NDA Multi-Disciplinary Review and Evaluation

Application Type	Efficacy Supplement
Application Number(s)	021506/S-023
Priority or Standard	Priority
Submit Date(s)	6/7/19
Received Date(s)	6/7/19
PDUFA Goal Date	12/7/19
Office/Division	CDER/OND/Office of Infectious Disease/Division of Anti-Infectives
Review Completion Date	12/18/19
Established/Proper Name	Micafungin
Trade Name	MYCAMINE
Pharmacologic Class	Echinocandin antifungal drug
Applicant	Astellas Pharma US, Inc.
Dosage form	Injection in single dose vials
Applicant proposed Dosing Regimen	10 mg/kg/day
Applicant Proposed Indication(s)/Population(s)	Treatment of (b) (4) Candidiasis in Neonates and Young Infants (Less than 4 Months of Ag (b) (4)
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	70572005 |Disseminated candidiasis (disorder) 414821002 | Neonatal candidiasis (disorder)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of Candidemia, Acute Disseminated Candidiasis, *Candida* Peritonitis and Abscesses **without** meningoencephalitis and/or ocular dissemination in pediatric patients younger than 4 months of age. Limitations of Use • The safety and effectiveness of MYCAMINE have not been established for the treatment of candidemia ***with*** meningoencephalitis and/or ocular dissemination in pediatric patients younger than 4 months of age as a higher dose may be needed. • MYCAMINE has not been adequately studied in patients with endocarditis, osteomyelitis or meningoencephalitis due to *Candida.* • The efficacy of MYCAMINE against infections caused by fungi other than *Candida* has not been established.
Recommended Dosing Regimen	4 mg/kg/day IV

Table of Contents

Table of Tables

Table of Figures

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Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
DMEPA	Division of Medication Error Prevention and Analysis
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonisation
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity

OCS	Office of Computational Science
OPDP	Office of Prescription Drug Promotion
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert (also known as Patient Information)
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

Micafungin is an intravenous echinocandin antifungal drug that inhibits synthesis of (1,3)-β-D-glucan, an important component of the fungal cell wall. It is given once daily, does not require dose adjustment for renal or hepatic insufficiency, and is active against most isolates of *Candida albicans, C. glabrata, C. krusei, C. parapsilosis, C. tropicalis, and C. guillermondii*.

Micafungin is approved for the treatment of candidemia, acute disseminated candidiasis, *Candida* peritonitis and abscesses and esophageal candidiasis in adults and children 4 months of age and older, and for prophylaxis of *Candida* infections in adults receiving hematopoietic stem cell transplant.

In sNDA 21506, the Applicant is seeking the indications for treatment of (b) (4) candidiasis, candidemia (b) (4) neonates and infants younger than 4 months of age (b) (4).

1.2. Conclusions on the Substantial Evidence of Effectiveness

The pathophysiology of candidemia and disseminated candidiasis in infants younger than 4 months of age is unique because of the high frequency of central nervous system (CNS) involvement, specifically meningoencephalitis, which is often associated with severe immediate and long-term morbidity, neurological sequelae, and mortality. Micafungin is currently labeled for a maximum dose of 3 mg/kg/day in pediatric patients 4 months of age and older. A relevant rabbit model of hematogenous *Candida* meningoencephalitis (HCME), described fully in Sections 6 and 9 demonstrated significant dose-dependent reduction in fungal burden in several CNS compartments, (b) (4) 10 mg/kg for treatment of invasive candidiasis and meningoencephalitis in patients younger than 4 months of age. However, due to insufficient clinical and nonclinical data supporting a 10 mg/kg/day dose for the indications of candidemia and acute disseminated candidiasis *with* meningoencephalitis, micafungin will be approved at a dose of 4 mg/kg/day for treatment of candidemia, acute disseminated candidiasis, *Candida* peritonitis and abscesses *without* meningoencephalitis in this population. The evidence and rationale supporting this conclusion is outlined in the following paragraphs.

Based on evidence from adequate and well-controlled studies in adult and pediatric patients 4 months of age and older and pharmacokinetic and safety data in patients younger than 4 months of age, a dose of 4 mg/kg/day was established for the treatment of candidemia, acute disseminated candidiasis, *Candida* peritonitis and abscesses *without* meningoencephalitis and ocular dissemination in patients younger than 4 months. Potential target populations for this dosing regimen may include full-term neonates and young infants < 4 months of age with line-associated candidemia and/or those with toxicity or resistance to

other drugs such as fluconazole or amphotericin for whom additional effective treatment options are essential.

The Applicant sought to establish efficacy and safety of micafungin for neonatal candidiasis in a Phase 3 trial comparing 21-day regimens of micafungin 10 mg/kg/day to amphotericin B 1 mg/kg/day in patients younger than 4 months of age. Because only 20/150 and 10/75 patients planned in the micafungin and amphotericin arms, respectively, were enrolled after 2 years, the trial was terminated, and additional sources of data were sought to support the safety and efficacy of micafungin for this age group.

The Applicant obtained right of reference to data from two Italian investigator-initiated open-label studies of micafungin in neonates and young infants with invasive candidiasis and *Candida* meningoencephalitis, that included 40 patients younger than 4 months treated with micafungin doses of 5-15 mg/kg/day. Additional neonatal data were obtained from the Pediatrix consortium database, containing information from more than 300 neonatal ICUs (NICUs) in the U.S., a previously conducted Phase 3 trial (Study 2108), and 4 other Phase 1 and Phase 2 open-label studies. In aggregate, data on 244 neonates and infants younger than 4 months were available from these 9 studies. Dosing regimens were specified in 168 of them; 22 infants received micafungin for ≥ 14 days, likely the minimum duration needed to treat CNS disease. Ten neonates and young infants received doses higher than 10 mg/kg/day – 5 each received >11<15 mg/kg/day and 15 mg/kg/day, 80% of patients in both dosing groups were treated for ≥ 14 days.

In the entire clinical development program, only 6 infants had proven CNS disease – 5 of them were < 4 months of age and 1 was 5.4 months old. Five of these patients were treated with micafungin alone but with varying doses of 2 and 10 mg/kg/day. Thus, the study population of patients younger than 4 months of age that received the proposed dose of 10 mg/kg/day for (b) (4) candidiasis and *Candida* meningoencephalitis was very limited and insufficient to establish safety and efficacy.

Analysis by the clinical pharmacology team of published data using the rabbit HCME model (detailed in the OCP Appendix and Section 6) showed that a statistically significant reduction in fungal burden in cerebrum, cerebellum and spinal cord was achieved at doses of 16-32 mg/kg/day and that equivalent human neonatal exposures would be achieved with doses of 11-27mg/kg/day. The clinical team noted that the safety profile of micafungin at doses of up to 15 mg/kg/day (the highest dose administered in supportive studies) in neonates < 4 months of age was similar to the safety profile noted in older children and adults, especially adults undergoing hematopoietic stem cell transplant (HSCT); TEAEs occurring at frequencies of ≥ 15% included anemia, thrombocytopenia, hypokalemia, and renal failure.

Given the difficulty of conclusively ruling out *Candida* meningoencephalitis in premature and often clinically unstable patients < 4 months of age with candidemia and the potential adverse consequences of under-treatment with a dose of 4 mg/kg/day, it was considered important to

include relevant information on fungal burden reduction obtained from the rabbit model of HCME as well as a brief summary of existing neonatal safety data for micafungin doses from 5-15 mg/kg/day in labeling. A limitation of use is included in labeling to clarify that micafungin is not approved for the treatment of meningoencephalitis and/or ocular disease.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

In this supplemental new drug application (sNDA), the Applicant is seeking approval of Mycamine (micafungin sodium) (b) (4) for the treatment of (b) (4) candidiasis in neonates and young infants (less than 4 months of age), including candidemia (b) (4).

Mycamine is approved for treatment of candidemia, disseminated candidiasis, *Candida* peritonitis, (b) (4) abscesses, esophageal candidiasis, and for prophylaxis of *Candida* infections in undergoing hematopoietic stem cell transplants in adult and pediatric patients 4 months of age and older. Current standard of care for neonatal candidiasis with meningoencephalitis consists of triazoles and amphotericin B. Based on a rabbit model of hematogenous *Candida* meningoencephalitis (HCME) that demonstrated a dose-dependent reduction in fungal burden in cerebrum and cerebellum, (b) (4)

The Applicant attempted to conduct a Phase 3 trial comparing 21-day regimen of micafungin 10 mg/kg/day to amphotericin B 1 mg/kg/day in patients younger than 4 months with candidemia, acute disseminated candidiasis, and suspected meningoencephalitis. Planned enrollment was 225 patients (150 in the micafungin arm and 75 in amphotericin B arm), but after just 20 and 10 subjects in the micafungin and amphotericin B arms, respectively, were enrolled over 2 years, the trial was terminated. As the trial is underpowered, no conclusions could be drawn regarding efficacy. The Applicant obtained right of reference to data from two Italian investigator-initiated open-label studies of micafungin in neonates and young infants with invasive candidiasis and *Candida* meningoencephalitis. Study 9463-CL-6001 was a phase 2 prospective, open-label, uncontrolled study and included 28 infants <120 days of age treated with micafungin at 8 mg/kg/day, and Study 9463-CL-6002 was a phase 2 retrospective analysis that included 12 patients <120 days of age treated with micafungin at 5-15 mg/kg/day. Other supportive studies included a retrospective database analysis of patients from over 300 NICUs in the U.S. (Study 9463-CL-7001 – Pediatrix database) and other phase 1-3 studies (9463-CL-2104, 98-0-046, 98-0-047, 99-0-063, FG-463-21-08) using varying doses of micafungin.

Although data on 244 neonates and infants younger than 4 months were available from these 9 studies, pooled analysis could not be conducted due to varying study designs and endpoints, and missing data. Dosing regimens were specified for 168 neonates, of these, 22 received micafungin for ≥14 days. Ten neonates and young infants received doses higher than 10 mg/kg/day (11-15 mg/kg/day) Across 9 studies, only 6 patients had proven or suspected CNS disease – 5 of them were < 4 months of age, and 1 was 5.4 months of age. Five of these patients were treated with micafungin alone at doses of either 2, 8 or 10 mg/kg/day. CSF PK samples were available for 4 patients.

Data submitted to the sNDA are sufficient to support a dose of 4 mg/kg/day for the treatment of candidemia, acute disseminated candidiasis, *Candida* peritonitis and abscesses without meningoencephalitis in patients less than 4 months of age based on evidence from adequate and well-controlled studies in adult and pediatric patients 4 months of age and older and pharmacokinetic and safety data in patients younger than 4 months of age. Potential target populations for this dosing regimen may include full-term neonates and young infants <4 months of age with line-associated candidemia and/or those with toxicity or resistance to other drugs such as fluconazole or amphotericin B for whom additional effective treatment options are essential. However, because the risk of CNS dissemination is high in premature, ill

infants with candidemia, a dose of 4 mg/kg/day may be insufficient. Thus, micafungin at 4 mg/kg/day should only be considered for patients younger than 4 months of age with candidemia or disseminated candidiasis in whom meningoencephalitis has been ruled out.

The data are insufficient to establish the efficacy of micafungin 10 mg/kg/day (b) (4). For the treatment of meningoencephalitis, efficacy cannot be extrapolated from adults or older pediatric patients and data from adequate and well-controlled trials are not available to conclude the efficacy of 10 mg/kg for the treatment of ME. In the rabbit model of HCME, statistically significant reduction in fungal burden in rabbit cerebrum, cerebellum and spinal cord were observed over micafungin dose regimens of 16-32 mg/kg/day corresponding to dose regimens of approximately 10-25 mg/kg/day in infants younger than 4 months (see Section 6). However, the correlation between fungal burden decline and outcome was not assessed in nonclinical studies. Thus, it is unclear whether the 10 mg/kg dose is optimal for treatment of ME in infants younger than 4 months.

