was inadequate to support approval alone. Given that the disease progression for *Candida* indications is similar between pediatric patients (> 4 months of age) and adult patients, the approval of micafungin in pediatric patients is based on matching the systemic exposure of micafungin with those observed earlier in adult patients. This exposure matching is the basis of the applicant's proposal to approve micafungin for all the three indications in pediatric patients, and the available efficacy data adds support to the overall justification for the approval of micafungin in the pediatric population.

Pharmacokinetic data from legacy studies and the PWR/PREA studies 1–3 (i.e., Studies 9463-CL-2101, 9463-CL-2102 and 9463-CL-2103) were used to create a pediatric population PK model that provides adequate information for a dosing recommendation in pediatric patients aged 4 months through 16 years for all corresponding adult indications. The approved once daily doses for adult patients are 50 mg, 100 mg and 150 mg for prophylaxis of *Candida* infections,

treatment of candidemia, and treatment of EC, respectively. Based on the OCP review, the following pediatric dosing regimens of micafungin were determined to provide pediatric patients with drug exposures comparable to those observed in adult patients who received the approved dosing regimens for each indication.

Pediatric Patients ≥ 4 months

Indication	**Recommended Reconstituted Dose Once Daily**	
Treatment of Esophageal Candidiasis	≤ 30 kg	>30 kg
	3 mg/kg	2.5 mg/kg up to adult dose (150 mg)
Treatment of Candidemia, Acute Disseminated Candidiasis, *Candida* Peritonitis and Abscesses	2 mg/kg up to adult dose (100 mg)	
Prophylaxis of *Candida* Infections in HSCT Recipients	1 mg/kg up to adult dose (50 mg)	

In contrast, the applicant has proposed the following dosing regimen for the use of micafungin in pediatric patients:

Pediatric Patients ≥ 4 months (b) (4)

- Treatment of Esophageal Candidiasis, (b) (4)
- Treatment of Candidemia, Acute Disseminated Candidiasis, *Candida* Peritonitis and Abscesses, **2 mg/kg**
- Prophylaxis of *Candida* Infections in HSCT Recipients, **1 mg/kg**

1.1. Recommendation

The clinical pharmacology information provided by the applicant in support of the application is acceptable. Based on the FDA analysis, the dosing regimen for the use of micafungin in pediatric patients differs from the regimen proposed by the applicant and is presented in the table above and recommended label (Appendix-A).

1.2. Phase 4 Commitments

There are no Phase 4 committments.

1.3. Summary of Important Clinical Pharmacology Findings

Four PK studies were conducted to support the approval of micafungin in pediatric patients. Three of these studies were conducted in patients >4 months – 16 years of age and one study included patients < 4 months of age. The PK studies evaluated various doses that ranged between 1-4.5 mg/kg, depending on patient age and body weight. Pharmacokinetic data from 229 pediatric patients aged 4 months through 16 years, including 170 with full pharmacokinetic profiles from a total of 8 studies (which included 4 legacy studies), were used to construct the pediatric population pharmacokinetic model. This model was used to determine the micafungin doses in pediatric patients that would achieve exposures comparable to those in adults dosed with micafungin at 100 mg, the dose approved for use in adults with C/IC.

Micafungin clearance increases with increasing pediatric patient weight, and the pediatric population pharmacokinetic model predicts that unadjusted CL varies more with weight than

with weight-adjusted micafungin clearance (CL/WGT). Thus, over a wide range of ages, micafungin exposures are less variable if pediatric patients are given a weight-adjusted dose, than if they are given a fixed dose. There was a weak, clinically insignificant relationship between clearance and AST and clearance and total bilirubin (TBL), and thus no dose adjustment is recommended based on these laboratory parameters.

Based on the population PK analysis conducted by the sponsor and independently verified by the FDA clinical pharmacology team, the dose of micafungin in C/IC was determined to be 2 mg/kg (up to a maximum of 100 mg, which is the approved adult dose). Similarly, the dose for prophylaxis of fungal infections was determined to be 1 mg/kg (up to a maximum of 50 mg, which is the approved adult dose). For EC, the sponsor recommended a dose of (b) (4). Based on the review by the clinical pharmacology team, this dose was not acceptable because of concerns of over-exposure of pediatric patients in this population. Specifically, systemic exposure in patients weighing >30 kg exceeded the exposure seen in adult patients who received 150 mg, which is the approved dose in adults for the treatment of EC. The clinical pharmacology team determined that a dose of 2.5 mg/kg up to the adult dose (150 mg) in patients weighing >30 kg and a dose of 3 mg/kg in patients weighing ≤30 kg will provide pediatric patients with comparable systemic exposure with adult patients who received the approved dose (i.e., 150 mg) in adults for the treatment of EC.

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2. QUESTION BASED REVIEW

2.1. General Attributes of the Drug

2.1.1. What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

Mycamine® is a sterile, lyophilized product for intravenous (IV) infusion that contains micafungin sodium. Each single-use vial contains 50 mg or 100 mg micafungin sodium, 200 mg lactose, with citric acid and/or sodium hydroxide (used for pH adjustment). Mycamine must be diluted with 0.9% Sodium Chloride Injection, USP, or 5% Dextrose Injection, USP. Following reconstitution with 0.9% Sodium Chloride Injection, USP, the resulting pH of the solution is between 5-7.

2.1.2. What is the proposed mechanism of action and therapeutic indication(s)?

Micafungin is an echinocandin anti-fungal antimicrobial. Echinocandins non-competitively inhibit 1,3-betaglucan-synthase, thereby disrupting the synthesis of 1,3 beta-D-glucan polysaccharides that are essential for the cell wall integrity of many filamentous fungi and yeasts.

Mycamine® is approved for the treatment of adult patients with EC, for prophylaxis of Candida infections in patients undergoing HSCT, and for the treatment of adults with candidemia, acute disseminated candidiasis, Candida peritonitis and abscesses. The sponsor is seeking the same indications in this pediatric supplement.

2.1.3. What is the proposed dosage and route of administration?

The FDA and applicant proposed dosage regimens of IV micafungin are given below in Tables 2.1.3-1 and 2.1.3-2, repsectively:

Table 2.1.3-1: FDA proposed recommendations for the dosing of micafungin in pediatric patients ≥ 4 months

Indication	**Recommended Reconstituted Dose Once Daily**	
Treatment of Esophageal Candidiasis	≤ 30 kg	>30 kg
	3 mg/kg	2.5 mg/kg up to adult dose (150 mg)
Treatment of Candidemia, Acute Disseminated Candidiasis, *Candida* Peritonitis and Abscesses	2 mg/kg up to adult dose (100 mg)	
Prophylaxis of *Candida* Infections in HSCT Recipients	1 mg/kg up to adult dose (50 mg)	

Table 2.1.3-2: Applicant proposed recommendations for the dosing of micafungin in pediatric patients

Indication	Recommended Reconstituted Dose Once Daily
	(b) (4)
Treatment of Esophageal Candidiasis	
Treatment of Candidemia, Acute Disseminated Candidiasis, *Candida* Peritonitis and Abscesses	
Prophylaxis of *Candida* Infections in HSCT Recipients	

2.2. General Clinical Pharmacology

2.2.1. What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The pathophysiology of IC is similar in adult and pediatric patients, but differs in the neonate population, who present with more subtle symptoms. EC in pediatric patients is similar to that of adults. Thus, the pediatric decision tree was applied in the case of micafungin whereby, PK trials were conducted in pediatric patients >4 months of age and compared with the PK in adults for determination of dosing for the IC and EC indications.

Out of the 11 studies (see Table 2.2.1-1) with pediatric data, two legacy studies (Study FG-463-21-08 and Study 98-0-050) were phase 3 double-blind, active-controlled efficacy/safety studies that supported the approval of the adult indications (C/IC and prophylaxis, respectively). In each study, the inclusion of both pediatric and adult patients permitted direct comparisons between the populations, and use of the same active control. Study FG-463-21-08 was a multicenter, randomized, active-controlled, double-blind, parallel group study in adult and pediatric patients with confirmed C/IC. Study 98-0-050 was a randomized, double-blind comparative study of micafungin and fluconazole for prophylaxis of *Candida* infections in adult and pediatric patients undergoing either allogeneic or autologous HSCT. A total of 95 pediatric patients were randomized to receive micafungin in studies FG-463-21-08 and 98-0-050. These studies also provide the evidence of efficacy for the corresponding pediatric indications. Additional studies investigating the efficacy and safety of micafungin in C/IC in the pediatric population include the phase 2 non-comparative open-label study 98-0-047/FG-463-21-02, and phase 1 safety and PK studies 9463-CL-2101 and 9463-CL-2102. Additional studies investigating the efficacy of micafungin for prophylaxis of invasive fungal infections include: Study 98-0-043, a phase 1 open-label dose escalation safety study in febrile neutropenic pediatric patients; and Study 9463-CL-2103, a phase 1 open-label safety and PK study in children and adolescents.

Table 2.2.1-1: Overview of Pediatric Studies with Micafungin

Study Number (Phase)	Study Title	Total Pediatric Patients†
Candidemia or Invasive Candidiasis		
98-0-047 (Phase 2)	An Open-Label, Non-Comparative Study of FK463 in the Treatment of Candidemia or Invasive Candidiasis	55

99-0-063 (Phase 1)	Pharmacokinetic, Safety, and Tolerance Study of Three Dose Levels of Micafungin (FK463) in Premature Infants	13‡
FG-463-21-08-CR-02§ (Phase 3)	A Multicentre, Double Blind, Comparative, Randomised Study to Evaluate the Efficacy and Safety of Micafungin (FK463) versus Liposomal Amphotericin B (AmBisome®) in the Treatment of Invasive Candidiasis and Candidaemia in Paediatric Patients	112 total 56 micafungin¶ 56 AmBisome
9463-CL-2102§ (Phase 1)	A Phase 1, Open-Label Study of the Safety and Pharmacokinetics of Repeated-Dose Micafungin (FK463) in Infants and Toddlers (≥ 4 Months to < 24 Months of Age) with Esophageal Candidiasis or Other Invasive Candidiasis	9
9463-CL-2104§ (Phase 1) and Amendment 1	A Phase 1, Open-Label Study of the Safety and Pharmacokinetics of Repeated-Dose Micafungin in Neonates	13
9463-CL-2101§ (Phase 1)	A Phase 1, Open-Label Study of the Safety and Pharmacokinetics of Repeated-Dose Micafungin (FK463) in Children (2-5 Years and 6-11 Years) and Adolescents (12-16 Years) with Esophageal Candidiasis or Other Invasive Candidiasis	78
Prophylaxis		
98-0-050§ [NIAID MSG 46] (Phase 3)	A Phase 3, Randomized, Double-Blind, Comparative Trial of Micafungin (FK463) Versus Fluconazole for the Prophylaxis of Fungal Infections in Patients Undergoing a Hematopoietic Stem Cell Transplant	91 Total 43 micafungin 48 fluconazole
98-0-043 (Phase 1)	A Phase 1 Study to Determine the Safety and Pharmacokinetics of FK463 in Febrile Neutropenic Pediatric Patients	74††
9463-CL-2103§ (Phase 1)	A Phase 1 Open-Label Study of the Safety and Pharmacokinetics of Repeated-Dose Micafungin (FK463) as Antifungal Prophylaxis in Children and Adolescents Undergoing Hematopoietic Stem Cell Transplantation	40
Invasive Aspergillosis		
98-0-046 (Phase 2)	An Open-Label, Non-Comparative Study of Micafungin (FK463) in the Treatment of Invasive Aspergillosis	78
Deep Seated Mycosis due to *Aspergillus* or *Candida*		
FJ-463-FP01 (Phase 3)	A Phase III Study of FK463 in the Treatment of Deep Mycosis in Pediatric Patients—Multicenter Uncontrolled Open-label Study	20
Total Number of Patients Treated with Micafungin		**479**

NIAID: National Institute of Allergy and Infectious Disease; MSG: Mycoses Study Group
† All studies: pediatric patients 0 – 16 years of age included in the Safety/Full Analysis Set: received at least 1 dose of study drug.
‡ Ten subjects rolled over from Study 99-0-063 to Study 98-0-047 and were accounted for in Study 98-0-047 for all analyses.
§ Study report included in this pediatric sNDA.
¶ Four subjects were enrolled at the end of the study in an open-label fashion to collect additional pharmacokinetic and safety information. These 4 subjects are included in this Summary of Clinical Safety but not in the Summary of Clinical Efficacy.
†† A total of 77 patients were enrolled and received at least 1 dose of study drug; 17 year olds enrolled in Study 98-0-043 were not counted as pediatric patients.