Across the 9 clinical studies submitted to this sNDA, the highest administered neonatal dose was 15 mg/kg/day. No death or discontinuation in these studies was clearly attributable to micafungin in this often premature and ill patient population receiving multiple concomitant medications and with several comorbidities; similarly, although serious adverse events and treatment emergent adverse events (TEAEs) were common in all studies, causality was difficult to adjudicate. TEAEs occurring at a frequency of >15% in pediatric patients younger than 4 months who received micafungin 5-15 mg/kg/day for at least 7 days included anemia, thrombocytopenia, elevated transaminases, elevated GGT, and cholestasis. A dose-response for safety was not observed with increasing doses of micafungin, but as noted, analysis was limited by small sample sizes, missing data and inconsistent collection of safety data.

While extending the indication of treatment of candidemia, acute disseminated candidiasis, *Candida* peritonitis and abscesses in patients younger than 4 months, it is important to emphasize that micafungin at a dose of 4 mg/kg may be insufficient to treat ME and should be used only in those patients in whom ME and ocular involvement has been ruled out. A limitation of use to convey this information is included in labeling. Given the difficulty of conclusively ruling out Candida meningoencephalitis in premature and often unstable patients <4 months of age with candidemia and the potential adverse consequences of under-treatment with dose of 4 mg/kg/day, relevant information on reduction in fungal burden demonstrated in the rabbit model of HCME as well as a brief summary of existing neonatal safety data for micafungin doses from 5-15 mg/kg/day is included in labeling.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Patients younger than 4 months with candidemia are at high risk for hematogenous dissemination to specific end organs such as CNS, eye, and liver resulting in meningoencephalitis, retinal disease and hepatosplenic candidiasis • There is unmet need for safe and effective antifungal drugs for these conditions • Meningoencephalitis can lead to significant immediate and delayed morbidity, neurological sequelae and mortality • CNS and ocular disease are difficult to diagnose; existing diagnostic modalities for these	Effective and safe antifungal drugs for treatment of infants younger than 4 months with candidemia and end-organ dissemination, particularly to the CNS, is an unmet need.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	infection sites include lumbar puncture, CSF and blood cultures, imaging, serial measurement of plasma β-D-glucan and retinal examination • These investigations are difficult to perform in sick and unstable neonates, so treatment is often empirical • Treatment of candidemia in patients younger than 4 months must therefore be effective for treatment of undiagnosed CNS or ocular infection. Nonclinical data, particularly from the rabbit model of hematogenous Candida meningoencephalitis, underscores the need for much higher doses of micafungin for treatment of CNS disease than currently labeled • Statistically significant, dose-dependent reductions in fungal burden in rabbit cerebrum, cerebellum and spinal cord were seen with micafungin doses of 16-32 mg/kg; this corresponds to doses of approximately 10-25 mg/kg in neonates.	
Current Treatment Options	• There are no FDA-approved drugs for treatment of neonatal candidiasis with meningoencephalitis • IDSA guidelines recommend Amphotericin B deoxycholate 1 mg/kg/day or liposomal Amphotericin B as first-line therapy, but its use can be limited by nephrotoxicity • Fluconazole is recommended as a second-line agent, but its use can be limited by hepatotoxicity and azole-resistance • There is limited evidence for use of other echinocandins for neonatal candidiasis	Current treatment options for treatment of candidemia with meningoencephalitis or ocular dissemination are often limited by adverse events and resistance.
Benefit	• Based on randomized controlled trials in adults and older pediatric patients, and PK in patients younger than 4 months, an extrapolated exposure-matched dose of 4 mg/kg was identified for treatment of candidemia in this population. • The labeled dose of 4 mg/kg/day for infants younger than 4 months for candidemia, disseminated candidiasis without meningoencephalitis or ocular disease, Candida peritonitis and abscesses is a safe alternative treatment option for full-term neonates with transient candidemia or those with toxicity to other antifungal agents	Micafungin is an effective alternative treatment option for treatment of candidemia without meningoencephalitis in infants younger than 4 months. Adverse events are similar to those seen in older children and adults and are readily monitorable.
Risk and Risk Management	• TEAEs occurring at frequency >15% in this population include thrombocytopenia, hypokalemia, renal insufficiency, anemia, elevated transaminases and cholestasis. However, these events can often also be attributed to underlying severity of illness, comorbidities and concomitant medications, and they are readily monitorable through regular laboratory assessments	Clinicians should be aware that micafungin at 4 mg/kg/day is not likely to be sufficient to treat meningoencephalitis or ocular disease. The optimal dose for treatment of *Candida* meningoencephalitis and ocular involvement is unknown.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Nonclinical data indicates that 4 mg/kg/day in neonates younger than 4 months may be insufficient for treatment of meningoencephalitis – this is indicated in Limitations of use and a footnote in Section 2 of the label • The optimal micafungin dose for treatment of meningoencephalitis is unknown - a summary of nonclinical data showing reduction of fungal burden in the CNS is provided in Section 8.4 of the label • Regular assessment of CBC, renal function and liver function is advised	

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☐	**The patient experience data that were submitted as part of the application include:**			Section of review where discussed, if applicable
	☐	Clinical outcome assessment (COA) data, such as		
		☐	Patient reported outcome (PRO)	
		☐	Observer reported outcome (ObsRO)	
		☐	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify):		
☐	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	☐	Input informed from participation in meetings with patient stakeholders		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Other: (Please specify):		
x	**Patient experience data was not submitted as part of this application.**			

2 Therapeutic Context

2.1. Analysis of Condition

Candidemia refers to the presence of *Candida* in the bloodstream. Disseminated/invasive candidiasis is generally used to describe the dissemination of *Candida* to another body site. Candidemia in neonates has a predilection to disseminate to sheltered sites such as the central nervous system (CNS, i.e meningoencephalitis), eye, and other organs such as liver and spleen, which is referred to as neonatal candidiasis. Neonatal candidiasis is associated with significant morbidity including neurodevelopmental abnormalities and mortality; it is most frequently treated in neonatal intensive care units (NICUs), as patients are typically ill with sepsis and other comorbidities. Its incidence has been decreasing in recent years, possibly due to factors such as better infection control practices and increased use of antifungal prophylaxis, but mortality remains high (>10%) in those who do get the disease[1]. Neonates who are premature, have low birth weight, or have indwelling foreign material, such as a central line or shunt in place are at increased risk for neonatal candidiasis including meningoencephalitis. There is currently no antifungal drug approved by the FDA for the treatment of neonatal candidiasis.

Candida disease of the CNS is difficult to diagnose in neonates for a variety of reasons. Lumbar punctures are often deferred due to patient instability; even if done, cerebrospinal fluid (CSF) parameters often do not follow predictable patterns, and cultures are often negative. CNS disease is often suspected and presumptively treated based on imaging findings or other signs and symptoms of neurological involvement such as seizures. Neurodevelopmental outcomes in survivors of *Candida* meningoencephalitis are often poor. Current guidelines recommend treating neonatal CNS disease with amphotericin B deoxycholate as first-line therapy and fluconazole as step-down therapy.

Echinocandins have been shown to reach therapeutic concentrations at most sites of infection except for the eye, central nervous system and urinary tract.

2.2. Analysis of Current Treatment Options

The 2016 IDSA clinical practice guidelines for management of candidiasis recommend echinocandins as initial therapy for candidemia, disseminated disease including hepatosplenic candidiasis, and prophylaxis of invasive candidiasis in the ICU setting (as an alternative to

[1] Fisher B, Ross R, Localio A et al. Decreasing Rates of Invasive Candidiasis in Pediatric Hospitals Across the United States. *Clinical Infectious Diseases*. 2014;58(1):74–77.

fluconazole)[2]. Either liposomal amphotericin B (given with or without flucytosine) or an echinocandin are recommended as initial therapy for *Candida* intravascular infections including endocarditis. For *Candida* osteoarticular infections, either fluconazole or an echinocandin are recommended as initial therapy. For oropharyngeal disease, echinocandins are recommended as an alternative for refractory disease. In patients with esophageal candidiasis who can't tolerate oral medications, either fluconazole IV or an echinocandin is recommended.

First-line treatment for neonatal candidiasis, including CNS infection, is amphotericin B deoxycholate, with fluconazole or liposomal amphotericin B as alternatives. Fluconazole may be used for stepdown therapy for susceptible isolates. Echinocandins are currently recommended by the IDSA for use in the neonatal population only as salvage therapy or in cases where patients have significant toxicities and/or resistance to the first-line drugs. The 2016 IDSA guidelines note that more information is needed regarding optimal dosages for these drugs and penetration into the CNS.

Table 2-1 describes the current treatment options for candidemia and invasive candidiasis. Some of the drugs are approved for pediatric patients, and the ages of approval are listed in the table.

Table 2-1: Treatment Armamentarium for Candidemia and Invasive Candidiasis

Pharmacologic Class	Product Name	Relevant Indication(s)	Pediatric Approval?	Dose	Comments
Echinocandins	Anidulafungin	• Candidemia • Other forms of *Candida* infections (intra-abdominal abscess and peritonitis	≥16 years	200 mg loading dose on Day 1 followed by 100 mg once daily	
	Caspofungin	• Empiric therapy for presumed fungal infections in febrile neutropenic patients • Candidemia • Intra-abdominal abscesses, peritonitis, and pleural space infections due to *Candida*	≥3 months	70 mg/m^2 loading dose on Day 1 followed by 50 mg/m^2 once daily	
	Micafungin	• Candidemia	≥4 months	2 mg/kg/day (maximum 100 mg/day)	Not approved for *Candida* endocarditis,

[2] Pappas P, Kauffman C, Andes D et al. Clinical practice guideline for the management of candidiasis: 2016 update by the Infectious Diseases Society of America. *Clinical Infectious Diseases*. 2016; 62(4): e1-e50.

Pharmacologic Class	Product Name	Relevant Indication(s)	Pediatric Approval?	Dose	Comments
		• Acute disseminated Candidiasis • *Candida* peritonitis and abscesses			osteomyelitis, or meningitis
Polyenes	Amphotericin B Deoxycholate	• Progressive, potentially life-threatening fungal infections	Not approved	"Should be limited to the smallest dose compatible with an effective therapeutic regimen"	First-line for neonatal candidiasis and CNS disease[2]
	Liposomal Amphotericin B	• Systemic *Candida* infections	≥1 month	3-5 mg/kg/day	Alternative to conventional Amphotericin B[2]
Nucleoside Analogs	Flucytosine	• Systemic candidiasis (in combination with amphotericin B)		50-150 mg/kg/day in divided doses every 6 hours	Recommended as salvage along with Amphotericin B for neonatal *Candida* CNS infections[2]
Triazoles	Fluconazole	• *Candida* UTIs • *Candida* peritonitis • Systemic *Candida* infections including candidemia, disseminated candidiasis, and pneumonia	≥6 months	6-12 mg/kg/day	Best CNS penetration of the triazole group[2]
	Voriconazole	• Candidemia in non-neutropenics and other deep tissue *Candida* infections	≥2 years	IV: Loading dose 9 mg/kg every 12 hours for the first 24 hours, then 8 mg/kg every 12 hours Oral: 9 mg/kg every 12 hours (maximum dose 350 mg every 12 hours	

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Micafungin was first approved in March 2005 for prophylaxis of *Candida* infections in adults receiving hematopoietic stem cell transplants, as well as treatment of esophageal candidiasis. In January 2008, micafungin was approved for treatment of candidemia, acute disseminated candidiasis, and *Candida* peritonitis and abscesses. In June 2013, the above indications were extended to pediatric patients ages 4 months and older.

3.2. Summary of Presubmission/Submission Regulatory Activity

At the time of initial approval in 2005, pediatric studies were deferred. A Pediatric Written Request (PWR) was issued in May 2007 for 5 studies: 4 Pharmacokinetic (PK) studies and 1 phase 3 safety and efficacy study in neonates (9463-CL-2303). The Pediatric Research Equity Act (PREA) requirements were outlined in the approval letter in 2008 for the indications of candidemia, acute disseminated candidiasis, and *Candida* peritonitis/abscesses in adults. A partial waiver was granted in patients younger than 4 months of age for treatment of the above indications, for treatment of esophageal candidiasis, and for prophylaxis of *Candida* infections in patients undergoing hematopoietic stem cell transplantation.