Although pediatric patients were not included in the pivotal phase 3 study for EC, efficacy data from Study 9463-CL-2101, a phase 1 open-label PK and safety study in pediatric patients that included 38 EC patients, provides supportive evidence for this indication. Additional data from four pediatric patients in Study 98-0-047, a phase 2 open-label, non-comparative study for the treatment of C/IC, with confirmed EC, provide more support. These supportive efficacy data from clinical studies, combined with the similarity in disease state between adult and pediatric patients, provide support for the use of micafungin to treat EC in pediatric patients.

2.2.2. What are the key efficacy findings for micafungin in pediatric patients?

In Study FG-463-21-08, micafungin was found to be efficacious in pediatric patients with C/IC and had similar outcomes as AmBisome and the adult patients in this study (Table 2.2.2-1). Descriptive analysis of the data showed that micafungin efficacy was consistent when analyzed for overall treatment success and by subgroups of age, infection site, *Candida* species and neutropenia status. Please consult the review by the Medical officer for additional details regarding the efficacy of micafungin in pediatric patients.

Table 2.2.2-1. Treatment Success at End of Treatment, Pediatric Patients, Study FG-463-21-08

	Number (%)		Treatment Difference (%)‡
	Micafungin (n = 48)	AmBisome (n = 52)	
Success † [95% CI] §	32 (66.7)	34 (65.4)	1.3% [-17.2, 20.6]
Failure †	16 (33.3)	18 (34.6)	–
Died During Treatment	1 (2.1)	6 (11.5)	
Unsuccessful	11 (22.9)	7 (13.5)	
Not Evaluable	1 (2.1)	0	
Additional Failure Based on Use of Systemic Antifungal Therapy	3 (6.3)	5 (9.6)	

AmBisome: liposomal amphotericin B; mFAS: modified full analysis set = Patients who had a confirmed diagnosis of C/IC and received at least a single dose of study drug, includes patients ≤ 16 years of age; –: not applicable

† The treatment success at end of treatment is defined as a positive clinical response (complete or partial) and a positive mycological response (eradication or presumed eradication) at the end of blinded therapy.

Patients who died during treatment (first dose day through last dose day +1), missed an evaluation, or met one of following systemic antifungal therapy use criteria were considered a failure: i) pre-treatment (within 72 hours of study drug administration) systemic antifungal use for therapeutic, non-prophylactics purposes for > 2 days; ii) any study treatment systemic antifungal use for > 1 day; or iii) post-treatment systemic antifungal use for therapeutic purposes (other than oral fluconazole) initiated within 48 hours of discontinuation of study therapy.

‡ Micafungin-AmBisome by Treatment difference

§ by 95% CI for Based on Cochran-Mantel-Haenszel method controlling for baseline neutropenia status

The randomized studies with micafungin in EC were limited to adults. Efficacy data from Study 9463-CL-2101 provides supportive evidence for the use of micafungin in pediatric patients with EC. Data from four patients from Study 98-0-047 also provide supportive efficacy for the treatment of pediatric patients with EC.

Study 9463-CL-2101, a phase 1 open-label PK and safety study in pediatric patients, included 38 patients with EC. At doses of 3 mg/kg and 4.5 mg/kg, clinical success was observed in 6/6 (100%) and 28/30 (93.3%) patients, respectively. Response rates in this pediatric population are similar to clinical outcomes in adult EC studies of micafungin (see Table 2.2.2-2).

Table 2.2.2-2. Esophageal Candidiasis Clinical Response at End of Treatment, Study 9463-CL-2101

Clinical Response	Micafungin 3 mg/kg (n = 6)	Micafungin 4.5 mg/kg (n = 30)	Total (n = 36)
Success	6 (100.0)	28 (93.3)	34 (94.4)
Complete	5 (83.3)	22 (73.3)	27 (75.0)
Partial	1 (16.7)	6 (20.0)	7 (19.4)
Failure	–	1 (3.3)	1 (2.8)
Not Successful	–	1 (3.3)	1 (2.8)
Not Assessed	–	1 (3.3)	1 (2.8)

EC: esophageal candidiasis; SAF: Safety analysis set; –: not applicable

Safety analysis set (SAF) = All enrolled patients who received at least one dose of micafungin

For patients with esophageal candidiasis infection at baseline a success is a complete or partial clinical response at end of treatment.

Study 98-0-047, an open-label, non-comparative study for the treatment of C/IC, included 4 patients with esophageal candidiasis documented histologically or cytologically by endoscopy. All four patients had either a complete or partial clinical response. Three of these four patients had complete clearing of esophageal lesions at the end of therapy; endoscopy was contraindicated in the fourth patient and response was based upon clearing of all clinical symptoms. None of these patients relapsed.

In Study 98-0-050, micafungin was found to be efficacious for the prophylaxis of *Candida* infections in pediatric patients undergoing an HSCT. These results were similar to the response of pediatric patients to fluconazole and to the micafungin efficacy in an at-risk adult population. The efficacy of micafungin was consistent when analyzed by age and type of transplant [Table 2.2.2-3].

Table 2.2.2-3. Treatment Success at Post Treatment 4-Week-Follow-Up Period, Pediatric Patients, FAS – Study 98-0-050

	Number (%)	
	Micafungin (n = 43)	Fluconazole (n = 48)
Success	31 (72.1)	26 (54.2)
95% CI†	58.7, 85.5	40.1, 68.3
Failure	12 (27.9)	22 (45.8)
All Deaths‡	5 (11.6)	6 (12.5)
Proven/Probable FI Prior to Death	1 (2.3)	0
Proven/Probable‡	0	3 (6.3)
Suspected FI§	7 (16.3)	13 (27.1)
Lost to Follow-Up	0	0

FI: fungal infection

FAS: Full analysis set; all patients who received at least 1 dose of study drug, includes patients ≤ 16 years of age

Treatment success: absence of proven, probable, or suspected systemic fungal infection through the end of therapy and absence of proven or probable systemic fungal infection through the end of study.

95% CI was estimated based on large sample normal approximation

† Micafungin rate minus the fluconazole rate.

‡ Through end-of-study (4 weeks post-therapy)

§ Through end of therapy.

In Study 98-0-050, the overall success rate for micafungin treated pediatric patients was similar to micafungin-treated adult patients and numerically higher than fluconazole-treated pediatric patients (micafungin: 81.7% and 72.1% versus fluconazole: 76.0% and 54.2%, in adults and pediatric patients respectively). In addition, the adult and pediatric patients undergoing allogeneic transplants showed similar trends (micafungin: 73.7% and 70.7% versus fluconazole: 72.9% and 52.2%, in adults and pediatric patients respectively).

2.2.3. What are the key safety findings for micafungin in pediatric patients?

Six events of special interest (hepatic events, renal events, infusion-related reactions, hemolysis events, histamine release/allergic-type reactions, and injection site reactions) were identified by the applicant. These events were selected because of their clinical significance and known relationship to micafungin in the adult safety and efficacy trials. Based on the discussions with the clinical team, the most important adverse events identified for micafungin were liver function test (LFT) elevations and skin reactions such as pruritis. Relationships between these AEs and systemic exposure were explored and were not apparent, given the low incidence of these adverse events. Please refer to the review by Dr. Yuliya Yasinskaya for a detailed discussion on the safety aspects of micafungin in pediatric patients.

2.2.4. What are the PK characteristics of micafungin in pediatric patients?

The PK characteristics of micafungin in pediatric patients were determined from data obtained from Trials 9463-CL-2101, 2102, 2103 and 2104 and a population PK analysis, as discussed below.

Trial 9463-CL-2101:

The objectives of this study were to evaluate the pharmacokinetics and safety of IV micafungin after repeated daily dosing at two dose levels in children (2–5 years and 6–11 years) and in adolescents (12–16 years) with proven or probable EC, proven or probable IC, or suspected *Candida* infection. Patients were enrolled in two groups: safety only, and PK and safety. Patients were enrolled according to age and stratified by weight at baseline to receive either 3.0 mg/kg micafungin (weight ≥ 25 kg) or 4.5 mg/kg micafungin (weight < 25 kg). Micafungin was administered as an infusion over 1 hour, once a day for 10 - 14 days. Eighty-four patients were enrolled in the study; 78 of whom received at least one dose of study drug and were included in the safety analysis set (26 patients in the 3 mg/kg group and 52 patients in the 4.5 mg/kg group).

Plasma micafungin, M1 and M5 concentrations were measurable in all patient samples at all time points, but M2 concentrations were close to or below the limit of quantification in most samples. The mean micafungin AUC_{tau} in 2 to 5 year old patients in the 4.5 mg/kg group was comparable to that in 6 to 11 year old patients in the 3 mg/kg group, but lower than that in 6 to 11 and 12 to 16 year old patients in the 4.5 mg/kg group (Table 2.2.4-1). Mean micafungin C_{max} was similar for all age cohorts within dose groups, with the exception of the 12 to 16 year olds in the 4.5 mg/kg group, whose values were larger.

Mean micafungin CL_{ss} increased with age, but this observationcould be explained by body weight. For example, in patients over 6 years of age, the weight-adjusted clearance for the 6 to 11 and 12 to 16 years age cohorts is similar. Weight-adjusted CL_{ss} in patients 2 to 5 years of age was approximately 50% higher than that in the older groups. This was likely due to one high value (40.90 mL/hr/kg) in the 2 to 5 year old age cohort. Mean M1 relative to micafungin AUC_{tau} ranged from 8% to 12% across age cohorts and dose levels, and mean M5 relative to micafungin AUC_{tau} ranged from 7% to 14% across dose levels and age cohorts.

Table 2.2.4-1. Pharmacokinetic Parameters for Pediatric Patients with Esophageal or Other Invasive Candidiasis, Study 9463-CL-2101 (Day 7, Mean [SD])

Doses	3 mg/kg		4.5 mg/kg		
Ages	6 y - 11 y n = 4	12 y -16 y n = 8	2 y - 5 y n = 8	6 y - 11 y n = 3	12 y - 16 y n = 1
PK Parameter	Micafungin				
AUC_{tau} (mcg·h/mL)	247.473 (46.3764)	193.270 (30.8701)	248.945 (68.1267)	278.389 (41.5759)	339.020 (NC)
C_{max} (mcg/mL)	20.800 (4.1320)	20.537 (10.3319)	21.125 (6.1038)	20.700 (3.0806)	24.900 (NC)
CL_{ss}(L/h)	0.433 (0.130)	0.749 (0.155)	0.242 (0.107)	0.324 (0.065)	0.307 (NC)
CL_{ss}/Wt (L/h/kg)	0.012 (0.002)	0.013 (0.003)	0.020 (0.009)	0.016 (0.002)	0.013 (NC)
PK Parameter	M-1 metabolite				
AUC_{24} (mcg·h/mL)	24.918 (11.7777)	19.197 (4.0815)	29.830 (9.5046)	25.168 (10.1336)	28.564 (NC)
C_{max} (mcg/mL)	1.158 (0.5318)	0.899 (0.2049)	1.379 (0.4478)	1.223 (0.5656)	1.310 (NC)
$PR_{M\text{-}1,\ AUC}$† (fraction)	0.099 (0.0324)	0.103 (0.0320)	0.123 (0.0304)	0.091 (0.0398)	0.084 (NC)
PK Parameter	M-5 metabolite				
AUC_{24} (mcg·h/mL)	33.396 (25.5058)	24.293 (16.9210)	32.833 (27.3824)	19.200 (3.4466)	34.687 (NC)
C_{max} (mcg/mL)	1.522 (1.1673)	1.221 (0.8651)	1.597 (1.2928)	0.895 (0.1711)	1.620 (NC)
$PR_{M\text{-}5,\ AUC}$‡ (fraction)	0.139 (0.1117)	0.132 (0.0983)	0.134 (0.0877)	0.071 (0.0219)	0.102 (NC)

M-1: metabolite of micafungin; M-5: metabolite of micafungin; NC: not calculated;
†$PR_{M\text{-}1,\ AUC}$: AUC ratio is calculated as AUC_{24} M-1/AUC_{tau} micafungin
‡$PR_{M\text{-}5,\ AUC}$: AUC ratio is calculated as AUC_{24} M-5/AUC_{tau} micafungin

Trial 9463-CL-2102:

The objectives of this study were to evaluate the PK and safety of IV micafungin after repeated daily dosing at 4.5 mg/kg in infants (≥ 4 months - < 2 years of Age) with proven or probable EC or other IC or suspected *Candida* infection. Micafungin was administered as an infusion over 1 hour, once a day for 10 – 14 days.

Nine patients were treated in this open-label study of IV micafungin 4.5 mg/kg in infants and toddlers with proven or suspected candidiasis (Table 2.2.4-2). The mean age was 8.8 months (range 4.0 to 19.0 months) and mean weight was 6.5 kg (range 3.7 to 9.2 kg).

Mean plasma micafungin AUC_{tau} was 299.422 mcg-hr/mL, with values ranging from 187.97 to 622.17 mcg-hr/mL (CV=46.82%; median 263.795). Mean plasma micafungin C_{max} was 32.825 mcg/mL, with values ranging from 18.20 to 84.80 mcg-hr/mL (CV=69.19%; median 21.700). For M1, mean C_{max} was 1.332 mcg/mL (median 0.862) and mean AUC_{tau} was 27.898 mcg-hr/mL (median 19.085) and for M5, mean C_{max} was 3.265 mcg/mL (median 2.870) and mean AUC_{tau} was 68.794 mcg-hr/mL (median 50.291). The M1 and M5 exposures relative to micafungin (PR_{AUC}) were 8.9% and 22.9%, respectively. PK parameters for M2 were not calculated because of the very low concentrations of this metabolite. One patient had micafungin, M1 and M5 concentrations that were substantially higher than most other patients at all time points on day 7 and trough micafungin, M1 and M5 concentrations that were substantially higher than all other patients on days 4, 6, 7 and 8.

Table 2.2.4-2. Pharmacokinetic Parameters at a Dose of 4.5 mg/kg of Micafungin for Study 9463-CL-2102 (Day 7, Mean [SD])

Analyte	C_{max} (mcg/mL)	AUC_{tau} or AUC_{24}† (mcg·h/mL)	CL_{ss} (L/h)	CL_{ss}/Wt (L/h/kg)	PR_{AUC}‡ (fraction)
Micafungin	32.825 (22.7)	299.422 (140.2)	0.110 (0.056)	0.017 (0.005)	NA
M-1	1.332 (0.9)	27.898 (20.4)	NC	NC	0.089 (0.0325)
M-5	3.265 (2.2)	68.794 (53.6)	NC	NC	0.229 (0.1040)

NA: not applicable; NC: not calculated; PR_{AUC}: AUC ratio of M-1 or M-5 metabolites vs micafungin

† AUC_{tau} is calculated for micafungin and AUC_{24} is calculated for M-1 and M-5.

‡ AUC ratio is calculated as AUC_{24} M-1 or M-5/AUC_{tau} of micafungin

Trial 9463-CL-2103:

The objectives of this study were to evaluate the PK and safety of IV micafungin after repeated daily doses in infants (4 months - < 24 months) and children (grouped 2 - 5 years, 6 - 11 years, and 12 - 16 years) undergoing autologous, syngeneic, or allogeneic HSCT. Patients were stratified by weight to receive either 1 mg/kg micafungin (weight > 25 kg) or 1.5 mg/kg micafungin (weight < 25 kg). Micafungin was administered as an infusion over 1 hour, once a day for 10 - 14 days.

Mean micafungin C_{max} and AUC_{tau} were higher in the 1.5 mg/kg treatment group than the 1 mg/kg group and mean $t_{1/2}$ was lower in the 1.5 mg/kg group than in the 1 mg/kg group. Within the 1.5 mg/kg group, these parameters were similar between the age cohorts of 4 to <24 months (8.1 mcg/mL, 77.3 mcg-hr/mL, and 11.5 hr for C_{max}, AUC_{tau}, and $t_{1/2}$, respectively) and 2 to 5 years (8.6 mcg/mL, 76.0 mcg-hr/mL, and 11.1 hr). However, within the 1.5 mg/kg group, the 6 to 11 years cohort showed higher mean AUC_{tau} and longer mean $t_{1/2}$ (8.7 mcg/mL, 113.6 mcg-hr/mL, and 15.2 hr for C_{max}, AUC_{tau}, and $t_{1/2}$, respectively) than the younger age cohorts. In the 1 mg/kg group, comparable mean C_{max}, AUC_{tau}, and $t_{1/2}$ values were observed between the age cohorts of 6 to 11 years (6.7 mcg/mL, 77.9 mcg-hr/mL, and 14.7 hr) and 12 to 16 years (5.6 mcg/mL, 76.0 mcg-hr/mL, and 11.1 hr).

Mean micafungin CL_{ss} and V_{ss} increased with age, resulting in apparent differences in overall mean CLss and V_{ss} between treatment groups (Table 2.2.4-3). Regardless of the treatment group, mean CL_{ss}/Wt and V_{ss}/Wt were almost equivalent in patients over 6 years of age suggesting that the increase in CL_{ss} and V_{ss} with age is fully explained by increasing body weight. However, significantly higher CL_{ss}/Wt and V_{ss}/Wt were observed in patients 4 months to 5 years of age, suggesting about 50% higher body-weight adjusted micafungin dose compared to the older children is needed to achieve comparable micafungin exposure in younger patients. Mean C_{max} for M1 was 0.28 mcg/mL and 0.32 mcg/mL for the 1 mg/kg and 1.5 mg/kg groups, respectively. Mean AUC_{tau} was 6.2 mcg*hr/mL and 7.0 mcg-hr/mL for the 1 mg/kg and 1.5 mg/kg groups, respectively. The overall mean relative AUC_{tau} of M1 to micafungin was 0.09 for both treatment groups and was consistent between age cohorts, suggesting that the difference in M1 exposure is fully explained by the micafungin exposure, regardless of micafungin dose or age.

Pharmacokinetic parameters for M2 were not calculated because of the very low concentrations of this metabolite. Mean M5 C_{max} was 0.30 mcg/mL and 0.58 mcg/mL for the 1 mg/kg and 1.5 mg/kg groups, respectively. Mean M5 AUC_{tau} was 6.3 mcg-hr/mL and 12.0 mcg-hr/mL for the 1 mg/kg and 1.5 mg/kg groups, respectively. The overall

mean relative AUC_{tau} of M5 to micafungin was 9 % for the 1 mg/kg group and 15% for the 1.5 mg/kg group. In the 1.5 mg/kg group, the mean relative AUC_{tau} of M5 to micafungin for the 4 to <24 months and 2 to 5 years age cohorts was 18% and 14%, respectively. However, the mean relative AUC_{tau} of M5 to micafungin in patients over 6 years of age was 9%-10% and was consistent regardless of micafungin dose or age cohort, resulting in the apparent difference in relative M5 AUC_{tau} between the treatment groups. Thus, in contrast to M1, M5 exposure was dependent on age and tended to be higher in the younger patient population.

Table 2.2.4-3. Pharmacokinetic Parameters for Pediatric Patients Undergoing HSCT in Study 9463-CL-2103 (Day 7, Mean [SD])

Doses	1 mg/kg		1.5 mg/kg		
Ages	6 y - 11 y n = 6	12 y - 16 y n = 9	4 mo - < 2 y n = 11	2 y - 5 y n = 11	6 y - 11 y n = 3
PK Parameter	Micafungin				
AUC_{tau} (mcg·h/mL)	77.938 (16.2359)	65.449 (11.1944)	77.313 (11.4472)	75.964 (14.9314)	113.618 (13.0364)
C_{max} (mcg/mL)	6.725 (0.9070)	5.553 (1.1543)	8.086 (2.8294)	8.620 (4.8768)	8.667 (1.2870)
CL_{ss} (L/h)	0.446 (0.045)	0.760 (0.150)	0.160 (0.033)	0.298 (0.088)	0.311 (0.020)
CL_{ss}/Wt (L/h/kg)	0.013 (0.002)	0.013 (0.002)	0.020 (0.003)	0.020 (0.003)	0.013 (0.002)
PK Parameter	M-1 metabolite				
AUC_{24} (mcg·h/mL)	7.271 (1.8984)	5.419 (0.5894)	6.349 (2.2354)	6.482 (1.3871)	11.323 (1.2000)
C_{max} (mcg/mL)	0.336 (0.0863)	0.248 (0.0301)	0.289 (0.1057)	0.297 (0.0649)	0.496 (0.0686)
$PR_{M-1, AUC}$† (fraction)	0.093 (0.0133)	0.085 (0.0145)	0.082 (0.0261)	0.086 (0.0158)	0.100 (0.0037)
PK Parameter	M-5 metabolite				
AUC_{24} (mcg·h/mL)	6.759 (2.7256)	6.041 (2.7275)	13.737 (4.9115)	10.306 (4.2221)	11.556 (5.0983)
C_{max} (mcg/mL)	0.326 (0.1244)	0.288 (0.1303)	0.662 (0.2245)	0.501 (0.2020)	0.525 (0.2313)
$PR_{M-5, AUC}$‡ (fraction)	0.087 (0.0336)	0.093 (0.0392)	0.184 (0.0737)	0.138 (0.0526)	0.104 (0.0529)

CL_{ss}/Wt: total body clearance at steady state normalized to body weight; M-1: metabolite of micafungin; M-5: metabolite of micafungin;
$PR_{M-1, AUC}$: AUC ratio of M-1 vs micafungin; $PR_{M-5, AUC,}$: AUC ratio of M-5 vs micafungin
† $PR_{M-5, AUC}$ AUC ratio is calculated as AUC_{24} M-5/AUC_{tau} micafungin ‡ $PR_{M-1, AUC}$ AUC ratio is calculated as AUC_{24} M-1/AUC_{tau} micafungin

Trial 9463-CL-2104:
The objectives of this study were to evaluate the safety and PK of IV micafungin in neonates and young infants (greater than 48 hours of age and up to 120 days of life) with suspected C/IC. Patients were assigned to a dosing regimen based on body weight; patients weighing <1000 grams were assigned to receive 10 mg/kg per day and patients ≥ 1000 grams were assigned to receive 7 mg/kg per day for 4 or 5 consecutive days, as appropriate. Each daily dose was administered as an infusion over 1 hour.

Median micafungin exposure (AUC) was higher in infants weighing < 1000 grams who received 10 mg/kg per day compared with infants weighing ≥ 1000 grams who received 7 mg/kg per day (median values: 291 mcg-h/mL versus 258 mcg-h/mL, respectively). Median total body clearance adjusted for weight was 26.7% higher in infants weighing < 1000 grams who received 10 mg/kg per day than in infants weighing ≥ 1000 grams who received 7 mg/kg per day (0.57 versus 0.45 mL/min/kg, respectively). Plasma micafungin concentration time profiles were similar in the 2 dose groups, as were the median C_{max} (23.3 mcg/mL for 7 mg/kg/day versus 24.9 mcg/mL for 10 mg/kg/day) and the median elimination half-life (11.30 h for 7 mg/kg/day versus 10.43 h for 10 mg/kg/day; calculated using 2 serial time points: 8–12 h and 20– 24 h after infusion start).

All plasma micafungin concentration and PK parameter data from Patient 04274004 in the 7 mg/kg per day treatment group were excluded from the descriptive statistics because this patient was inadvertently dosed at 10 mg/kg/day. This larger (1440 grams), older (33 days) infant who received micafungin 10 mg/kg per day had similar exposure (AUC_{tau}: 314.7 mcg-h/mL) to the median exposure in the 10 mg/kg group (AUC_{tau}: 291.2 mcg-h/mL). Patient 04274009 (7 mg/kg/day treatment group) was atypical, compared to the other infants, in that she was 119 days old and weighed 4.5 kg. This patient had a substantially higher AUC_{tau} (643.2 mcg-h/mL) than that seen in the smaller infants who received 7 mg/kg. The corresponding clearance for this patient was 0.18 mL/min/kg, which was well below the median clearance of 0.45 mL/min/kg for the 7 mg/kg dose group. While the mean AUCs of the 7 mg/kg and 10 mg/kg groups are similar (307.6 and 307.9 mcg-h/mL, respectively), the 7 mg/kg mean is strongly influenced by the higher AUC of patient 04274009. Apart from this patient, the plasma concentration profiles of the 7 mg/kg patients as a group are lower than those of the 10 mg/kg patients, as reflected in the median AUC values of 258.1 and 291.2 mcg-h/mL, respectively (Table 2.2.4-4).

Table 2.2.4-4. Pharmacokinetic Parameters for Patients < 4 Months Suspected to Have Candidemia or Invasive Candidiasis in Study 9463-CL-2104 (Day 4/5, Median [range])

Parameter	7 mg/kg/day Body Weight ≥ 1000 g n = 6†	10 mg/kg/day Body Weight < 1000 g n = 6
Micafungin		
AUC_{tau} (mcg·h/mL)	258.1 (162.6 – 643.2)	291.2 (185.3 – 460.5)
C_{max} (mcg/mL)	23.3 (17.4 – 48.1)	24.9 (19.2 – 39.9)
CL_{ss} (L/h)	0.040 (0.032 – 0.125)	0.023 (0.014 – 0.032)
CL_{ss}/Wt (L/h/kg)	0.027 (0.011 – 0.035)	0.034 (0.022 – 0.049)
M-5		
AUC_{24} (mcg·h/mL)	270.7 (86.8 – 330.3) [4]	288.0 (174.9 – 303.5) [5]
C_{max} (mcg/mL)	12.7 (3.6 – 21.9)	12.8 (8.5 – 13.6)
$PR_{M\text{-}5,\ AUC}$ (fraction)‡	0.8 (0.4 – 1.5) [4]	0.9 (0.6 – 1.2) [5]

[n]: number of patients used to calculate the parameter, if different than group n

CL_{ss}/Wt: total body clearance at steady state normalized to body weight; $PR_{M\text{-}5,\ AUC}$: AUC ratio of M-5 metabolite to micafungin

† Number of patients for whom the parameter was calculated, if different than n indicated in group. Excludes 1 patient in the 7 mg/kg/day treatment group who was inadvertently given 10 mg/kg/day.