Final reports for 4 of the 5 postmarketing requirements (PMRs) listed in the 2008 approval letter were submitted in September 2012. In August 2014, a partial waiver was granted in patients birth to less than 4 months of age, and the Applicant was released from the PREA postmarketing requirement (PMR) to evaluate the safety and efficacy of intravenous micafungin in comparison to an appropriate comparator for treatment of serious *Candida* infections in patients from birth to less than 4 months of age because studies are impossible or highly impractical.

The phase 3 study, 9463-CL-2303, underwent multiple amendments. (b) (4) the study was stopped after enrolling 30 out of a desired 225 patients.

In 2017, Astellas proposed to pool data on micafungin-treated neonates from their phase 3 study with other randomized and open label studies as well as a retrospective analysis of micafungin-treated patients in the Pediatrix database. In December 2017, the Division issued a revised PWR. The revised PWR requested 2 studies describing safety, PK, outcomes and CSF penetration. The first study (9463-CL-2303) was the phase 3, randomized, double-blind trial comparing micafungin (minimum n=20) and conventional amphotericin B (minimum n=10), with a PK substudy with about 12 patients in the micafungin group. The second study was to be a noncomparative study with a minimum of 30 patients exposed to micafungin 8 mg/kg/day, with plasma micafungin concentration to be collected in at least 5 patients, and to compare at

least 4 concurrent plasma and CSF micafungin concentrations. Communications between Astellas and FDA are summarized in Table 3-1.

Table 3-1: Regulatory Correspondence

Submission/Date	Event
NDA 21,506 Sequence 062 April 17, 2014	Astellas request for PREA waiver of neonatal patients and PWR revision to remove Study 9463-CL-2303.
NDA 21,506 Letter; Reference ID: 3616660 August 26, 2014	FDA agreement with the removal of the PREA commitment to conduct Study 9463-CL-2303.
IND 55,322 Correspondence July 26, 2016	FDA comments on proposed revision to PWR
IND 55,322 Serial No. 507 August 16, 2016	Type C Meeting Request and briefing document to discuss PWR
October 4, 2016	Type C Meeting held
IND 55,322 Letter; Reference ID: 4007425 November 1, 2016	FDA Meeting Minutes provided to Astellas
IND 55,322 Serial No. 509 April 10, 2017	Astellas proposed neonatal study submitted to FDA.
NDA 21,506 Letter; Reference ID: 4191793 December 2017	**Updated Written Request issued by FDA with revisions to neonatal data requirements.**
IND 55,322 Serial No 0513 March 27, 2018	Type C Meeting Request and briefing document – Request for FDA Feedback on Astellas' proposals to address PWR Amendments (Request for New Study in Neonates)
IND 55,322 Letter; Reference ID: 4272675 June 4, 2018	FDA Written Feedback regarding the requests outlined in the Type C Meeting Request. Also included request for additional information.
IND 55,322 Serial No. 0516 February 19, 2019	Astellas response to FDA request for information included in the FDA Written Feedback received on June 4, 2018.
IND 55,322 Correspondence March 11, 2019	Request from FDA for further clarification regarding the PWR revisions.
IND 55,322 Serial No. 0517 March 15, 2019	Astellas response to FDA request for information included in the FDA Written Feedback received on March 11, 2019.
IND 55,322 Correspondence March 20-29, 2019	Further revisions by FDA and Astellas on the proposed PWR text.
IND 55,322 Correspondence April 9, 2019	Email from the Division indicating that the PeRC determined that no further revision of the December 2017 version of the PWR was necessary.

Source: Applicant table, Module 1.9.6

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

Dr. Yiyue Zhang, Ph.D. from the Office of Study Integrity and Surveillance (OSIS) and the Office of Regulatory Affairs (ORA) conducted the analytical data audit of Study 9463-CL-2303 (NDA 021506/S023, Micafungin) at Astellas Pharma US, Inc., Northbrook, IL.

Objectionable conditions such as unjustified and undocumented manual integration and questionable stock solution stability were observed during inspection, and Form FDA 483 was issued at the inspection close-out. The final inspection classification was Voluntary Action Indicated (VAI). Astellas' response to Form FDA 483, was adequate as assessed by Dr. Zhang, and in her assessment, the objectionable conditions do not impact the concentration data from Study 9463-CL-2303; therefore, concentration data from Study 9463-CL-2303 were considered reliable to support a regulatory decision.

4.2. Product Quality

No new product quality information was provided with this sNDA.

The applicant's request for a categorical exclusion from the requirement of an environmental assessment for this supplement is acceptable, based on the applicant's statement that no extraordinary circumstances exist to its knowledge and on the estimated value of EIC-Aquatic = (b) (4) ppb (*well below the 1 ppb threshold*).

Updated labeling (PI), submitted in an amendment dated December 11, 2019, included all OPQ recommended revisions, and is acceptable from the CMC standpoint.

This supplement is recommended for approval from a CMC perspective.

4.3. Devices and Companion Diagnostic Issues

Not applicable.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

No new nonclinical pharmacology, PK or toxicology data were submitted with this sNDA. A review of the published literature pertaining to pregnancy, lactation, nursing and or/fertility conducted by the Applicant did not identify any relevant publications. A pharmacology/toxicology review was conducted for study AE-2968 submitted to the original NDA to support the Applicant's proposed PLLR updates made to the labeling. Additional pharmacology/toxicology reviews were conducted for 4-week juvenile toxicity studies and toxicokinetic studies conducted in rat (study Nos. O-1263 and B-4925, respectively). Pharmacology/Toxicology has no objection to the approval of this sNDA.

5.2. Referenced NDAs, BLAs, DMFs

None

5.3. Toxicology

Study title/number: Pharmacokinetic Studies on FR179463: Study on Transfer to Placenta, Fetus, and Milk in Rats/AE-2968.

Conducting laboratory: [redacted] (b) (4)

Methods: Timed pregnant Sprague Dawley rats (*n*=3-4) were given a single intravenous injection of 1 mg/mL/kg ^{14}C-FR179463 in the caudal vein on gestation day (GD) 13 and 18 to study micafungin transfer to placenta and fetus. Whole body autoradiograms were prepared at 5 min, 6, 24, 168, and 240 hours post injection. To determine radioactivity concentration in milk, on day 8 post-delivery, lactating rats (*n*=3) were given single intravenous injection of 1 mg/mL/kg ^{14}C-FR179463 in the metatarsal vein. Milk was serially collected from thoracic and abdominal nipples and blood was collected from the caudal vein at 5 min, 1, 2, 6, 34, 72, 168, and 240 hr after administration.

Radiochemical purity of the labeled compound was 97% at receipt and during storage in dosing formulation. The report does not indicate whether the study was conducted in compliance with Good Laboratory Practices.

Results: Radioactivity was distributed to mammary glands, placenta and fetal membranes following IV administration of ^{14}C-FR179463 to pregnant rats on GD13 or GD18. Transfer of radioactivity to fetuses peaked at 24 hr and 48 hr when ^{14}C-FR179463 was administered on GD13 and GD18, respectfully.

After IV administration of ^{14}C-FR179463 to lactating rats on day 8 post-delivery, radioactivity concentration in milk increased gradually and was comparable with or lower than that in plasma up to 6 hours after administration and was 3.65-1.61 times that in the plasma after 24 hours. In milk, t_{max} = 6h, C_{max}= 1139 ng eq./mL, $AUC_{0-\infty}$=80.53 mcg eq.·h·mL^{-1} and $t_{1/2}$=1.4 days. In plasma, the concentration of radioactivity was 3367 ng eq./mL at 5 min and declined biphasically thereafter. Radioactivity concentration in plasma decreased in parallel with that in the milk with an $AUC_{0-\infty}$= 48.69 mcg eq.·h·mL^{-1} and $t_{1/2}$=1.5 days.

Equal volume of milk samples from 3 animals were combined and subjected to HPLC analysis to determine metabolite composition (described in the study report *Pharmacokinetic studies on FK463: Composition of metabolites in the milk after intravenous administration of ^{14}C-FK463 to lactating rats*). The extraction rate of radioactivity from the milk at 2, 6, 24 and 72 hr after intravenous administration of ^{14}C-FK463 was 99.0, 95.2, 77.7 and 54.7%, respectively. Unchanged FK463 (i.e., FR179463) peaked at 81.4% at 6h following administration. Metabolites M2, M3 and M5 were detected in the milk samples, with M3 accounting for 47.1% of the radioactivity at 2 hr. Overall, unchanged FK463 was considered to be the major component of the radioactivity, which transferred to the milk of lactating rats up to 24h after IV administration of ^{14}C-FK463.

The findings from these studies support the added labeling text under 8.2 Lactation *"Micafungin is excreted in the milk of lactating rats following intravenous administration."* NDA-021506/S-023 does not require any additional pharmacology/toxicology review.

Study title: A 4-week intravenous toxicokinetic study of FR179463 in newborn rats; (Study No. O-1263; GLP (Japan); 2005). *(English version translated from Japanese final report by* (b) (4)

Sponsor: Astellas Pharma, Inc. Osaka Japan
Study Initiation Date: 5/2005
Conducting facility: (b) (4)

A GLP 4-week repeat-dose toxicokinetic study was conducted by (b) (4) to evaluate toxicokinetic parameters of FR179463 (micafungin) in saline when administered intravenously to newborn male and female SD rats (age day 4 after birth) at doses of 0, 3.2, 10, 32 mg/kg. Dose volume was set at 5 mL/kg body weight, and dose solutions were administered (slow bolus) via the cervical vein (during the lactation period) and via the tail vein (after weaning). Four pups/sex were assigned to a healthy lactating dam and weaned on Day 21 after birth. The study design including the number of animals in each group can be seen in Table 5-1. below.

Table 5-1. Study Design for 4-week intravenous toxicokinetic study in newborn rats (Study No. O-1263)

Test group	Dose level (mg/kg)	Dose concentration (mg/mL)	Dose volume (mL/kg)	Sex	Group for Blood Collection After First Dosing		Group for Blood Collection After 2-Week Administration		Group for Blood Collection After 4-Week Administration	
					Number of animals	Animal number	Number of animals	Animal number	Number of animals	Animal number
Control group	0	0	5	Male Female	24 24	1001 to 1024 1101 to 1124	28 28	1025 to 1052 1125 to 1152	8 8	1053 to 1060 1153 to 1160
Low dose group	3.2	0.64	5	Male Female	24 24	2001 to 2024 2101 to 2124	28 28	2025 to 2052 2125 to 2152	8 8	2053 to 2060 2153 to 2160
Middle dose group	10	2	5	Male Female	24 24	3001 to 3024 3101 to 3124	28 28	3025 to 3052 3125 to 3152	8 8	3053 to 3060 3153 to 3160
High dose group	32	6.4	5	Male Female	24 24	4001 to 4024 4101 to 4124	28 28	4025 to 4052 4125 to 4152	8 8	4053 to 4060 4153 to 4160

(Text table 2 from the study report)

Study parameters included assessments of mortality and clinical signs (3x daily); body weight (Days 1, 4, 8, 11, 14, 18, 21, and 28 of dosing); TK blood collection (15 minutes, 1, 2, 4, 8, and 24 hours after dosing on Days 1, 14, and 28 of dosing). No clinical pathology or gross or histopathological evaluations were conducted.