‡AUC ratio is calculated as AUC_{24} M-5/AUC_{tau} of micafungin

Although the populations and doses were different in studies with pediatric and neonatal/young infant patients requiring anti-fungal therapy, the PK results from these disparate were generally consistent. Mean micafungin AUC_{tau} and C_{max} increased with increasing dose, with weight-normalized CL_{ss} larger in younger patients. There is a tendency for micafungin clearance to be greater in older (heavier) patients, but changes in micafungin clearance with age appear to be substantially explained by changes in body weight.

Population PK Analysis:
The population PK model of micafungin in pediatric patients was developed by the sponsor and was used to simulate pediatric micafungin exposure at steady state in order to investigate different candidate doses. The development and validation of the proposed population PK model are summarized in Pharmacometrics Review (Appendix-B) and was found to be acceptable.

Population PK: Age-dependent CL
Micafungin PK in 229 pediatric patients ≥4 months through 16 years of age were characterized using a population PK approach. The estimated body weight-normalized CL values (ml/min/kg) were decreased with increasing body weight (Figure 2.2.4-1), as expected from the final population PK model (Equation 5 on page 35). The mean values in the ≤10 kg, 10-20 kg, and 20-30 kg groups (0.330, 0.346 and 0.303 ml/min/kg, respectively) were approximately 30% higher compared with those in the 30-40 kg, 40-50 kg, and >50 kg groups (0.258, 0.248 and 0.247 ml/min/kg, respectively) (Table 2.2.4-5), suggesting that the same dosing regimen (mg/kg) regardless of body weight may not provide comparable exposure (i.e., AUC) in pediatric patients.

Figure 2.2.4-1. The estimated CL (ml/min/kg) values of micafungin as a function of body weight for pediatric patients ≥4 months through 16 years of age.

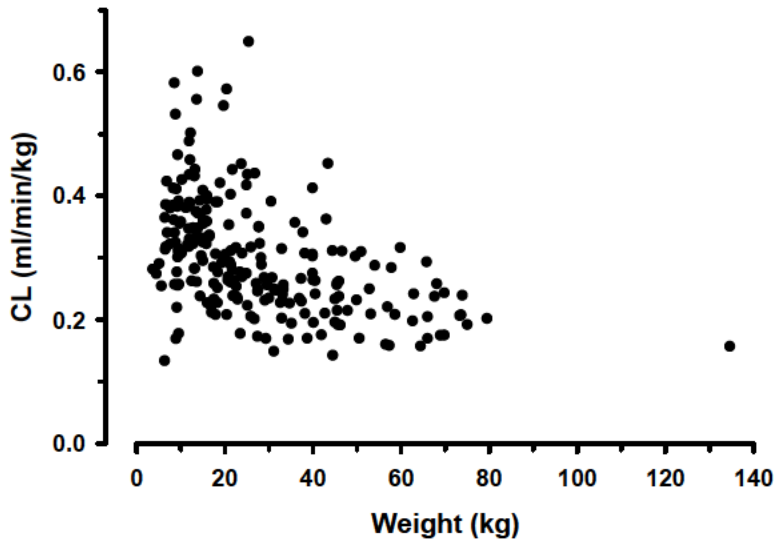


Table 2.2.4-5. The estimated CL (ml/min/kg) values of micafungin for pediatric patients ≥4 months through 16 years of age as a function of body weight.

Weight groups (N)	Mean	SD	Median	P10[a]	P90[a]
≤10 kg (35)	0.330	0.093	0.321	0.219	0.423
10kg-20kg (67)	0.346	0.083	0.335	0.232	0.442
20kg-30kg (47)	0.303	0.097	0.276	0.205	0.436
30kg-40kg (29)	0.258	0.063	0.247	0.169	0.356
40kg-50kg (23)	0.248	0.067	0.237	0.191	0.311
>50kg (28)	0.218	0.048	0.207	0.158	0.293

[a]: The 10th (P10) and 90th (P90) percentile

Dosing regimen for pediatric patients:

The FDA Clinical Pharmacology reviewers determined the following pediatric dosing regimens of micafungin (Table 2.2.4-6) to provide pediatric patients with drug exposures (specifically AUC) comparable to those observed in adult patients who received the approved dosing regimens for each indication. The approved once daily doses for adult patients are 50 mg, 100 mg and 150 mg for prophylaxis of *Candida* infections, treatment of Candidemia, and treatment of esophageal candidiasis, respectively.

Table 2.2.4-6. Mycamine dosage regimens in pediatric patients >4 months providing steady-state AUCs comparable to adults who received approved doses

Indication	**Recommended Reconstituted Dose Once Daily**	
Treatment of Esophageal Candidiasis	≤ 30 kg	>30 kg
	3 mg/kg	2.5 mg/kg up to adult dose
Treatment of Candidemia, Acute Disseminated Candidiasis, *Candida* Peritonitis and Abscesses	2 mg/kg up to adult dose	
Prophylaxis of *Candida* Infections in HSCT Recipients	1 mg/kg up to adult dose	

No pivotal clinical trials to evaluate the efficacy and safety of micafungin in pediatric patients were conducted. Although two Phase 3 studies were conducted to evaluate the efficacy of micafungin for the treatment of C/IC (Study FG-463-21-08) and the prophylaxis of *Candida* infections in pediatric patients, the number of patients in the two studies (~50 patients in each study) were not sufficient to determine the safe and effective dosing regimen of micafungin in pediatric patients. In addition, in pediatric patients, no randomized phase 3 studies were conducted for the treatment of EC. One safety and PK study was conducted in total 78 pediatric patients with EC or IC with 3 mg/kg or 4.5 mg/kg. It should be noted that, in adult patients, the approved dose of micafungin for the treatment of esophageal candidiasis (150 mg QD) is higher than the approved doses for the treatment of C/IC (100 mg QD) and for the prophylaxis of *Candida* infections (50 mg QD). The exposure-response relationship for effectiveness and safety of micafungin, which can be used to determine micafungin dosing regimen in pediatric patients, has not been established in either adult and pediatric patients. Accordingly, adequate pediatric dosing regimens of micafungin were evaluated in order to provide pediatric patients with drug exposures comparable to that observed in adult patients who received the approved dosing regimens for each indication

In contrast, the sponsor has proposed the following dosing regimen for the use of micafungin in pediatric patients:

Pediatric Patients ≥ 4 months (b) (4)

- Treatment of Candidemia, Acute Disseminated Candidiasis, *Candida* Peritonitis and Abscesses, **2 mg/kg**
- Treatment of Esophageal Candidiasis, (b) (4)
- Prophylaxis of *Candida* Infections in HSCT Recipients, **1 mg/kg**

The sponsor's rationale for the proposed dosing regimens is summarized at the end of this section with the Clinical Pharmacology reviewers' assessment.

Micafungin Exposures in Adult Patients:

The noncompartmental micafungin exposure parameters (the 10th and 90th percentile) for patients (n=40) dosed 100 mg from Study FG-463-21-08 (IC or candidemia) and Study FG-463-21-09 (EC) were used to determine appropriate dosing recommendations for pediatric patients (Table 2.2.4-7).

Table 2.2.4-7. Summary of steady state micafungin exposure for adults dosed 100 mg QD.

Statistic	AUC_{tau} (µg·hr/mL)	C_{max} (µg/mL)	C_{tr} (µg/mL)
N	40	40	40
MEAN	106	10.1	2.4
STD	28.2	3.54	1.03
MEDIAN	101	9.1	2.3
P10[a]	75	7.0	1.3
P90[a]	139	14.6	3.3
MIN	31	3.3	0.6
MAX	175	20.9	6.7
RANGE	144	17.6	6.2

[a]: The 10th (P10) and 90th (P90) percentile

The micafungin steady-state AUC_{tau} 10th and 90th percentiles (P10 and P90 in Table 10, respectively) following 100 mg QD are 75 and 139 µg•hr/mL, respectively, (mean: 106 µg•hr/mL) and were used as a reference range to facilitate obtaining the pediatric IC dose. The PK of micafungin in adults is dose-proportional when dose was increased from 100 mg to 150 mg. Thus, the micafungin steady-state AUC_{tau} 10th and 90th percentiles following 150 mg QD can be estimated to be 112.5 and 208.5 µg•hr/mL, respectively, (mean: 159 µg•hr/mL) and were used as a reference range to facilitate obtaining the pediatric EC dose. Similarly, the corresponding values following 50 mg QD can be estimated 37.5 and 69.5 µg•hr/mL (mean: 53 µg•hr/mL) and were used as a reference range to facilitate obtaining the pediatric dose for prophylaxis of *Candida* infections.

Pediatric dosing regimen of micafungin for the treatment of EC:

The approved once daily dose of micafungin for the treatment of EC in adult patients is 150 mg. The P10 and P90 of steady-state AUC_{tau} in adult patients who received 150 mg once daily were 112.5 and 208.5 µg•hr/mL, respectively. Thus, the dosing regimen which results in this range of steady-state AUC_{tau} in pediatric patients was determined using pediatric micafungin exposure (AUC_{tau}) at steady state estimated via the population PK model. Because the body-weight

normalized CL are different in different weight groups (discussed above), the steady state AUC_{tau} at different doses were evaluated as a function of body weight. Because the body-weight normalized CL are clearly lower in patients with >30 kg of body weight compared with in patients with ≤30 kg of body weight, the steady state AUC_{tau} were evaluated in the ≤30 kg, 30-50 kg, and >50kg groups. The resulting steady-state AUC_{tau} are summarized in Table 2.2.4-8 for each of the dose and body weight groups as the percentage of pediatric patients whose steady state micafungin exposures fell below, within, and above the range of 10th to 90th percentiles (i.e., 112.5 and 208.5 μg•hr/mL) of steady-state AUC_{tau} in the adult patients dosed at 150 mg.

At a dose of 3 mg/kg, among patients with ≤30 kg of body weight, (a) 76.5% of patients had micafungin exposures within 112.5-208.5 μg•hr/mL, (b) the mean steady-state AUC_{tau} in this patient group was also comparable to the value in adult patients who received 150 mg QD (i.e., 159 *vs.* 164 μg•hr/mL), and (c) the percentages of patients with steady-state AUC_{tau} <112.5 μg•hr/mL and AUC_{tau} >208.5 μg•hr/mL were similar to 10% (8.1% and 15.4%, respectively). Together, this suggested that 3 mg/kg once daily dosing regimen will provide pediatric patients weighing ≤30 kg with micafungin AUC_{tau} comparable to the adult patients who received 150 mg QD (i.e., the approved dose for the treatment of EC).

However, at a dose of 3 mg/kg, the exposures (i.e., steady state AUC_{tau}) in patients weighing >30 kg were substantially greater than in the adult patients who received 150 mg QD: (a) the mean steady-state AUC_{tau} in the older age groups (209 and 239 μg•hr/mL for the 30-50 kg and >50 kg groups, respectively) were greater than in the adult patients who received 150 mg QD (159 μg•hr/mL), (b) the percentage of patients with micafungin exposures within 112.5-208.5 μg•hr/mL was only 52% and 32% for the 30-50 kg and >50 kg groups, respectively, and (c) 46% of patients in the 30-50 kg group and 68% of patients in the >50 kg group had steady-state AUC_{tau} greater than the adult 90th percentile (i.e., 208.5 μg•hr/mL). For the patients with >30 kg of body weight, 2.5 mg/kg provided pediatric patients with more comparable adult drug exposure than 3.0 mg/kg based on mean steady state AUC_{tau} and the percentage of patients with micafungin exposures within 119-208 μg•hr/mL (Table 2.2.3-8). However, it should be noted that 2.5 mg/kg would provide the patients weighing ≤ 30 kg with lower exposure than that in adult patient who received 150 mg QD, which may result in lack of efficacy on micafungin in pediatric patients weighing ≤ 30 kg.