Overall, 28 consecutive days of daily dosing with FR1O-179463 (up to 32 mg/kg/dose) to male and female juvenile rats appeared to be generally well tolerated, with no treatment related mortality or clinical observations noted in this study. For males and females in the 32 mg/kg group, mean body weight was slightly lower than the control group after Day 11 for the remainder of the study. All other dose groups showed body weight data comparable to control through the administration period. FR179463 was not detected in plasma from control animals at any time point. FR179463 plasma concentrations increased with dose in a near dose-proportional manner across all dose groups in both male and female animals (Table 4). Tmax was at 15 minutes after dosing in all group and elimination from plasma was relatively slow, with a half-life (t1/2) of approximately 6-7 hours across all timepoints in the low and mid-dose groups, increasing to 8-9 hours in the highest dose group on Days 1 and 14, and decreasing back to 6 hours in this group by the end of the study (Day 28). Although Cmax and AUC0-24h appeared to increase within each dose group with repeated dosing, there were no clear differences between TK values observed at the end of the 2 and 4-week treatment periods, suggesting the drug concentration reached steady state. In the 32 mg/kg dose group, AUC0-24h also appeared to be greater at the end of the 2-week treatment period compared to the 4-week period, which might reflect the shorter half-life noted for this high dose group at the later 4-week timepoint. There were no clear sex differences noted in any of the TK parameters.

Table 5-2. TK Parameters for FR179463

TK measurement day	Sex	Dose level (mg/kg)	T_{max} (min)	C_{max} (μg/mL)	$AUC_{0\text{-}24h}$ (μg·h/mL)	$T_{1/2}$ (h)
Starting day of administration	Males	0	–	0	–	–
		3.2	15	3.81	40.69	6.11
		10	15	11.92	150.17	7.32
		32	15	50.89	531.00	9.15
	Females	0	–	0	–	–
		3.2	15	5.58	39.73	5.98
		10	15	15.85	151.12	6.46
		32	15	57.10	520.40	8.45
Week 2 of administration	Males	0	–	0	–	–
		3.2	15	5.68	52.73	6.34
		10	15	20.55	192.31	6.88
		32	15	84.70	860.95	8.38
	Females	0	–	0	–	–
		3.2	60	4.74	48.72	5.89
		10	15	18.72	189.68	6.62
		32	60	79.31	915.60	8.79
Week 4 of administration	Males	0	–	0	–	–
		3.2	15	6.68	48.91	5.37
		10	15	21.23	180.39	6.28
		32	15	75.53	631.23	6.73
	Females	0	–	0	–	–
		3.2	15	7.13	51.68	4.91
		10	15	23.11	188.36	6.12
		32	15	77.73	657.10	6.51

–: Not detected.

(Text table 6 in the study report)

Study title: A 4-week intravenous toxicity study of FR179463 in newborn rats; (Study No. B-4925; GLP (Japan); 2002). (*English version translated from Japanese final report by* (b) (4)

Sponsor: (b) (4)

Study Initiation Date: 4/2002

Conducting facility: (b) (4)

A GLP, 4-week repeat-dose toxicokinetic study was conducted by (b) (4) to evaluate the toxicity of FR179463 (micafungin) in saline when administered intravenously to newborn male and female SD rats (age day 4 after birth) at doses of 0, 3.2, 10, 32 mg/kg. Dose volume was set at 5 mL/kg body weight, and dose solutions were administered via the cervical vein (2 mL/min) to all newborn rats. Four pups/sex were assigned to a healthy lactating dam and weaned on Day 21 after birth. The study design including the number of animals in each group can be seen in Table 5-3. below.

Table 5-3. Study Design for 4-week intravenous toxicity study in newborn rats (Study No. B-4925)

Test group	Dose level (mg/kg)	Concentration (mg/mL)	Dose volume (mL/kg)	Sex	No. of Animals	Animal No.
Control Group	0	0	5	Males Females	10 10	1001-1010 1101-1110
Low Dose Group	3.2	0.64	5	Males Females	10 10	2001-2010 2101-2110
Middle Dose Group	10	2	5	Males Females	10 10	3001-3010 3101-3110
High Dose Group	32	6.4	5	Males Females	10 10	4001-4010 4101-4110

(Text table 2 from the study report)

Study parameters included assessments of mortality and clinical signs (3x daily); body weight (Days 1, 4, 8, 11, 14, 18, 21, and 28 of dosing); developmental endpoints (abdominal hair, eruption incisors, eyelid opening on Days 4, 8, 11, 14); functional examinations (pupillary-, corneal-, righting-, air righting-, and pinnae reflexes on Day 18); ophthalmological examination (Day 23); Urinalysis (Day 25, 26, 27, 28); hematology/serum chemistry (Day 28); gross necropsy, organ weights, and tissue histopathology (Day 28 necropsy).

Overall, 28 consecutive days of daily dosing with FR179463 (up to 32 mg/kg/dose) to male and female juvenile rats appeared to be generally well tolerated, with no test article related effects on mortality, clinical observations, external differentiation, functional and ophthalmological examinations, noted in this study. Males and female pups in the 32 mg/kg group showed a slightly lower mean body weight than the control group after Day 21, which persisted for the remainder of the study (with no corresponding decrease in body weight gain versus control). All other dose groups showed body weight data comparable to control through the administration period. Slight decrease in RBC counts and slightly higher mean corpuscular volume (MCV) values were observed in males in the 32 mg/kg group, with no corresponding change in females in the same group. Splenic weights (relative to birth weight) appeared to increase marginally in males but not females in this high dose group above controls, but there were no histological changes noted in any hematopoietic tissues to suggest an adaptation to the decreased RBC counts. All other hematological changes in all groups were comparable to the controls. Serum chemistry evaluations showed a slight increase in β-globulin in males and α2-globulin in females in the 32 mg/kg group compared to controls. Similarly, small increase in small round epithelial cells were noted in the urine of female rats at 32 mg/kg/day, with no corresponding change in males in the same group. There were no test article-related histological changes in kidney in treated groups that were different in incidence and severity from the control group. Slight vacuolation of mucosal epithelium in the urinary bladder was observed in 9/10 males and 10/10 females in the 32 mg/kg group. All other noted changes in organ weights, and gross and microscopic analysis were similar in incidence and severity between the control and treated

groups. The No-Observed-Adverse-Effect-Level (NOAEL) of this study was determined to be 10 mg/kg/day.

Labeling: The Applicant updated Section 8.1 Pregnancy and Section 8.2 Lactation to be PLR/PLLR compliant: the reproductive toxicology data in pregnant rabbits was moved from Section 13 to Section 8.1 and a statement regarding excretion of micafungin in the milk of lactating rats was added to Section 8.2. Pharmacology/Toxicology provided suggested edits to the relevant nonclinical information in Section 8.1 and Section 8.2 to describe the types of studies (embryo-fetal development) and timing of micafungin administration (during organogenesis).

6 Clinical Pharmacology

6.1. Executive Summary

The Office of Clinical Pharmacology reviewed the information contained in the sNDA. The clinical pharmacology information submitted in this sNDA supports the approval of MYCAMINE™ (micafungin) for the treatment of candidemia, acute disseminated candidiasis, peritonitis and abscesses (also referred to as invasive candidiasis/candidemia in this review) in pediatric patients younger than 4 months of age who do not have meningoencephalitis (also referred to as CNS dissemination in this review) at a dose regimen of 4 mg/kg once daily (QD). The clinical pharmacology review team determined that a micafungin dose regimen of 4 mg/kg QD in pediatric patients less than 4 months of age for treatment of invasive candidiasis/candidemia without CNS dissemination provides comparable AUC exposure to adults administered the approved 100 mg QD micafungin dose regimen for the same indication.

For the treatment of invasive candidiasis/candidemia with CNS dissemination in pediatric patients younger than 4 months of age, (b) (4) a micafungin dose regimen of 10 mg/kg QD. This regimen was selected based on a rabbit model of hematogenous *Candida* meningoencephalitis (HCME) that was published in the literature.[3,4] Invasive candidiasis/candidemia in pediatric patients generally less than 4 months of age and particularly neonates 0-28 days old and very low/extremely low birth weight premature infants is deemed to be pathophysiologically different from invasive candidiasis/candidemia in adults and older pediatric patients greater than 4 months of age, as it is often accompanied by CNS dissemination. Thus, PK extrapolation from adults and older pediatric patients to the pediatric patient population less than 4 months of age with candidemia, acute disseminated candidiasis with meningoencephalitis cannot be done. The clinical and clinical pharmacology review teams deemed that the submitted clinical efficacy data were insufficient to support a dose regimen of micafungin in pediatric patients less than 4 months of age with invasive candidiasis/candidemia with meningoencephalitis. However, after further discussions with the clinical team and the Pediatrics Review Committee (PeRC), a decision was made by the clinical and clinical pharmacology review teams to provide information in the labeling describing the rabbit HCME study and the corresponding pediatric equivalent dose regimens without providing an indication for meningoencephalitis. See Section 6.2 below for further details.

[3] Hope WW, Mickiene D, Petraitis V, et al. The pharmacokinetics and pharmacodynamics of micafungin in experimental hematogenous Candida meningoencephalitis: implications for echinocandin therapy in neonates. J Infect Dis. 2008;197(1):163-71.
[4] Petraitiene R, Petraitis V, Hope WW, et al. Cerebrospinal fluid and plasma (1-->3)-beta-D-glucan as surrogate markers for detection and monitoring of therapeutic response in experimental hematogenous Candida meningoencephalitis. Antimicrob Agents Chemother. 2008;52(11):4121-9.

See Table 6-1 for a summary of clinical pharmacology-related recommendations and comments on key review issues.

Table 6-1. Summary of OCP Recommendations & Comments on Key Review Issues.

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness for invasive candidiasis/candidemia without CNS dissemination	The pivotal evidence of effectiveness of micafungin in the treatment of adult patients with invasive candidiasis/candidemia was provided in previous submissions of NDA 21,506. In pediatric patients under 4 months of age with candidemia without CNS dissemination, the pathophysiology is assumed to be comparable to adults. Thus, the effective plasma AUC of micafungin in adults with invasive candidiasis/candidemia is predicted to be effective in pediatric patients under 4 months of age as well. The PK results from the conducted clinical trials demonstrated that the micafungin AUC estimates from a dose regimen of 4 mg/kg QD in pediatric patients under 4 months of age with invasive candidiasis/candidemia and without CNS dissemination are similar to the AUC estimates in adult patients receiving the approved 100 mg QD dose regimen of micafungin.
General dosing instructions	The recommended dose regimen of micafungin in pediatric patients younger than 4 months of age with invasive candidiasis/candidemia and without CNS dissemination is 4 mg/kg QD.
Labeling	The following sections in the Applicant's proposed labeling were revised: • Sec 2. Dosing and Administration: Inclusion of recommended dosage regimens as described above • Sec 7. Drug Interactions: Updated formatting • Sec 8.4. Pediatric Use: Addition of information regarding rabbit HCME model • Sec 12.3 Pharmacokinetics in Pediatrics: Addition of information regarding PK of micafungin for 4 mg/kg QD in pediatric patients younger than 4 months without CNS dissemination

6.2. Comprehensive Clinical Pharmacology Review

6.2.1. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness for the proposed dosing regimen in the patient population of interest?

Yes, the clinical pharmacology program provides supportive evidence of effectiveness for micafungin in the treatment of pediatric patients younger than 4 months of age with invasive candidiasis/candidemia. The clinical pharmacology team proposes a dose regimen of 4 mg/kg

QD micafungin for the treatment of invasive candidiasis/candidemia without CNS dissemination in pediatric patients younger than 4 months of age.

For the treatment of invasive candidiasis/candidemia with CNS dissemination in pediatric patients younger than 4 months of age, (b) (4) a micafungin dose regimen of 10 mg/kg QD. However, the clinical pharmacology team disagrees with this (b) (4) dose regimen, as will be discussed below.

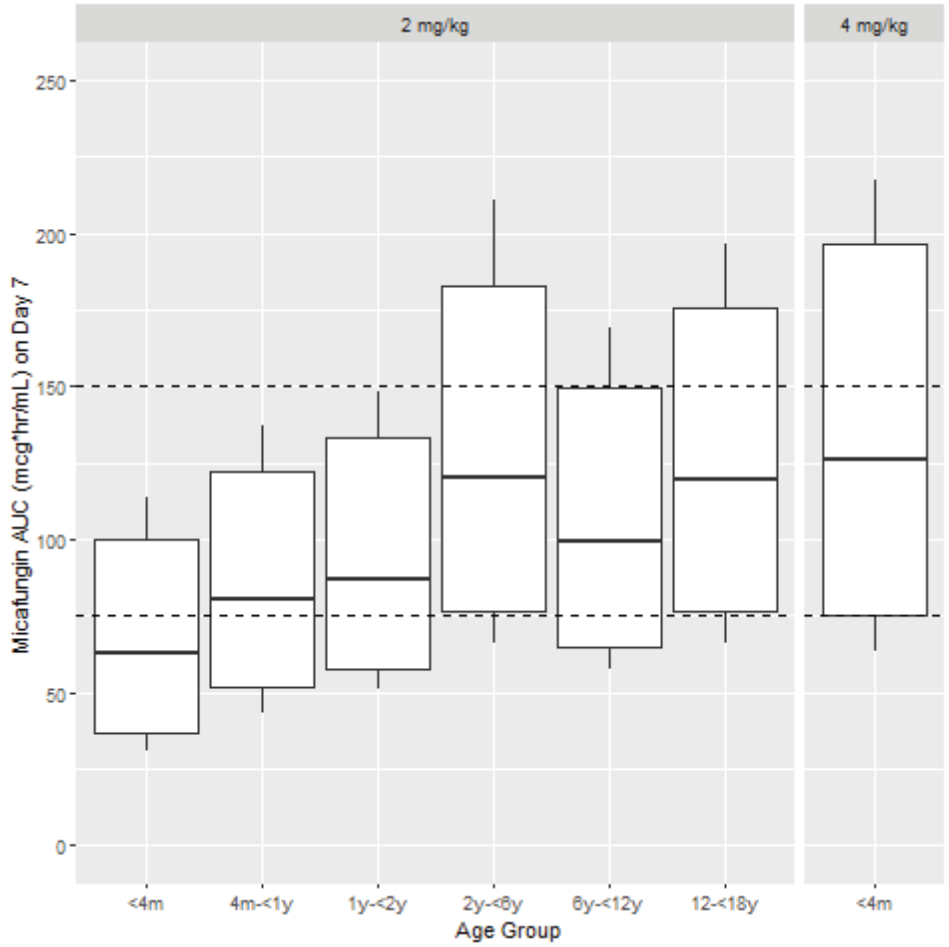
This review will consider the treatment of candidemia without CNS dissemination and invasive candidiasis with CNS dissemination separately.

Invasive Candidiasis/Candidemia Without CNS Dissemination

In invasive candidiasis/candidemia without CNS dissemination, the primary evidence of effectiveness is provided by the finding that plasma exposure of micafungin—using AUC as the exposure metric—in pediatric patients younger than 4 months of age at the clinical pharmacology review team's proposed dose regimen of 4 mg/kg QD is comparable to the AUC estimates of micafungin in adult patients with candidemia receiving the approved dose regimen of 100 mg QD. Because invasive candidiasis/candidemia without CNS dissemination is assumed to be pathophysiologically similar in adults and pediatric patients of all ages, the AUC of micafungin following the approved dosage regimen of 100 mg QD in adults is predicted to be safe and effective in pediatric patients younger than 4 months of age without CNS dissemination. Thus, safety and efficacy in invasive candidiasis/candidemia can be fully extrapolated from adults to pediatric patients under 4 months of age without CNS dissemination if the AUC exposures in pediatric and adult patients are comparable.

The Applicant used PK data collected from pediatric patients younger than 4 months of age in six studies to build a population PK model. For a review of the population PK model, see Section 17.2.3. The population PK model was then used to simulate AUC estimates of micafungin at two dose regimens at steady state: 2 mg/kg QD and 4 mg/kg QD, up to a maximum of 100 mg QD. 2 mg/kg QD was selected as it is the current approved dose in pediatric patients with candidemia. 4 mg/kg QD was selected to identify the AUC at a higher dose. The 10^{th} percentile steady state AUC estimate of 75 mcg·hr/mL in adult patients receiving 100 mg QD micafungin from Study FG-463-21-08 was used as the plasma PK target. The predicted AUC of micafungin in pediatric patients younger than 4 months compared to the adult AUC target is illustrated in Figure 6-1 and Table 6-2.

Figure 6-1. Simulated Micafungin AUC Following Administration of Micafungin in Patients with Candidemia at Steady Sate Stratified by Dose Regimen and Age



The dashed lines signify the approximate 10th and 90th percentiles of AUC in adult patients with candidemia administered 100 mg micafungin QD at steady-state, i.e., 75 and 150 mcg·hr/mL. Each boxplot represents the 10th, 50th, and 90th percentiles of AUC in each age group while the whiskers represent the 5th and 95th percentiles of AUC.

Table 6-2. Simulated Geometric Mean AUC (CV%) of Micafungin Following Administration of Micafungin in Patients with Candidemia at Steady State Stratified by Dose Regimen and Age.

Micafungin Dose Regimen	Age	AUC (mcg·hr/mL)
2 mg/kg QD	<4m	61.3 (39%)
	4m - <1yr	79.5 (35%)
	1yr - <2yr	87.3 (32%)
	2yr - <6yr	118.5 (35%)
	6yr - <12yr	99.2 (33%)
	12yr - <18yr	117 (34%)
4 mg/kg QD	<4m	123 (37%)

A dose regimen of 2 mg/kg QD micafungin results in steady-state micafungin AUC estimates comparable to the adult AUC target in pediatric patients 4 months of age and older but not in pediatric patients younger than 4 months of age. On the other hand, 90% of pediatric patients younger than 4 months of age administered 4 mg/kg QD micafungin are predicted to have an AUC greater than the adult AUC target of 75 mcg·hr/mL. Thus, 4 mg/kg QD micafungin in pediatric patients younger than 4 months of age produces comparable exposure to 100 mg micafungin QD in adult patients and is predicted to have similar efficacy in the treatment of candidemia without CNS dissemination.

Invasive Candidiasis/Candidemia with CNS Dissemination

Invasive candidiasis/candidemia in pediatric patients younger than 4 months of age is presumed to require a higher exposure of micafungin relative to adults due to the need for the drug to penetrate into the CNS. CNS dissemination is not a common feature of invasive candidiasis/candidemia in adult patients; thus, the invasive candidiasis/candidemia with CNS dissemination indication cannot be supported by extrapolation of comparable AUC exposures from adult patients. The Applicant provided clinical data in pediatric patients under four months of age with invasive candidiasis/candidemia, some of whom had confirmed CNS dissemination. However, due to small sample sizes and other confounding factors, the clinical data were deemed insufficient to demonstrate the efficacy of micafungin in this pediatric population. See Section 8 for the clinical review of the efficacy data and Section 17.2.3 for a review of the dose-response relationship for mycological response.

To supplement the clinical data, the Applicant submitted a rabbit model of HCME that was judged by the clinical review team to be reflective of the pathophysiology of invasive candidiasis/candidemia in pediatric patients under four months of age as manifested by a high rate of CNS dissemination.

Rabbit HCME Infection Model

The Hope (2008) and Petraitiene (2008) papers report two analyses of a single experiment of a rabbit HCME model as described further in Section 9.3.2. Briefly, female New Zealand White rabbits weighing 2.4-3.7 kg were inoculated with a clinical isolate of *Candida albicans* (NIH-8621) with a micafungin MIC of 0.125 mg/L at a dose of 10^6 organisms administered intravenously. Once daily (QD) dose regimens of micafungin at doses of 0.25 mg/kg to 32 mg/kg and amphotericin B at 1 mg/kg QD were initiated 48 hr after inoculation; duration of drug treatment was for 7 days. A no treatment control group was also included. Eight samples of blood for PK analysis were collected around the sixth dose of micafungin. Rabbits were sacrificed 0.5 hr. after the last dose of antifungal drug treatment, at which point tissue samples were collected for analysis.

The authors of the aforementioned papers found relationships between micafungin dose and lowering of *Candida* fungal burden in selected brain tissues relative to untreated controls as shown in Figure 6-2 and Figure 6-3.

Figure 6-2. Change in Candida Fungal Burden in HCME Rabbits Administered Micafungin (MFG) or Amphotericin (AMB) as a Function of Dose and Infection Site. Adapted from Petraitiene et al. (2008).

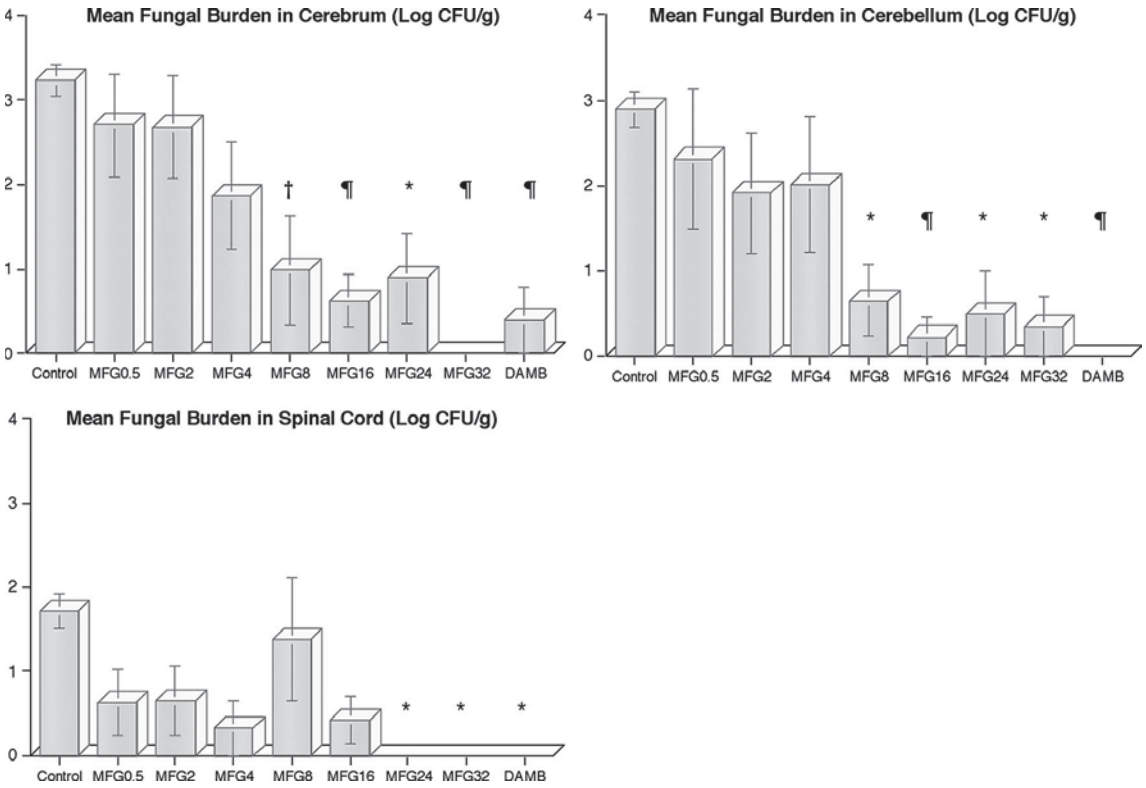
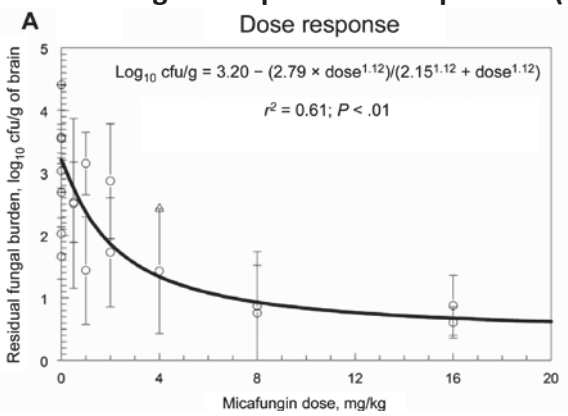