Table 2.2.4-8. Summary statistics for micafungin AUC_{tau} by weight group and dose

		Dose (mg/kg)			
Weight Group		2	2.5	3.0	3.5
≤ 30 kg (n=149)	Mean AUC_{tau} (μg•hr/mL)	109	137	164	192
	% Patients with AUC_{tau}				
	<112.5	61.1	29.5	8.05	4.7
	112.5-208.5	38.3	66.4	76.5	63.1
	>208.5	0.67	4.03	15.4	32.2
30 kg -50 kg (n=52)	Mean AUC_{tau} (μg•hr/mL)	139	174	209	244
	% Patients with AUC_{tau}				
	<112.5	25.0	5.77	1.92	0
	112.5-208.5	71.2	75.0	51.9	25.0
	>208.5	3.85	19.2	46.2	75.0
>50 kg (n=28)	Mean AUC_{tau} (μg•hr/mL)	160	200	239	279
	% Patients with AUC_{tau}				

	<112.5	7.14	0	0	0
	112.5-208.5	78.6	64.3	32.1	17.9
	>208.5	14.3	35.7	67.9	82.1

As discussed above, because the body weight-normalized CL is decreased with body weight, it is expected that one dose (i.e., 3 mg/kg) that provided the ≤30 kg groups with drug exposure comparable to adult patients would provide patients weighing >30 kg with higher drug exposure than in the adult patients who received 150 mg QD. Currently, there were no sufficient data to support the safety of 3 mg/kg in patients weighing >30 kg, which is most likely to result in higher drug exposure than that observed in adult patients who received the highest approved dose (i.e., 150 mg QD). Although no safety signals were observed in currently available data (i.e., in pediatric patients who received ≥3 mg/kg), from a clinical pharmacology perspective, there appears to be no reason to use the dose which will provide pediatric patients with exposure greater than that observed in adults who received the highest approved dose as long as there is no loss of efficacy. Thus, further analyses were conducted to identify a dose which will provide pediatric patients weighing >30 kg with drug exposure comparable to adult patients who received 150 mg QD. First, pediatric patients may have weights greater than 50 kg so that dosing at 3 mg/kg can result in a dose (in milligrams) greater than 150 mg in those pediatric patients. Accordingly, it was considered to use a dosing regimen in which patients weighing greater than a fixed weight are given the 150 mg dose, and those less than or equal to this weight receive 3 mg/kg (maximum dose at a weight cutoff). Second, although it is desirable to recommend a dosing regimen as simple as possible (i.e., same mg/kg dose for all age groups), it should be considered to use a different dosing regimen (i.e., different mg/kg dose) based on body weight in order to match PK adults.

***Maximum dose with a weight cutoff*:** In Table 2.2.4-9, the steady-state AUC_{tau} following a dosing regimen in which patients weighing greater than a fixed weight (either 40 kg or 50 kg) received the 150 mg dose, and those less than or equal to this weight received 3 mg/kg is summarized. When the maximum dose, 150 mg QD, was applied with 40 kg or 50 kg body weight cutoffs, the percent of patients with steady-state AUC_{tau} >208.5 μg•hr/mL was decreased from 68% (no maximum dose) to 21% in the >50 kg group. Accordingly, the percent of patients with steady-state AUC_{tau} between 112.5 and 208.5 μg•hr/mL was increased from 32% (no maximum dose) to 79% in the >50 kg group, supporting that applying a maximum dose would provide pediatric patients with drug exposure comparable to the adult patients who received 150 mg QD.

Table 2.2.4-9. Summary statistics of micafungin AUC_{tau} by weight group at a dosing regimen in which patients weighing greater than a fixed weight (40 kg or 50 kg) were given the 150 mg dose, and those less than or equal to this weight receive 3 mg/kg

Weight Group		40 kg cutoff	50 kg cutoff	No maximum dose[a]
≤ 30 kg (n=149)	Mean AUC_{tau} (μg•hr/mL)	164	164	164
	% Patients with AUC_{tau}			
	<112.5	8.05	8.05	8.05
	112.5-208.5	76.5	76.5	76.5
	>208.5	15.4	15.4	15.4
30 kg -50 kg	Mean AUC_{tau} (μg•hr/mL)	221	209	209
	% Patients with AUC_{tau}			

(n=52)	<112.5	0	1.92	1.92
	112.5-208.5	44.2	51.9	51.9
	>208.5	55.8	46.2	46.2
>50 kg (n=28)	Mean AUC_{tau} (µg•hr/mL)	186	186	239
	% Patients with AUC_{tau}			
	<112.5	0	0	0
	112.5-208.5	78.6	78.6	32.1
	>208.5	21.4	21.4	67.9

[a]: All patients received 3 mg/kg regardless of body weight

The different weight cutoff (i.e., 40 kg *vs.* 50 kg) resulted in different doses only for patients weighing between 40 kg and 50 kg. Either patients weighing ≤40 kg or patients weighing >50 kg would received same dose (i.e., 3 mg/kg or 150 mg, respectively) regardless of a weight cutoff. Based on the percent of patients with steady-state AUC_{tau} >208.5 µg•hr/mL in the 30-50 kg group, 50 kg as a body weight cutoff appears to be more appropriate than 40 kg. In individual patients who weighed between 40 kg and 50 kg, the steady-state AUC_{tau} was determined using 40 kg and 50 kg body weight cutoffs (Table 2.2.4-10). In patients who weighed close to 40 kg (e.g., Patient IDs 10025 and 90010), the steady-state AUC_{tau} increased by 24%-38%, depending on the CL, when a 40 kg body weight cutoff was used compared to 50 kg, indicating that a 50 kg body weight cutoff, for which 150 mg rather than 3 mg/kg will be given, is more appropriate than 40 kg.

Table 2.2.4-10. Comparison steady-state AUC_{tau} in individual pediatric patients weighing between 40 kg and 50 kg when they received 150 mg (i.e., 40 kg weight cutoff) or 3 mg/kg (i.e., 50 kg weight cutoff).

Patient ID	CL (mL/h)	Weight (kg)	AUC with 150 mg (40 kg weight cutoff)	AUC with 3 mg/kg (50 kg weight cutoff)
10025	0.63	40.10	237	190
90010	0.47	40.20	319	257
10010	0.64	40.60	235	191
70078	0.59	40.60	256	208
30001	0.44	42.00	340	286
70014	0.54	42.80	279	238
80078	0.94	43.10	160	138
80431	1.18	43.50	127	111
70055	0.83	44.50	181	161
70060	0.38	44.60	395	353
30003	0.63	45.10	238	215
90002	0.53	45.10	284	256
70072	0.70	45.50	215	196
70024	0.71	45.60	212	193
90009	0.59	45.60	256	233
70003	0.53	45.80	286	262
10002	0.65	46.00	229	211
10061	0.72	46.00	208	191
70036	0.53	46.30	283	262
80279	0.87	46.70	173	161
90012	0.62	47.95	243	233
10011	0.90	49.70	167	166
70067	0.69	50.00	216	216

***Different dosing regimen as a function of age*:** At a dose of 3 mg/kg with a maximum dose of 150 mg for patients with >50 kg of body weight, 46% and 21% of patients in the 30-50 kg and >50 kg groups, respectively, had steady-state AUC_{tau} greater than 208.5 μg•hr/mL (i.e., 90th percentiles of AUC following 150 mg QD in adults). Conversely, at a dose of 3 mg/kg, the steady-state AUC_{tau} in the ≤30 kg group were comparable with that observed in adult patients who received 150 mg QD, indicating that 3 mg/kg once daily would be an appropriate dosing regimen in pediatric patients with ≤30 kg of body weight for the treatment of EC. Table 2.2.4-11 summarizes the steady-state AUC_{tau} at different dosing regimens in the patients weighing >30 kg. At a dose of 2.5 mg/kg, compared with 3 mg/kg, the steady-state AUC_{tau} values in patients with 30-50 kg of body weight were more comparable to that in adult patients who received 150 mg QD. For patients with >50 kg of body weight, a dose of 125 mg provided the patients with steady-state AUC_{tau} comparable to that in adult patients who received 150 mg QD [i.e., almost identical mean steady-state AUC_{tau} (i.e. 155 *vs.*159 μg•hr/mL) and the 10^{th} and 90^{th} percentile of steady-state AUC_{tau} between pediatric patients weighing >50 kg and adults)]. However, at a dose of 150 mg, (a) mean steady-state AUC_{tau} in pediatric patients weiging >50 kg were higher than that in adults, (b) 21% of patients weighing >50 kg had steady-state AUC_{tau} greater than 208.5 μg•hr/mL, and (c) no pediatric patients weighing >50 kg had steady-state AUC_{tau} lower than 112.5 μg•hr/mL.

Table 2.2.4-11. Steady state AUC_{tau} distribution of micafungin at different dosing regimen by weight group. The maximum dose in each dosing regimen was given for the patients with >50 kg of body weight.

Weight Group			
≤ 30 kg (n=149)	Dosing Regimen	3 mg/kg	
	Mean AUC_{tau} (μg•hr/mL)	164	
	% Patients with AUC_{tau}		
	<112.5	8.05	
	112.5-208.5	76.5	
	>208.5	15.4	
30 kg -50 kg (n=52)	Dosing Regimen	3 mg/kg	2.5 mg/kg
	Mean AUC_{tau} (μg•hr/mL)	209	174
	% Patients with AUC_{tau}		
	<112.5	1.92	5.77
	112.5-208.5	51.9	75.0
	>208.5	46.2	19.2
>50 kg (n=28)	Dosing Regimen	150 mg	125 mg
	Mean AUC_{tau} (μg•hr/mL)	185	155
	% Patients with AUC_{tau}		
	<112.5	0	10.7
	112.5-208.5	78.6	78.6
	>208.5	21.4	10.7

[a]: The maximum dose for the patients with >50 kg of body weight

Although a dose of 125 mg for patients with >50 kg of body weight provided pediatric patients with steady-state AUC_{tau} most comparable to that in adult patients who received 150 mg QD, it is common in clinical practice to use a dosing regimen for adult patients as the maximum dosing

regimen for pediatric patients. In order to reconcile this and make a dosing recommendation that is simple for implementation in clinical practice and that minimizes dosing errors, a dose of 2.5 mg/kg up to adult dose (i.e., 150 mg) for patients weighing >30 kg is proposed. At this dosing recommendation, (a) patients weighing between 30 and 50 kg will receive 2.5 mg/kg as shown in Table 2.2.4-11, (b) patients weighing between 50 and 60 kg patients will receive 2.5 mg/kg as well (i.e., varying from 125 mg to 150 mg as a function of body weight), and (c) patients weighing >60 kg will receive the adult dose (i.e., 150 mg). Accordingly, in patients weighing >50 kg receiving the proposed 2.5 mg/kg dose, the mean steady-state AUC_{tau} would be 179 µg•hr/mL and the % of patients with steady-state AUC_{tau} <112.5, 112.5-208.5, and >208.5 were 0%, 82%, and 18%, respectively. This range of exposures in patients weighing >50 kg receiving the proposed 2.5 mg/kg dose is comparable to that in adult patients who received 150 mg QD and is therefore acceptable.

In summary, the following dosing regimen is recommended for the treatment of EC in pediatric patients for the purpose of providing pediatric patients with steady-state AUC comparable to adult patients who receive 150 mg QD (approved dose for the treatment of EC in adult patients).

For patients with ≤ 30 kg of body weight: 3 mg/kg
For patients with >30 kg of body weight: 2.5 mg/kg up to adult dose (150 mg)

Pediatric dosing regimen of micafungin for the treatment of Candidemia/IC

The approved dosing regimen for the treatment of C/IC in adult patients is 100 mg QD. Based on the analyses for the pediatric dosing regimen for the treatment of EC and dose-proportional PK of micafungin, a dosing regimen of 2 mg/kg with maximum dose of 100 mg for patients with >50 kg of body weight was evaluated as to whether it provides pediatric patients with comparable exposure to adult patients who received 100 mg QD. The reference of steady-state AUC_{tau} for adult patients who received 100 mg QD is between 75 and 139 µg·hr/mL (10th and 90th percentiles following 100 mg QD, see Table 2.2.3-7). Table 2.2.4-12 summarizes the steady-state AUC_{tau} at a dose of 2 mg/kg with maximum dose of 100 mg for patients with >50 kg of body weight in different age groups. In the ≤30 kg groups, the steady-state AUC_{tau} was comparable to adult patients. In the 30-50 kg and >50 kg groups, 46% and 21% of the pediatric patients, respectively, had the steady-state AUC_{tau} greater than 139 µg·hr/mL. However, the exposure in these pediatric patients would be substantially lower than the exposure observed in adult patients who received 150 mg QD (i.e., the highest approved dose in adult patients), indicating that 2 mg/kg with maximum dose of 100 mg for patients with >50 kg of body weight would not cause a safety concern in pediatric patients with steady-state AUC_{tau} greater than 139 µg·hr/mL. Accordingly, 2 mg/kg with maximum dose of 100 mg for patients with >50 kg of body weight (i.e., 2 mg/kg up to adult dose) is considered to be acceptable for the treatment of C/IC in pediatric patients.

Table 2.2.4-12. Steady state AUC_{tau} distribution of micafungin at 2 mg/kg once daily with the maximum dose of 100 mg QD for the patients with >50 kg of body weight in different weight groups.