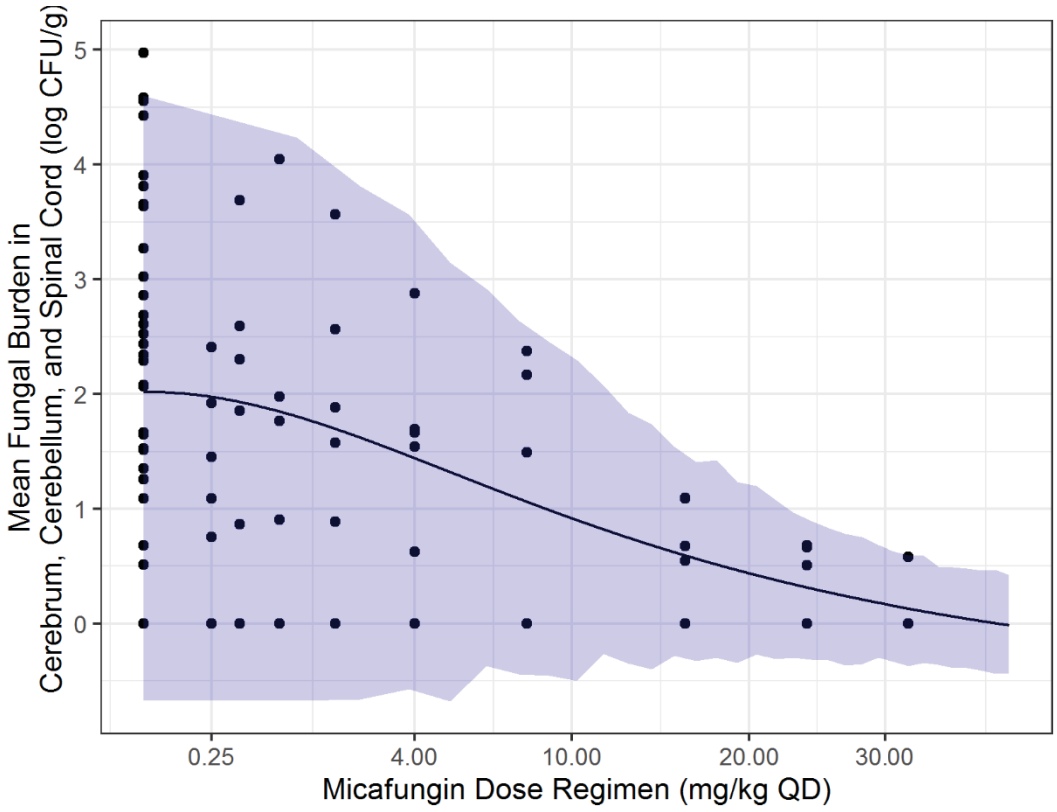
Figure 6-3. Micafungin Dose-Response Relationship for Change in Candida Fungal Burden in HCME Rabbits Administered Micafungin. Adapted from Hope et al. (2008).



The review team requested the original data from the Hope and Petraitiene studies. The clinical pharmacology team reanalyzed the individual animal PK and tissue fungal burden data as discussed in Section 17.2.3. The primary conclusions from the clinical pharmacology team's assessment of the rabbit HCME model are as follows:

- There is significant variability in the measurements of fungal burden in CNS tissues of treated and untreated rabbits.
- In this model, micafungin dose regimens of 16 to 32 mg/kg QD produced significantly lower mean residual fungal burden in cerebrum, cerebellum, and spinal cord relative to untreated controls at a statistical significance level of 0.05 as shown in Figure 6-4 and Table 6-3.

Figure 6-4. Relationship Between Rabbit Micafungin Dose and Mean Fungal Burden in Selected CNS Compartments.



The line represents the trend of median fungal burden across the micafungin dose range and the blue shaded area represents the 95% prediction interval.

Table 6-3. Change in Residual Mean Fungal Burden in Cerebrum, Cerebellum, and Spinal Cord at Different Doses of Micafungin.

Rabbit Micafungin Dose Regimen (mg/kg QD)	Mean (95% Confidence Interval) Change in Mean Fungal Burden	p-value
0.25	0 (-0.7, 0.7)	0.35
0.5	-1 (-1.95, -0.06)	1
1	-0.39 (-1.77, 0.99)	1
2	-0.54 (-2.37, 1.3)	1
4	-0.53 (-1.85, 0.79)	0.88
8	-0.87 (-1.94, 0.2)	0.38
16	**-1.27 (-2.48, -0.05)**	**5.82E-06**
24	**-1.85 (-2.46, -1.23)**	**2.82E-05**
32	**-1.81 (-2.42, -1.2)**	**3.00E-08**

Statistically significant rabbit micafungin dose regimens are highlighted in yellow.

Limitations of Rabbit HCME Model

The primary limitation of the Hope and Petraitiene studies is that survival was not assessed. While the highest dose regimen of micafungin tested in the rabbit model (32 mg/kg QD) appeared to result in an approximately 2 log10 CFU/g lower mean residual fungal burden in the cerebrum, cerebellum, and spinal cord relative to untreated controls, the clinical significance of the lower fungal burden is unknown. Amphotericin B 1 mg/kg QD was used as a positive control in this experiment, because it is currently used in infants with candidiasis involving the CNS at a dose of 1 mg/kg/day. However, PK assessment of amphotericin B was not conducted in the rabbits, and thus, a comparison of PK and/or systemic PK exposure between infants and rabbits in the HCME model for amphotericin B cannot be made. Thus, the clinical pharmacology team is unable to infer the significance of lower fungal burden by comparison to amphotericin B.

Another limitation of this animal model study is that only a single isolate and MIC of *Candida albicans* was used, however, the pediatric patients in the clinical study were infected with more than 8 species of *Candida*. The species of *Candida* isolated in the clinical trial had MIC values up to 2 mcg/mL, which is significantly higher than the MIC of 0.125 mcg/mL tested in the rabbit HCME model. Based on the assumption that the dose for antifungal activity is proportional to MIC, doses approximately 16 times higher than 16-32 mg/kg QD may have been necessary if the experiment was conducted with a *Candida* isolate having an MIC of 2 mcg/mL. Thus, any PK targets obtained from this study may only be applicable for patients infected with a *Candida* isolate MIC of 0.125 mcg/mL or lower.

There may be differences in micafungin plasma distribution between rabbits in the HCME model and pediatric patients younger than 4 months. Plasma protein binding was not assessed in this study, but available data submitted by the Applicant and in the literature suggest that

micafungin protein binding is roughly comparable or slightly higher in rabbits (99.7%) relative to human adults (99.6%) and human infants (96.7%); thus, the unbound fraction of micafungin in plasma is most likely higher in pediatric patients younger than 4 months relative to rabbits and human adults.[5] At the same time, the use of the rabbit HCME model assumes that penetration of micafungin into the CNS is similar between rabbits and pediatric patients younger than 4 months. This claim cannot be validated without a radiolabeled mass balance study in the brains of pediatric patients younger than 4 months, which is practically infeasible.

Additionally, the bioanalytical assay reports for micafungin were not available to validate the Applicant's estimates of micafungin concentrations and AUC estimates in the rabbits. The clinical pharmacology review team cannot confirm the accuracy of the AUC estimates. Therefore, we cannot reliably determine what pediatric doses result in comparable AUC exposures to the rabbit doses that produced a lowering of mean fungal burden in the cerebrum, cerebellum, and spinal cord.[6]

Furthermore, there was significant intra-treatment group variability in the fungal burden in the CNS compartments the rabbit HCME model. There were many untreated rabbits who had no mean residual fungal burden in the cerebrum, cerebellum, and spinal cord, which signifies a failed negative control. The failed negative control could be a result of technical error or an inappropriate experimental design. To our knowledge, this experiment was never replicated; thus, we do not have insight into the reproducibility of the experiment. All these factors result in uncertainty in the interpretation of fungal burden lowering estimates.

Evaluation of Pediatric Dose Regimens Based on Exposures in Hope and Petraitiene Studies

Notwithstanding the limitations in the data generated from the Hope and Petraitiene studies, the clinical pharmacology review team assessed what doses administered to pediatric patients younger than 4 months with invasive candidiasis/candidemia with CNS dissemination would provide comparable AUC exposure to the pharmacologically active doses in the rabbit model of HCME. Using the population PK model described in the Pharmacometrics review (Section Pharmacometrics Review17.2.3), a range of micafungin dose regimens from 10 to 30 mg/kg QD were simulated and assessed to determine a regimen(s) in pediatric patients that would produce predicted AUC estimates that are similar to the AUC exposures in rabbits at the dose regimens that achieved statistically lower mean residual fungal burden in the cerebrum, cerebellum, and spinal cord. Table 6-4. shows the micafungin dose regimens (range of 10 to 30 mg/kg QD) and the predicted AUC estimates for pediatric patients under 4 months of age. Pediatric dose regimens of 11 and 27 mg/kg QD produce predicted AUC estimates comparable

[5] Yanni SB, Smith PB, Benjamin DK, Augustijns PF, Thakker DR, Annaert PP. Higher clearance of micafungin in neonates compared with adults: role of age-dependent micafungin serum binding. Biopharm Drug Dispos. 2011;32(4):222-32.
[6] US Food and Drug Administration. Bioanalytical Method Validation Guidance for Industry. Available at: https://www.fda.gov/media/70858/download. Accessed Dec 2019.

to the AUC estimates observed in rabbits administered 16 and 32 mg/kg QD, i.e., 353 and 889 mcg·hr/mL, respectively. For the sake of simplicity, when rounding 11 and 27 mg/kg QD to the nearest factor of 5, this results in pediatric micafungin dose regimens of 10 and 25 mg/kg QD, which also result in predicted AUC estimates comparable to the aforementioned rabbit AUC estimates.

Table 6-4. Predicted Arithmetic Mean (CV%) AUC Estimates at Steady State in Pediatric Patients Younger than 4 Months Administered Various Micafungin Dose Regimens

Micafungin Pediatric Dose Regimen	Predicted Pediatric AUC (mcg·hr/mL)
10 mg/kg QD	331 (35%)
11 mg/kg QD	373 (38%)
12 mg/kg QD	403 (40%)
13 mg/kg QD	427 (37%)
14 mg/kg QD	465 (38%)
15 mg/kg QD	502 (38%)
25 mg/kg QD	821 (38%)
26 mg/kg QD	851 (38%)
27 mg/kg QD	876 (38%)
28 mg/kg QD	933 (38%)
29 mg/kg QD	968 (37%)
30 mg/kg QD	996 (39%)

Dose regimens producing predicted pediatric AUC estimates closest to the rabbit AUC estimates of 353 and 889 mcg·hr/mL are highlighted in yellow.

Overall, the available data in the literature taken together with the PK data submitted with the sNDA suggest a micafungin dose regimen in the range of approximately 10 mg/kg to 25 mg/kg QD in pediatric patients younger than 4 months with invasive candidiasis/candidemia and CNS dissemination. However, the clinical relevance of the lowering in CNS tissue fungal burden in the rabbit model of HCME, as reported in the cited literature papers, has not been determined. Therefore, there currently are insufficient data to support the efficacy of micafungin at a specific dose regimen for invasive candidiasis/candidemia with CNS dissemination.