≤ 30 kg (n=149)	Mean AUC_{tau} (µg•hr/mL)	110
	% Patients with AUC_{tau}	
	<75	8.05
	75-139	76.5

	>139	15.4
30 kg -50 kg (n=52)	Mean AUC_{tau} (µg•hr/mL)	139
	% Patients with AUC_{tau}	
	<75	1.92
	75-139	51.9
	>139	46.2
>50 kg (n=28)	Mean AUC_{tau} (µg•hr/mL)	124
	% Patients with AUC_{tau}	
	<75	0
	75-139	78.6
	>139	21.4

Pediatric dosing regimen of micafungin for the prophylaxis of *Candida* infections

The approved dosing regimen for the prophylaxis of *Candida* infections in adult patients is 50 mg QD. Based on the same analyses and the same rationale as determining the pediatric dosing regimen for the treatment of candidemia/IC, 1 mg/kg with maximum dose of 50 mg for patients with >50 kg of body weight (i.e., 1 mg/kg up to adult dose) is considered to be acceptable for the prophylaxis of *Candida* infections in pediatric patients.

The sponsor's rationale for the proposed dosing regimens

The sponsor did the same simulations in order to determine the pediatric dosing regimen for the treatment of Candidemia/IC which will provide pediatric patients with steady-state AUC_{tau} comparable to that in adult patients who received 100 mg QD. Figures 2.2.4-2 and 2.2.4-3 show distributions of steady state micafungin exposures for the pediatric age groups for 2 mg/kg dose regimens with a weight cut-off of 40 kg and 50 kg, respectively.

Figure 2.2.4-2. Steady-state AUC_{tau} distribution for 2 mg/kg by pediatric age group, where pediatric patients weighing ≥ 40 kg are dosed 100 mg and adults are dosed 100 mg

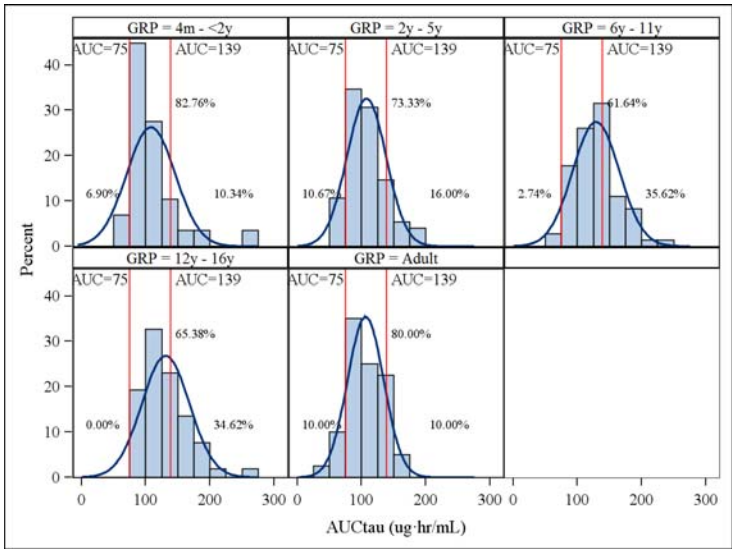
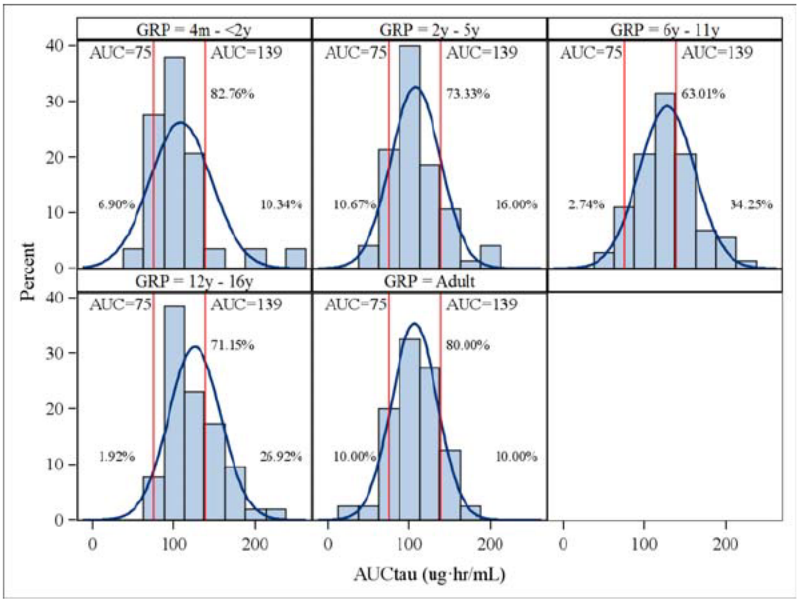


Figure 2.2.4-3. Steady-state AUC_{tau} distribution for 2 mg/kg by pediatric age group, where pediatric patients weighing ≥ 50 kg are dosed 100 mg and adults are dosed 100 mg



Similar to the clinical pharmacology reviewers' findings, the sponsor found that more that 30% of the pediatric patients in the age groups of 6y-11y and 12y-16y had the steady-state AUC_{tau} greater than 139 µg·hr/mL (i.e., 90th percentile of steady-state AUC_{tau} in adult patients who received 100 mg QD). The sponsor also agreed that the 50 kg weight cut-off shows a "slight" improvement in percentages over the 40 kg weight cut-off in the 6y-11y and 12y-16y age group. However, the sponsor proposed that a dose of 2 mg/kg, with 100 mg for patients weighing larger than 40 kg, may be the appropriate pediatric dosing regimen for the treatment of IC in pediatric patients because (a) the dosing regimen has been used in a clinical study and (b) the results of the study demonstrated a "good" safety profiles. After the sponsor proposed the dosing regimen (i.e., 2 mg/kg, with 100 mg for patients weighing larger than 40 kg) for the treatment of C/IC pediatric patients, then the sponsor proposed the dosing regimens for the treatment of EC and the prophylaxis of *Candida* infections in pediatric patients [redacted] (b) (4) The sponsor did not address the potential safety concerns for the proposed dosing regimen for the treatment of EC (i.e., [redacted] (b) (4)) which provided more than 30% of pediatric patients ≥6 years with steady-state AUC_{tau} >208.5 µg·hr/mL (i.e., 90th percentile of steady-state AUC_{tau} in adult patients who received the highest approved dose, 150 mg QD).

In summary, the applicant's proposed dosing regimen for the EC indication is different from what is being recommended by the FDA clinical pharmacology team, specifically for pediatric patients weighing >30 kg. In order to provide exposure (i.e., AUC) comparable to adults who received the approved dose of 150 mg, as well as provide a dosing regimen as simple as possible to prevent potential dosing errors while providing a dosing regimen is effective and safe, the clinical pharmacology team recommends 2.5 mg/kg (to a maximum of the adult dose) in these patients. The clinical pharmacology team refers to the FDA medical officer review (by Dr. Yuliya Yasinskaya) for evaluation of the safety of the sponsor's proposed [redacted] (b) (4) dose for EC, specifically of the limited safety data for pediatric and adult patients who received micafungin

doses greater than 3 mg/kg and the overall acceptability of the applicant's proposed dose for the treatment of EC with a correction of weight cut off for adult dose from (b) (4) to 50 kg (i.e (b) (4) (b) (4) up to adult dose).

2.3. Intrinsic Factors

The effect of age and body weight on micafungin PK in pediatric patients was evaluated and described in section 2.2.4 (Population PK). Please see the same section for the recommendation of dosing regimen as a function of age and body weight in pediatric patients. The influence of other intrinsic factors on the exposure and exposure-response relationship for micafungin was not evaluated in pediatric patients. Please see the previous Clinical Pharmacology Review by Jang-Ik Lee (2005) for the information in adult patients.

2.4. Extrinsic Factors

The current analyses did not evaluate the effect of extrinsic factors on the PK of micafungin. These factors are already evaluated and the findings are reflected in the label. No additional evaluations were conducted. Please see the previous Clinical Pharmacology Review by Jang-Ik Lee (2005) for the information in adult patients.

2.5. General Biopharmaceutics

Not applicable.

2.6. Analytical Section

2.6.1. What bioanalytical methods are used to determine drug concentrations? Briefly describe the methods and summarize the assay performance.

The applicant used a high-performance liquid chromatography (HPLC)/fluorescence method of bioanalysis to determine concentrations of micafungin (FK463) and its metabolites in the plasma samples. One of the assay methods was an investigational method, the liquid chromatography/mass spectrometry (LC/MS) method, used for the purpose of investigating reasons for low concentrations in one trial. The assay methods are validated per the FDA Guidance. In Table 2.6.1-1, the bioanalytical reports and the corresponding trials are given.

Table 2.6.1-1 Bioanalytical Method Reports Used in Pediatric Clinical Studies Method Validation for Determination of Micafungin and Metabolites in Human Plasma

Study Detection Method	Bioanalytic Report Number(s)	Laboratory Site	Analyte(s)
FG-463-21-08-R-PK-02 HPLC/Fluorescence	(b) (4) 150/2003(A) 150/2003(A), Addendum 1 (b) (4) 150/2003(A), Addendum 2 (b) (4) 150/2003(A), Version 2 (b) (4) 150/2003(B) 150/2003(B), Addendum 1 (b) (4) 150/2003(B), Addendum 2 (b) (4) 150/2003(B), Version 2	(b) (4)	FK463, M1, M2, M5
9463-CL-2101 HPLC/Fluorescence	7668-150	(b) (4)	FK463, M1, M2, M5
LC/MS	MGC1100856 (Document Control Number)†	Astellas Skokie, Illinois	FK463
9463-CL-2102 HPLC/Fluorescence	7668-151	(b) (4)	FK463, M1, M2, M5
9463-CL-2103 HPLC/Fluorescence	7668-148		FK463, M1, M2, M5
9463-CL-2104 LC/MS	7668-143		FK463
	MS-2009-010	Astellas Skokie, Illinois	M5

Method Validation for Determination of Micafungin and its M5 Metabolite in Human Plasma via HPLC

Sample preparation, extraction, and chromatographic conditions were kept the same for analysis of FK463, M1, M2, and M5 for all studies (except 9463-CL-2104). In this method, plasma samples were separated from whole blood and acidified with 1% diluted phosphoric acid (distilled water: phosphoric acid, 2:1, v/v). Acetonitrile (50 µL) was used for extraction of analyte from the plasma matrix (sample volume: 50 µL). The samples were centrifuged and the supernatant (100 µL) mixed with 20 mmol/L potassium dihydrogen phosphate (200 µL). This solution was injected into the HPLC system. Two separate HPLC systems were used; one for the separation of M5, and another for the separation of FK463, M1, and M2. Separation on both systems was achieved on a TSK gel ODS-80 TM (15 cm x 4.6 mm ID, TosoHaas) column using a mobile phase consisting of acetonitrile/20 mM potassium dihydrogen phosphate.

All method validation assays at the various laboratories reported:

- LLOQ of 0.05 µg/mL and a calibration range of 0.05 – 25 µg/mL for FK463
- LLOQ of 0.05 µg/mL and a calibration range of 0.05 – 10 µg/mL for its metabolites M1 and M2
- LLOQ of 0.05 µg/mL and a calibration range of 0.05 – 10 µg/mL for its metabolite M5

The precision and accuracy of the method were within acceptance criteria for each validation report [Table 2.6.1-2], and show that the analytical method used in the clinical studies with pediatric patients was valid for the determination of micafungin and its metabolites in human plasma.

Table 2.6.1-2. High Performance Liquid Chromatography Fluorescence Detection Assays for Micafungin and Metabolites in Human Plasma, Precision and Accuracy in Method Validation

Report Parameter	FK463	M1	M2	M5
	160/2002(A)			160/2002(B)
Intrabatch precision (CV%)	1.8% – 8.0%	2.1% – 7.8%	2.2% – 7.8%	0.8% – 6.9%
Intrabatch accuracy (% nom)	93.7% – 107.3%	91.9% – 105.1%	88.1% – 108.0%	88.7% – 106.7%
Interbatch precision (CV%)	3.6% – 6.7%	3.7% – 6.3%	4.1% – 6.9%	2.0% – 8.1%
Interbatch accuracy (% nom)	91.5% – 100.8%	90.5% – 100.1%	87.1% – 100.1%	94.2% – 100.0%
	6332-155			6332-214
Intrabatch precision (%RSD)	0.5% – 5.2%	0.4% – 14.4%	0.4% – 15.0%	2.0% – 4.9%
Intrabatch accuracy (%DMT)	0.8% – 5.3%	-4.7% – 2.9%	-0.1% – 12.7%	0.0% – 6.6%
Interbatch precision (%RSD)	2.8% – 3.6%	2.6% – 9.1%	2.6% – 9.5%	2.5% – 4.2%
Interbatch accuracy (%DMT)	2.5% – 3.3%	-2.0% – 1.2%	2.7% – 7.3%	0.7% – 4.9%

FK463: micafungin; M1, M2, M5: metabolites of micafungin; % nom: percentage of the nominal concentration; CV%: coefficient of variation; %RSD: percent relative standard deviation; %DMT: percent deviation of the mean from theoretical.