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

Table 7-1: Listing of Clinical Trials Relevant to this NDA/BLA

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
		Controlled Studies to Support Efficacy and Safety						
9463-CL-2303	NCT00815516	Phase 3 MC, R, DB, AC	Micafungin: 10 mg/kg/day IV Amphotericin B: 1 mg/kg/day IV	Primary: Fungal-free survival 1-week post study drug Secondary: mycological response	Minimum of 21 days up to a maximum of 28 days for infants without EOD or 42 days for infants with EOD Follow-up 30 days following last study dose	Micafungin: 20 Amphotericin B: 10	Neonates and infants up to 120 days of age with a diagnosis of invasive candidiasis proven by a positive fungal culture for *Candida*	17 centers 12 countries
		Studies to Support Safety						
-								
		Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)						
9463-CL-6001	NCT03421002	Prospective, uncontrolled	Micafungin: 8 mg/kg/day IV	Primary: PK endpoints Secondary: Treatment response at EOT, Fungal free survival at EOT, and end of study	Minimum of 21 days until stopping criteria were met	Micafungin: 35	Neonates up to 180 days old with systemic candidiasis	1 site in Italy
9463-CL-6002		Retrospective chart review, uncontrolled	Micafungin: 8 to 15 mg/kg/day IV	Primary: PK endpoints Secondary: Treatment response at EOT, all-cause mortality		Micafungin: 18	Newborns and small infants treated with micafungin because of sepsis and/or meningitis due to *Candida*	1 site in Italy

Abbreviations: MC: multi-center, R: randomized, DB: double-blind, AC: active controlled, EOD: end-organ dissemination, PK: pharmacokinetic, EOT: end of treatment

7.2. Review Strategy

The studies to be reviewed in Section 8.1 are the studies conducted in response to the Pediatric Written Request. Study 9463-CL-2303 was originally designed as an adequate well-controlled trial. However, given enrollment issues due to changes in the standard of care in neonatal candidiasis and the decreasing incidence of the disease, the study was stopped well before its planned enrollment. Studies 9463-CL-6001 and 9463-CL-6002 were uncontrolled studies primarily conducted to evaluate the pharmacokinetics of micafungin. Limited efficacy data were collected in these two studies.

The assessment of these studies is limited to a descriptive presentation of the data. The results presented are based on a review of the study reports and analyses conducted on the datasets provided in the submission.

8 Statistical and Clinical Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Study 9463-CL-2303

8.1.1.1 Study Design

Trial Design

Study 9463-CL-2303 was a phase 3, randomized, double-blind, multicenter study to evaluate the efficacy and safety of micafungin in comparison to conventional amphotericin B in the treatment of proven neonatal candidiasis. The study was a multinational study conducted in the following regions: Africa, Asia Pacific, Europe, Latin America, Middle East, and North America.

Eligible subjects included infants greater than 48 hours of life up to 120 days with a diagnosis of invasive candidiasis proven by a positive fungal culture for *Candida*. The culture results to confirm *Candida* species may have been pending at the time of enrollment as long as staining/microscopy of a blood culture sample revealed preliminary evidence of yeast or histology/cytology revealed findings consistent with yeast. Subjects were not eligible if they had received more than 48 hours of systemic antifungal therapy prior to the first dose of study drug for treatment of the current *Candida* infection, had a breakthrough systemic fungal infection while receiving an amphotericin B product or an echinocandin as prophylaxis, failed prior systemic antifungal therapy for the current episode of invasive candidiasis including recurrence of the same *Candida* infection within 2 weeks of completing systemic antifungal therapy, or were co-infected with a non-*Candida* fungal organism.

Patients were randomized in a 2:1 ratio to receive daily infusions of micafungin or amphotericin B. Micafungin was dosed at 10 mg/kg and amphotericin B was dosed at 1 mg/kg. Treatment was to be administered daily for a minimum of 21 days up to a maximum of 28 days for infants without end-organ dissemination or a maximum of 42 days for infants with end-organ dissemination. Randomization was stratified by estimated gestational age (< 27 weeks, ≥27 weeks) and region (North America/Europe, Latin America/Mexico, other region) using an internet-based interactive randomization system.

The dose of micafungin used in the study was chosen based on achieving exposures shown to have activity in a rabbit model of HCME. Simulation demonstrated that over 80% of neonates would achieve at least the desired micafungin AUC exposure at a dose of 10 mg/kg/day. Doses higher than 10 mg/kg were expected to add little incremental value and doses lower would decrease the chance of achieving the desired exposure level. The dose of amphotericin B used was based on current recommendations from the IDSA for treating neonatal candidiasis.

Study drug was blinded to all subjects and study staff except for the hospital pharmacist preparing the study drug. Amber covering on the infusion bags/syringes/ IV tubing was used to maintain the blind during study drug infusion as well as to protect the solution from light.

An independent Data Review Panel (DRP) reviewed data in a blinded fashion to confirm the diagnosis of invasive candidiasis and evaluate treatment outcome for each subject at end of study therapy, one week after the end of study drug therapy, and at end of study. Additionally, a Data and Safety Monitoring Board (DSMB) monitored subject safety during the conduct of the trial. The DSMB was comprised of independent reviewers who were not directly involved in the conduct of the study.

Study Endpoints

The primary endpoint was fungal free survival at one week following the last dose of study drug as assessed by the DRC. Fungal free survival was defined as being alive and fungal free (eradication) with no requirement for alternative systemic antifungal therapy for continued treatment. All other subjects were considered failures including those with missing data.

Secondary endpoints included time to mycological clearance of invasive candidiasis, clinical response at end of study drug therapy and at one week after last dose of study drug, and the incidence of emergent and recurrent fungal infections through the end of the study. Mycological response was assessed as eradication, persistence, or not assessed. Outcomes of persistence, not assessed, or missing assessment were classified as mycological failures (i.e. non-eradication). Clinical response was assessed as complete, partial, stable or progression. Complete or partial response were defined as a positive response. The evaluation of clinical response was only applicable to those infants who had clinical signs and symptoms related to the fungal infection at baseline.

Statistical Analysis Plan

The statistical analysis plan was finalized prior to study unblinding and database hard lock to ensure lack of bias.

<u>Analysis Populations</u>
The full analysis set (FAS) includes all randomized infants who are administered any amount of study drug. The primary efficacy analysis population is the FAS. Subjects in FAS are analyzed based on the treatment arm to which they were randomized regardless of the actual treatment received.

The modified FAS (MFAS) includes all infants in the FAS who have a confirmed invasive candidiasis or candidemia at baseline as confirmed by the independent DRP. The MFAS is used for secondary analyses of efficacy.

The safety population includes all randomized infants who are administered any amount of study drug. Subjects in the safety population are analyzed based on the treatment arm actually received. The safety population is used for all safety analyses.

Analysis Methods

The protocol specified analysis of the primary endpoint was to be based on a two-sided 95% confidence interval about the difference in fungal-free survival rates (micafungin- amphotericin B) based on the Cochran-Mantel-Haenszel method adjusting for estimated gestational age and region. If the lower bound of the confidence interval was greater than -20%, then micafungin was to be considered non-inferior to amphotericin B. However, since the study was terminated well below the initially planned sample size, statistical inference based on the non-inferiority hypothesis was considered not applicable by the Applicant. Therefore, statistical comparisons and inferences for the study are considered to be of limited relevance. The results of the study will, therefore, be summarized descriptively by treatment group and for the primary endpoint, with 95% exact confidence intervals for the point estimates.

Sample Size Calculation

Assuming a fungal-free survival rate of 75% for both treatment arms, a one-sided 2.5% significance level, and a non-inferiority margin of 20%, a total sample size of 225 infants (randomized 2:1) was to provide at least 90% power to demonstrate non-inferiority of micafungin compared to amphotericin B with respect to the difference in fungal-free survival.

The non-inferiority margin of 20% was based on statistical and clinical judgement. Based on data from the Neonatal Research Network and systematic reviews of the literature conducted by the Applicant, fungal free-survival following treatment with amphotericin B for neonatal candidiasis was estimated to be 75%. From medical review, it was estimated that fungal free survival in neonates with invasive candidiasis was unlikely to be more than 10% if left untreated. Therefore, M1 was estimated to be more than 55%. Based on clinical considerations, M2 was chosen to be 20% and expected to preserve at least 60% of the effect of amphotericin B compared to placebo.

However, the study was terminated early well below the fully powered sample size. Therefore, statistical inference based on the planned non-inferiority testing is not applicable.

Protocol Amendments

The original protocol was dated January 20, 2012. One substantial amendment to the protocol (Version 1) was issued on August 22, 2013. The changes in the amendment were primarily for clarification purposes. Most subjects (13 micafungin and 8 amphotericin B) were enrolled under the original protocol. The remaining subjects (7 micafungin and 2 amphotericin B) were enrolled under protocol version 1. The modifications to the protocol did not have an impact on the integrity of the trial or the interpterion of the results.

8.1.1.2 Study Results

Compliance with Good Clinical Practices

The Applicant states that "the study was conducted in accordance with the protocol, Good Clinical Practice (GCP), ICH (International Committee on Harmonization) guidelines, applicable regulations and guidelines governing clinical study conduct and the ethical principles that have their origin in the Declaration of Helsinki."

Financial Disclosure
See Section 17.1 for the study's financial disclosure information.

Patient Disposition

A total of 30 subjects were randomized in the study: 20 to micafungin and 10 to amphotericin B. All subjects received at least one dose of the study drug to which they were randomized. Therefore, the Safety analysis set, the FAS, and the randomized population are the same. Six subjects (4 micafungin and 2 amphotericin B) did not have confirmed invasive candidiasis or candidemia at baseline per the DRP and were excluded from the MFAS.

Table 8-1: Analysis Populations-Study 9463-CL-2303

Analysis Population	Micafungin	Amphotericin B
Randomized	20 (100%)	10 (100%)
Safety	20 (100%)	10 (100%)
FAS	20 (100%)	10 (100%)
MFAS	16 (80%)	8 (80%)

Overall, 50% of randomized subjects completed treatment with study drug. Nine (45%) micafungin-treated subjects and 6 (60%) amphotericin B-treated subjects discontinued treatment early. The reasons for discontinuing treatment early were due to adverse event (3), physician decision (3), death (2), and/lack of efficacy (1) for micafungin treated subjects and adverse event (3), protocol violation (2), and lack of efficacy (1) for amphotericin B treated subjects.

The majority (88%) of subjects completed the study through the 30-day follow-up visit. Four (20%) micafungin treated subjects and 1 (10%) amphotericin B treated subject discontinued the study early. One micafungin treated subject discontinued the study early due to the physician's decision. The remaining subjects were considered having discontinued the study early because of death before completing the 30-day follow-up visit.

Table 8-2: Subject Disposition -Study 9463-CL-2303

Randomized	Micafungin 20 (100%)	Amphotericin B 10 (100%)
Completed Treatment	11 (55%)	4 (40%)
Discontinued Treatment	9 (45%)	6 (60%)
Adverse event	3 (15%)	3 (30%)
Death	2 (10%)	0
Lack of efficacy	1 (5%)	1 (10%)
Physician Decision	3 (15%)	0
Protocol violation	0	2 (20%)
Completed Study	16 (80%)	9 (90%)
Discontinued Study	4 (20%)	1 (10%)
Death	3 (15%)	1 (10%)
Physician Decision	1 (5%)	0

Protocol Violations/Deviations

Overall, 2 (10%) micafungin and 4 (40%) amphotericin B-treated subjects had protocol deviations. All but 1 amphotericin B-treated subject had a protocol deviation of entering the study despite not meeting all inclusion/exclusion criteria, primarily related to the diagnosis of invasive candidiasis. One subject in each treatment group also had a protocol deviation due to using the incorrect weight to calculate some of the doses received.

Demographic and Other Baseline Characteristics

The following table summarizes demographic and baseline characteristics of subjects in the FAS. The majority (60%) of the micafungin-treated subjects were male, whereas the majority (60%) of the amphotericin B-treated subjects were female. The majority of the subjects were white and from North America or Europe. Micafungin-treated subjects were slightly older than amphotericin B-treated subjects. Five (25%) micafungin-treated subjects were between 4 weeks and 4 months old whereas all amphotericin B- treated subjects were 4 weeks old or less. The mean baseline weight was 2.1 kg.