In Study 9463-CL-2101, the results from the validated method assayed at (b) (4) showed very low exposures in some samples obtained from clinical sites in South Africa. Astellas investigated the possibility that these low exposures could be related to the bioanalysis. A non-GLP, validated method using liquid chromatography with mass spectrometric detection was used to analyze FK463 in plasma of pediatric patients from these sites. The results of this non-GLP investigation were consistent with the results of the (b) (4) assay, and it was concluded that the low exposures were not related to the bioanalysis. These results are under investigation by the OSI and the review is pending.

Method Validation for Determination of Micafungin and its M5 Metabolite in Human Plasma via LC/MS (Study 9463-CL-2104)

Different analytical methods were used for Study 9463-CL-2104 due to the small sample volume obtained from the neonates and young infants in the study. Astellas validated a method for the measurement of FK463 and M5, and (b) (4) validated a method for the measurement of FK463. In these validated methods, plasma samples were separated from whole blood using protein precipitation. Acetonitrile (150 µL) was used for extraction of analyte from the plasma matrix (sample volume: 10 µL). The samples were centrifuged at approximately 3000 rpm for about 5 minutes. The supernatant (100 µL) was mixed with 10 mmol/L ammonium acetate (100 µL). This solution was also centrifuged at approximately 3000 rpm for about 5 minutes, and 5 µL of the supernatant injected directly into the LC/MS system. Separation was achieved on a Genesis C18 (50 mm x 4.6 mm ID) column using a mobile phase consisting of acetonitrile and 10 mM ammonium acetate in water.

These method validation assays had a LLOQ of 0.05 µg/mL and a calibration range of 0.05 to 25 µg/mL for FK463 (Astellas and (b) (4)) and its metabolite M5 (Astellas). The precision and accuracy of the methods were within acceptance criteria for each validation report [Table 2.6.1-3], and show that the analytical methods used in this clinical study of neonates and young infants was valid for the determination of micafungin and its metabolite M5 in human plasma.

Table 2.6.1-3. Liquid Chromatography/Mass Spectrometry Assays for Micafungin and M5 in Human Plasma, Precision and Accuracy in Method Validation

Report Parameter	FK463	M5
MS-2009-009		
Intrabatch precision (%CV)	2.3% – 10.2%	2.5% – 14.7%
Intrabatch accuracy (%RE)	-6.1% – 9.3%	-11.2% – 8.1%
Interbatch precision (%CV)	4.5% – 8.2%	6.3% – 12.7%
Interbatch accuracy (%RE)	0.1% – 6.9%	-3.7% – 5.2%
6332-247		
Intrabatch precision (%RSD)	3.0% – 7.6%	NA
Intrabatch accuracy (% nom)	89.0% – 104.7%	NA
Interbatch precision (%RSD)	5.4% – 6.3%	NA
Interbatch accuracy (% nom)	94.0% – 99.3%	NA

FK463: micafungin; M5: metabolite of micafungin; CV%: coefficient of variation; %RE: percent relative error; %RSD: percent relative standard deviation; % nom: percentage of the nominal concentration.

2.6.1.1. What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used?
See above section 2.5.1

2.6.1.2. What are the lower and upper limits of quantification (LLOQ/ULOQ)?
See above section 2.5.1

2.6.1.3. What are the accuracy, precision, and selectivity at these limits?
See above section 2.5.1

2.6.1.4. What is the sample stability under the conditions used in the study (long-term, freeze-thaw, sample-handling, sample transport, autosampler)?
Stability of the short-term and long-term storage of plasma samples at -60 to -80°C was established. For freeze-thaw matrix stability, six replicates of low QC (LQC) and high QC (HQC) samples were subjected to three freeze-thaw cycles. The mean accuracy of each concentration was in the range of 85-115% of the theoretical concentration. For room temperature matrix stability, six replicates of LQC and HQC samples were processed after storage at room temperature for at least 24 hours. The mean accuracy of each concentration was in the range of 85-115% of the theoretical concentration. For long-term stability, six replicates of the LLOQ, LQC and MQC samples were extracted after storage for 112 days. The QC results indicated that the mean accuracy was in the range of 85-115%.

3. Appendix-A: LABELING RECOMMENDATIONS

The label will be filed in DARRTS separately after agreement with the sponsor on the specific wording.

4. Appendix-B: Pharmacometric Review

The population PK model of micafungin in pediatric patients was developed by the sponsor and was used to simulate pediatric micafugin exposure at steady state in order to investigate different candidate doses. The development and validation of the proposed population PK model are summarized below and were found acceptable from the perspective of Clinical Pharmacology.

4.1. Population PK modeling

Model Development

The data used to develop the population PK models came from 4 pediatric phase I studies (9463-CL-2101, 9463-CL-2102, 9463-CL-2103, and 98-0-043) and 2 pediatric phase III studies (FG-463-21-08 and FJ-463-FP01). A brief summary of the study designs is given below:

1. 9463-CL-2101 (N=78): Open-label study of the safety and PK of repeated dose 1- hour infusions of 3.0 mg/kg (weight ≥ 25 kg) or 4.5 mg/kg (weight < 25 kg) micafungin for a minimum of 10 consecutive days to a maximum of 14 consecutive days in children (2-5 years and 6-11 years) and adolescents (12-16 years) with esophageal candidiasis or other invasive candidiasis.

2. 9463-CL-2102 (N=9): Open-label study of the safety and PK of repeated dose 1-hour infusions of 4.5 mg/kg micafungin for a minimum of 10 consecutive days to a maximum of 14 consecutive days in infants and toddlers (≥ 4 months - < 2 years of age) with esophageal candidiasis or other invasive candidiasis.

3. 9463-CL-2103 (N=40): Open-label study of the safety and PK of repeated dose 1- hour infusions of 1.5 mg/kg (weight < 25 kg) or 1.0 mg/kg (weight ≥ 25 kg) micafungin for a minimum of 10 consecutive days to a maximum of 14 consecutive days as antifungal prophylaxis in children and adolescents (4 months - 16 years) undergoing hematopoietic stem cell transplantation.

4. 98-0-043 (N=74): Open-label, sequential group, dose escalation (maximum tolerated dose), and PK study in febrile, neutropenic pediatric patients (2-17 years) dosed once daily for 4 days, 1-hour infusion of 0.5, 1, 1.5, 2, 3 or 4 mg/kg/day micafungin (maximum 200 mg/day).

5. FJ-463-FP01 (N=20): Open-label study evaluating the safety, PK and efficacy of micafungin in pediatric patients (8 months - 15 years) with deep seated mycosis due to *Aspergillus* or *Candida* spp. administered once daily, 1-hour infusion (or longer) of micafungin at an initial dose of 1.0 mg/kg/day, with dose escalation up to a maximum of 6.0 mg/kg/day.

6. FG-463-21-08 (N=56): Randomized (1:1), double-blind, micafungin vs. AmBisome® in patients (including children 0-15 years) with candidemia or invasive candidiasis administered once daily, 1-hour infusion; 100 mg/day micafungin (2 mg/kg/day ≤ 40 kg weight) or 3 mg/kg/day AmBisome®.

Base model: The modeling for micafungin began by applying the model used in earlier work (NDA 21- 506, July 14, 2011, Sequence Number 0025). The initial model (model: c511) was a 2-compartment model parameterized by clearance (CL), volume of central compartment (V1), intercompartmental clearance (Q), and volume of peripheral compartment (V2). A log-normal random effect was assumed for inter-subject variability on each PK parameter and a mixture of proportional and absolute random errors was assumed for residual error models on plasma analyte concentration data, respectively, as shown in Equations 1 and 2 below.

$$CL_j = CL_{pop} \times \exp(\eta_j) \quad (1)$$

$$C_{obs,ij} = C_{pred,ij} \times (1 + \varepsilon_{prop\ ij}) + \varepsilon_{abs\ ij} \quad (2)$$

Here CL_j is a model parameter (clearance, in the example) for the j^{th} subject, CL_{pop} is the typical value of the parameter in the population, and η_j is a random variable representing inter-subject variability of the parameter, with mean 0 and variance ω^2. The variables $C_{obs,ij}$ and $C_{pred,ij}$ represent the i^{th} observed and predicted analyte concentrations, respectively, for the j^{th} subject, and $\varepsilon_{prop\ ij}$ or $\varepsilon_{abs\ ij}$ are the proportional or absolute random residual errors, which are normally distributed with mean 0 and variance σ_{prop}^2 or σ_{abs}^2.The process was guided through inspection of objective function values derived using the first order conditional estimation with interaction (FOCEI) method in NONMEM, as well as examination of diagnostic plots for assessing the goodness of fit.Based on the final base model, individual post-hoc empirical Bayes estimates were obtained. Normality of the distributions of these estimates were assessed graphically.

Covariate model building: Effects of covariates were modeled, typically using the following equations (Equations 3 and 4) for continuous and binary variables, respectively.

$$CL_{pop|X=Xj} = CL_{pop|X=Xpop} \times \exp(\theta_{power} \times \ln(X_j/X_{pop})) \quad (3)$$

$$CL_{pop|Z=Zj} = CL_{pop|Z=0} \times \theta_{ratio}^{Z_j} \quad (4)$$

Here X_j and Z_j are a continuous variable and an indicator variable for the j^{th} subject, respectively, and θ (θ_{power} or θ_{ratio}) is a fixed effect parameter describing the strength of the covariate effect. The X_{pop} is a representative value of X in the population, which is the population median or some arbitrary value close to the median, which was to be used for imputation for a missing value of a continuous covariate. Z_j has a value of 1 when the j^{th} subject belongs to the category and otherwise has a value of 0. Exploration of covariates was conducted based on a step-wise forward addition and backward deletion strategy in NONMEM. Significance of covariates was judged on the basis of a log likelihood ratio test at an acceptance p-value of 0.05 and 0.01 for the forward addition and backward deletion methods, respectively. The model containing only the covariates that meet the above statistical criteria was considered the final population pharmacokinetic model.

The influences of key covariates on exposure were explored, with continuous covariates varied to the 10th and 90th percentiles of the population, keeping all other covariates at nominal values. The effects of the following demographic and laboratory variables on each model parameter were investigated: Sex (SEX), Age (AGE), Body weight (WGT), Albumin (ALB), Platelet (PLT), Red blood cells (RBD), Serum creatinine (CRE), Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), and Total bilirubin (TBL).

Final model: Similar to the assessment of the base model, a graphical assessment using goodness of fit plots was conducted to confirm the adequacy of the final model. In addition, the empirical Bayes residuals in model parameters from the final model for those in which a significant relationship with a covariate was seen were plotted against the relevant covariates to examine if any trend still existed.

Model validation: An internal validation of the final population PK model was performed using a nonparametric bootstrap resampling technique. Parameter estimates, along with the estimation errors, were examined to ensure that they were well-estimated and plausible. Only those models that minimized successfully were used in the calculation of the nonparametric confidence interval.Using SAS, three hundred bootstrap datasets were constructed based on random sampling with replacement of patients' analyte data. For a given bootstrap dataset, the final model was fit to the data and the population PK parameters were estimated. This exercise was repeated with 300 bootstrap data sets to obtain more than 200 sets of bootstrap parameter estimates with successful convergence. For each model parameter, bootstrap estimates were summarized to obtain means, standard deviations, and non-parametric 95% confidence intervals (the lower and upper limits of the CI are the approximate 2.5 and 97.5 percentiles, respectively). The adequacy of the parameter estimates of the final model was examined by comparing with the summary statistics of the bootstrap estimates.

Results

Base model: A two compartmental base model fit the micafungin data well. The base model had one random effect on each of CL, V1, Q, and V2 and two different proportional error terms based on whether or not the data were from South Africa, and a constant error term for all the data. During preliminary modeling, correlations between CL, V1, Q, and V2 were seen; hence, a common random effect on each of CL, V1, Q, and V2 was included. It was also established (see NDA 21-506, July 14, 2011, Sequence Number 0025) that body weight well explains the differences in PK parameters between different age cohorts in pediatrics. Therefore, the fixed effect of WGT as a basic structure of the pediatrics' micafungin base model has been included to handle the large variation in body size in the pediatric population. Figure 1 provides a schematic of the base model for micafungin.

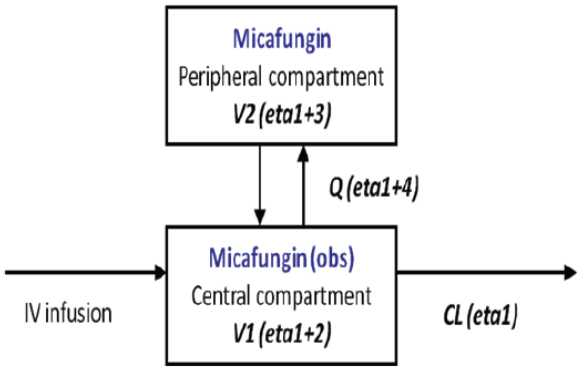


Figure 1. Base model for Micafungin

The parameter estimates and their estimation errors are listed in Table 3 (see below) and the diagnostic plots are shown in Figure 2. The parameters were typically well estimated. The model predictions of plasma micafungin concentrations show good agreement with the observed data.

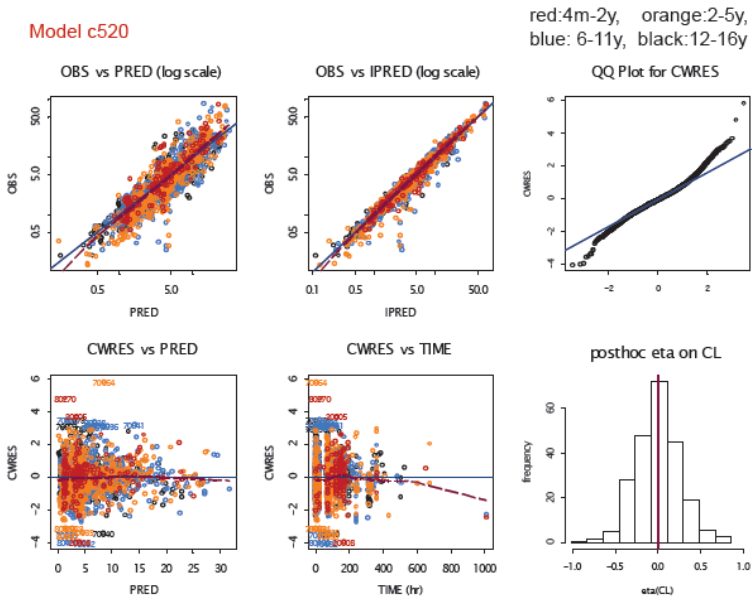


Figure 2. Diagnostic plots for the base model for micafungin

Covariate model building for micafungin: As a result of covariate screening, potential correlations of the Bayes residuals with covariates listed in Table 1 were suggested. These candidate Bayes residual/covariate pairings were selected to be further investigated via a forward addition algorithm.The process of the forward addition is also summarized in Table 1. The effect of AST on CL showed the strongest significance (p = 0.0019) among the covariates investigated and was included in the base model. Secondly, the effect of ALT on CL was recognized as the next strongest covariate (p = 0.0040) and thus included in the model. The effect of TBL on CL was the next strongest covariate (p = 0.0071) and included in the model. None of the remaining covariates met the 0.05 significance level criterion for inclusion and, hence, no further forward addition evaluation was performed.

In the second step, AST and ALT on CL were added to the base model. The result was not statistically significant (p = 0.2817). Next, AST and TBL on CL were added to the base model. The result was statistically significant (p = 0.0053). In the backward deletion process, AST was deleted from the model that extended the base model to include both AST and TBL on CL. The result was statistically significant (p = 0.0014) and met the 0.01 significance level criterion for inclusion. This process was repeated for TBL, and the outcome was also statistically significant (p = 0.0053).

The final model, therefore, is an extension of the base model to include AST and TBL on CL.

Table 1. Process of forward addition and backward deletion for assessment of covariates in the micafungin population model

Step	Model	Covariate model	OFV	ΔOFV	ΔDF	p-value	
Forward	c520	(base model)	2072.864	—	—	—	
Addition	c536	AST on CL	2063.178	-9.686	1	0.0019	*
(Step 1)	c534	ALT on CL	2064.585	-8.279	1	0.0040	*
	c538	TBL on CL	2065.626	-7.238	1	0.0071	*
	c529	PLT on V1	2069.472	-3.392	1	0.0655	
	c539	TBL on V1	2069.655	-3.209	1	0.0732	
	c528	PLT on CL	2070.259	-2.605	1	0.1065	
	c537	AST on V1	2070.638	-2.226	1	0.1357	
	c535	ALT on V1	2071.734	-1.130	1	0.2878	
	c532	CREAT on CL	2071.993	-0.871	1	0.3507	
	c524	ALB on CL	2072.219	-0.645	1	0.4219	
	c530	RBC on CL	2072.428	-0.436	1	0.5091	
	c523	AGE on V1	2072.491	-0.373	1	0.5414	
	c533	CREAT on V1	2072.565	-0.299	1	0.5845	
	c521	SEX on CL	2072.772	-0.092	1	0.7616	
	c540	SEX on V1	2072.781	-0.083	1	0.7733	
	c525	ALB on V1	2072.786	-0.078	1	0.7800	
	c531	RBC on V1	2072.809	-0.055	1	0.8146	
	c522	AGE on CL	2072.846	-0.018	1	0.8933	
(Step 2)	c536	AST on CL	2063.178	—	—	—	
	c542	AST/TBL on CL	2055.392	-7.786	1	0.0053	*
	c541	AST/ALT on CL	2062.019	-1.159	1	0.2817	
Backward	c542	AST/TBL on CL	2055.392	—	—	—	
Deletion	c538	delete AST	2065.626	10.234	-1	0.0014	#
	c536	delete TBL	2063.178	7.786	-1	0.0053	#

*: Meet criteria of selection for next step

#: Selection for final model

OFV: Objective function value

DF: Degrees of freedom

An investigation of the relationship between AMT (micafungin dose) and η for CL or a relationship between AMT and η for V1 revealed statistically non-significant relationships. This suggests that neither model parameter changes with dose, or that there is a dose-linearity evident in the pediatric population. An investigation was made to determine whether or not the fixed effect model term involving WGT scaling fully explains the PK difference between the four age cohorts (Table 2). The term AGEGG represents the mean relative changes from reference cohort 12-16y of each of the other three age cohorts. The lack of any statistical significance suggests the weight scaling term does its desired function.

Table 2. Determination of the adequacy of weight scaling

Model	Model Description	OFV	ΔOFV	ΔDF	p-value
c545	AGEGG on CL	2053.393	-1.999	3	0.5726
c546	AGEGG on V1	2053.286	-2.106	3	0.5507
c547	AGEGG on V2	2053.801	-1.591	3	0.6614
c548	AGEGG on Q	2050.430	-4.962	3	0.1746

Micafungin final model: The final model was constructed from the base model including the fixed effects of AST and TBL on CL. The parameter estimates of the final model are shown in Table 3, in addition to those from the base model. The estimation errors of the estimates were adequately low, in general.

The diagnostic plots are shown in Figure 3. Good agreement between the observations and the model predictions suggested the final model adequately fit the data. No obvious trend remained, suggesting the covariate model adequately described the effect of AST and TBL on CL.

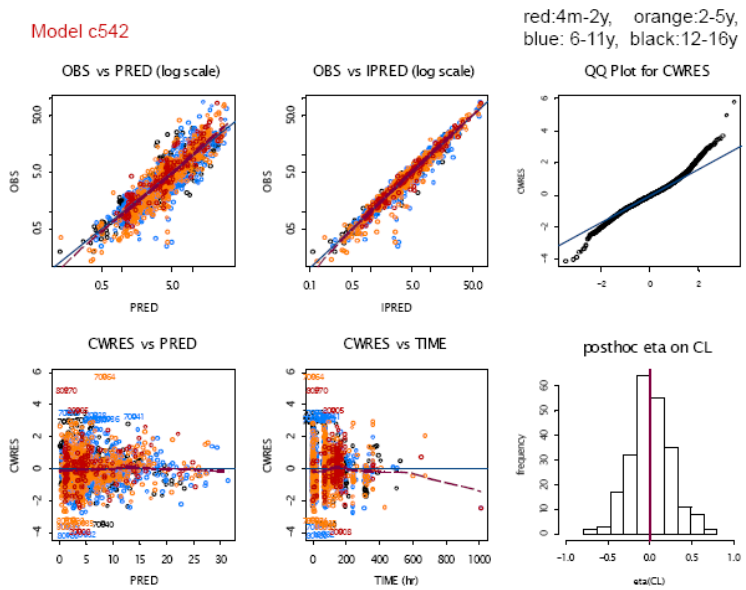


Figure 3. Diagnostic plots for the final model for micafugin

Table 3. Parameters estimates of final and base models

Parameter		Final Model		Base Model	
		Estimate	Error (CV%)	Estimate	Error (CV%)
Structural PK	CL (L/hr)	0.356	2.5	0.369	2.2
	V1 (L)	1.21	10.7	1.21	14.4
	Q (L/hr)	5.54	12.7	5.54	13.9
	V2 (L)	4.62	3.2	4.62	3.4
	power_WGT	0.787	3.7	0.790	4.0
	fixed_AST	-0.0601	-36.6	NA	
	fixed_ TBL	-0.0492	-47.0	NA	
eta_CLbase		0.0763	12.0	0.0835	13.1
eta_addV1		0.953	18.6	0.967	18.4
eta_addQ		1.52	13.1	1.52	13.9
eta_addV2		0.0277	40.1	0.0276	39.9
err_prop		0.0313	8.2	0.0313	8.2
err_prop SA		0.130	21.8	0.129	21.7
err_abs		0.00461	54.9	0.00443	56.7
OFV		2055.392		2072.864	

Based on the covariate model (Equation 5), individual CL (CLj) was expressed as follows:

$$CLj = 0.356 \times (WGT_j/21.5)^{0.787} \times (AST_j/50)^{-0.0601} \times (TBL_j/12)^{-0.0492} \qquad (5)$$

where WGT_j, AST_j, and TBL_j are the j^{th} individual's WGT, AST, and TBL values at baseline. In particular, 0.356 (L/hr) is the population mean CL for a typical patient weighing 21.5 kg, with an AST value of 50 U/L, and a total bilirubin value of 12 μmol/L. Inter-subject variability (CV%) in CL is 28%. Comparing the estimate of variance for CL from the final model, which includes the two additional covariates (AST, TBL), and the estimate of variance for CL from the base model explains < 10% [8.6%=(0.0763-0.0835)/0.0835)] of the remaining random effect on CL. From the equation for clearance above, one can infer that there is a tendency toward larger micafungin clearance in heavier patients. However, weight adjusted micafungin clearance (CL/WGT) is expected to have much less dependency on body weight in comparison to that of CL, though CL/WGT will tend to be slightly smaller in heavier patients. Furthermore, patients with larger AST or TBL will tend to have smaller micafungin clearances. For example, a value of AST of 750 U/L is expected to reduce CL by 15% from the typical value. Larger values of these laboratory parameters are seen in patients with poor bile flow, which is the major pathway for micafungin excretion.

Micafungin model validation: The final micafungin model was internally validated using a nonparametric bootstrap with resampling approach that randomly sampled with replacement 300 data sets from the final analysis dataset. There was successful convergence for the fitting of the final model to 243 data sets, resulting in 243 data sets that each contained estimates of the final model parameters. The bootstrap estimate (mean) and 95% CI for each parameter are shown in Table 4, along with the final model's estimates and the 95% CIs based on the estimation error. The close similarity in the means and the 95% CIs of the bootstrap estimates and final model estimates for not only the fixed effect parameters but also the random effect parameters indicated reliability of the parameter estimates, as well as stability of the final model.

Table 4. Bootstrap estimate of final micafungin model

Parameter		Bootstrap (n=243)		Final Model	
		estimate	95% CI	estimate	95% CI
Structural PK	CL (L/hr)	0.356	0.338 — 0.373	0.356	0.338 — 0.373
	V1 (L)	1.21	0.796 — 1.67	1.21	0.951 — 1.46
	Q (L/hr)	5.65	3.80 — 7.83	5.54	4.16 — 6.92
	V2 (L)	4.64	4.18 — 5.02	4.62	4.33 — 4.90
	power_WGT	0.782	0.719 — 0.843	0.787	0.730 — 0.844
	fixed_AST	-0.0623	-0.117 — -0.0180	-0.0601	-0.103 — -0.0170
	fixed_ TBILI	-0.0493	-0.0937 — -0.00652	-0.0492	-0.0944 — -0.00393
eta_CLbase		0.0752	0.0583 — 0.0952	0.0763	0.0584 — 0.0943
eta_addV1		0.878	0.513 — 1.28	0.953	0.606 — 1.30
eta_addQ		1.48	1.00 — 1.99	1.52	1.13 — 1.91
eta_addV2		0.0265	0.00800 — 0.0521	0.0277	0.00590 — 0.0494
err_prop		0.0313	0.0268 — 0.0365	0.0313	0.0263 — 0.0364
err_prop SA		0.129	0.0786 — 0.178	0.130	0.0742 — 0.185
err_abs		0.00464	0.000761 — 0.0107	0.00461	0 — 0.00956

Reviewer Assessment:
The population PK model for micafungin in pediatric patients was developed by the sponsor and was used to simulate pediatric micafugin exposure at steady state in order to investigate different candidate doses. From the perspective of Clinical Pharmacology, the development and validation of the proposed population PK model are acceptable and the model is considered adequate for simulation of dosing regimens for micafungin in pediatric patients.

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/s/

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