Table 8-3: Demographic and Baseline Characteristics (FAS) -Study 9463-CL-2303

Parameter	Micafungin (n=20)	Amphotericin B (n=10)
Sex		
Male	8 (40.0)	6 (60.0)
Female	12 (60.0)	4 (40.0)
Race		
White	18 (90.0)	9 (90.0)
Black	0	1 (10.0)

Parameter	Micafungin (n=20)	Amphotericin B (n=10)
Asian	1 (5.0)	0
Other	1 (5.0)	0
Age (days)		
Mean (sd)	30.2 (28.0)	16.9 (5.1)
Median	17.5	15.5
Min, Max	9, 117	12, 26
Age Group		
≤ 4 weeks	15 (75.0)	10 (100.0)
More than 4 weeks to 4 months	5 (25.0)	0
Gestational Age		
<27 weeks	3 (15.0)	2 (20.0)
≥27 weeks	17 (85.0)	8 (80.0)
Region		
North America/Europe	15 (75.0)	9 (90.0)
Latin America	4 (20.0)	1 (10.0)
Other	1 (5.0)	0
Baseline Weight (kg)		
Mean (sd)	2.2 (1.4)	2.1 (1.0)
Median	1.735	2.15
Min, Max	0.68, 4.845	0.6, 3.71
Baseline Weight Categories		
>1500 g	11 (55.0)	7 (70.0)
1000-1500 g	4 (20.0)	1 (10.0)
<1000 g	5 (25.0)	2 (20.0)

The majority of the subjects had candidemia only. Invasive candidiasis, primarily involving the urinary tract, was diagnosed in 8 (40%) micafungin-treated subjects and 2 (20%) amphotericin B-treated subjects. All but 2 micafungin-treated subjects demonstrated clinical signs of infection at baseline. The most common organisms isolated in the micafungin group were *C. parapsilosis* and *C. albicans*. *C. albicans* was isolated in half of the amphotericin B-treated subjects. Per the DRP, end-organ dissemination was present at baseline in 7 (35%) micafungin-treated subjects and 3 (30%) amphotericin B-treated subjects. CNS/brain was the site of end-organ dissemination for 2 of the 7 micafungin-treated subjects. This was based on imaging and not on positive CSF fungal cultures.

Table 8-4: Fungal Infection Characteristics (FAS)- Study 9463-CL-2303

Parameter	Micafungin (n=20)	Amphotericin B (n=10)
Fungal Infection Type		
Candidemia Only	12 (60.0)	7 (70.0)
Invasive Candidiasis	8 (40.0)	2 (20.0)

Parameter	Micafungin (n=20)	Amphotericin B (n=10)
Peritonitis and blood	1	0
Urinary tract and blood	3	0
Urinary tract and eye	1	0
Urinary tract only	3	2
Missing		1 (10.0)
DRP Diagnosis		
Proven	16 (80.0)	8 (80.0)
Not confirmed	1 (5.0)	1 (10.0)
Outside Enrolling Window	3 (15.0)	1 (10.0)
Organism		
C. albicans	8 (40.0)	4 (40.0)
C. albicans and *C. tropicalis*	0	1 (10.0)
C. glabrata	0	2 (20.0)
C. lusitaniae	1 (5.0)	1 (10.0)
C. parapsilosis	9 (45.0)	2 (20.0)
C. famata and *C. guilliermondii*	1 (5.0)	0
C. tropicalis	1 (5.0)	0
Clinical Signs at Baseline		
Yes	18 (90.0)	10 (100.0)
No	2 (10.0)	0
Presence of End-Organ Dissemination (DRP)		
Yes	7 (35.0)	3 (30.0)
No	13 (65.0)	7 (70.0)

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Since subjects were hospitalized for IV administration of the study drug, compliance with study treatment was high. A single subject in each treatment group was considered to be non-complaint with study drug.

The duration of treatment with micafungin was a mean (SD) of 18.6 (10.7) days and ranged from 1 to 42 days. The duration of treatment with amphotericin B was a mean (SD) of 15.5 (11.2) days and ranged from 6 to 42 days.

All subjects received at least 1 concomitant medication. During the treatment period, 6 (30%) micafungin-treated subjects and 1 (10%) amphotericin B-treated subject received concomitant anti-fungal treatment. These were all due to overlapping treatments during Day 1. Up to 48 hours of systemic antifungal therapy prior to the first dose of study drug was allowed per the protocol. During the 1-week post-treatment and after 1 week post-treatment, 4 (20%)

micafungin-treated subjects and 7 (70%) amphotericin B-treated subjects received concomitant anti-fungal treatment.

Efficacy Results-Primary Endpoint

Fungal free survival at 1 week following the last dose of study drug as assessed by the DRC for the FAS was observed for 12 (60%) micafungin-treated subjects and 7 (70%) amphotericin B-treated subjects. Of the 8 micafungin-treated subjects who were considered failures, 2 subjects died and 2 subjects were alive but were not mycologically eradicated. The remaining subjects were alive but mycological eradication was unknown or not assessed due to the *Candida* infection not being confirmed. The 3 amphotericin B subjects who were considered failures were alive but 2 were not mycologically eradicated and 1 was not assessed due to the *Candida* infection not being confirmed. Results were consistent for the MFAS where 11 (68.8%) micafungin-treated subjects and 6 (75%) amphotericin B-treated subjects had fungal free survival at 1 week following the last dose of study drug.

Table 8-5: Fungal Free Survival One Week After Last Dose of Study Drug Assessed by DRP (FAS)- Study 9463-CL-2303

Response	Micafungin (n=20)	Amphotericin B (n=10)
Success	12 (60%)	7 (70%)
95% Confidence Interval	(36.1, 80.9)	(34.8, 93.3)
Failure	8 (40%)	3 (30%)
Died	2 (10%)	0
No mycological eradication	2 (10%)	2 (20%)
Mycological Eradication Unknown	3 (15%)	0
Not Assessable	1 (5%)	1 (10%)

Fungal free survival at 1 week following the last dose of study drug by various subgroups is summarized in the following table for the FAS. Interpretation of these results must be made with caution given the extremely limited sample sizes.

Table 8-6: Fungal Free Survival One Week After Last Dose of Study Drug Assessed by DRP for Various Subgroups (FAS)- Study 9463-CL-2303

Subgroup	Micafungin	Amphotericin B
Sex		
Males	3/8 (37.5)	5/6 (83.3)
Females	9/12 (75.0)	2/4 (50.0)
Age		
<3 weeks	8/13 (61.5)	5/7 (71.4)
≥ 3 weeks	4/7 (57.1)	2/3 (66.7)
Region		

Subgroup	Micafungin	Amphotericin B
North America/Europe	10/15 (66.7)	7/9 (77.8)
Latin America	2/4 (50.0)	0/1
Other	0/1	-
Fungal Infection Type		
Candidemia only	5/12 (41.7)	5/7 (71.4)
Invasive Candidiasis	7/8 (87.5)	2/2 (100.0)
Missing	-	0/1

Efficacy Results-Secondary and Other Relevant Endpoints

Time to mycological clearance was a secondary endpoint. Per the DRP assessment, the median time to mycological clearance was numerically longer for micafungin treated subjects (16 days) than that for amphotericin B treated subjects (6 days). The 25th percentile of time to mycological clearance was 3 days for both treatment groups.

A single emergent fungal infection (*Candida* infection in the urinary tract) was noted in a micafungin-treated subject. No amphotericin B-treated subjects experienced an emergent infection.

No recurrent infections were noted in micafungin-treated subjects. A single recurrent infection was noted in an amphotericin B-treated subject following initial eradication. The infection recurred approximately 1 month after the completion of study treatment and was localized to the urinary tract.

For the 2 micafungin-treated subjects with end organ dissemination of the CNS/brain, both subjects were alive but the follow-up status was considered worsened for one subject and not assessed in the other as the subject went on to receive fluconazole.

Clinical response for subjects that experienced clinical signs and symptoms at baseline was assessed by the DRC at the end of study drug therapy and one week after the last dose of study drug. Two micafungin-treated subjects in the FAS did not have clinical signs and symptoms at baseline and were not assessed for clinical response. At the end of study drug therapy, positive clinical response (complete or partial) was achieved in 11 (61.1%) of micafungin-treated subjects and 7 (70%) of amphotericin B-treated subjects. The results at one week after the last dose of study drug were the same as at the end of study drug therapy with the exception that 2 micafungin-treated subjects with progression at end of study drug therapy were not assessed the following week.

Table 8-7: Clinical Response at End of Study Drug Assessed by DRP (FAS)- Study 9463-CL-2303

Response	Micafungin (n=18)	Amphotericin B (n=10)
Complete	10 (55.6)	7 (70.0)
Partial	1 (5.6)	0
Stable	1 (5.6)	1 (10.0)
Progression	3 (16.7)	2 (20.0)
Missing	3 (16.7)	0

8.1.2. Study 9463-CL-6001

Trial Design

Study 9463-CL-6001 is a prospective, multicenter, open-label uncontrolled Phase 2 clinical trial that was designed to evaluate the plasma and CNS levels of micafungin administered at a dose of 8 mg/kg per day to neonates and young infants who had systemic candidiasis and/or *Candida* meningitis. Secondary objectives were to evaluate the safety and efficacy in infants treated with micafungin.

The study was initiated by Ospedale Pediatrico Bambino Gesù (OPBG) and conducted at 2 sites in Italy. On December 5, 2017, the sponsorship of the study was transferred to the Applicant, Astellas. However, Site 2's independent ethics committee did not approve the transfer of sponsorship from OBPG to Astellas. This site enrolled only 1 subject. Therefore, the study report submitted in this sNDA is only based on the subjects enrolled at Site 1.

Neonates up to 180 days old with systemic candidiasis expected to survive at least 3 days were eligible for enrollment. Subjects with hepatopathy or known allergy or hypersensitivity to echinocandins were not eligible for enrollment.

All enrolled subjects received 8 mg/kg per day of micafungin administered through intravenous infusion. The duration of treatment was expected to last a minimum of 14 days and until one of the following occurred: negative results (absence of *Candida* growth) from at least 2 consecutive blood cultures and/or resolution of clinical and laboratory symptoms and reduction of mannan antigen blood level were obtained; in case of meningitis, hydrocephalus with or without external ventricular drainage, negative results (absence of *Candida* growth) from at least 2 consecutive CSF cultures associated with resolution of clinical and laboratory symptoms; or the addition or switch to another antifungal agent or dosage change of micafungin due to demonstration of therapy failure. The dose used in this study was based on nonclinical pharmacology and pharmacokinetic bridging studies which indicated that the dose that ensures a good distribution into the CNS appeared to be at least 8 mg/kg per day.

Study Endpoints

The primary endpoints of the study were related to the quantification of micafungin levels in the blood and cerebrospinal fluid. The secondary endpoint for efficacy was success/failure of therapy with micafungin. The definitions of success/failure were the following:

- In the case of systemic candidiasis: Success is survival associated with negative *Candida* results of two consecutive blood cultures or by resolution of clinical and laboratory symptoms together with reduction of mannan antigen blood level (< 125 pg/ml). Failure is death due to *Candida* sepsis, confirmation of persistence of positive *Candida*, the need to add or switch to another antifungal agent and/or change of micafungin dosage for the resolution of infection, or the persistence of *Candida* colonization with the persistence of clinical and laboratory symptoms with high blood level of the mannan antigen at the 14th day from the start of therapy.
- In the case of *Candida* meningitis: Success is survival associated with negative *Candida* results of two consecutive CSF cultures and resolution of clinical and laboratory symptoms. Failure is death due to *Candida* meningitis, persistence of *Candida* infection by confirmation of positive CSF culture, or the need to add or switch to another antifungal agent and/or change of micafungin dosage for the resolution of infection.

Additional efficacy endpoints specified in the SAP are fungal-free survival at end of treatment (EOT) and at the end of the trial, all-cause mortality through the end of the trial, mycological response at EOT and at the end of the trial, and overall incidence of emergent and recurrent fungal infections through the end of the trial. Fungal free survival is defined as alive, mycological response of eradication, and no requirement for alternative systemic antifungal therapy for continued treatment.

Analysis Populations

The FAS consists of all enrolled subjects who received at least 1 administration of the study medication and from whom the blood draws for the PK analysis were collected. The FAS was used for PK analyses.

The Safety Analysis Set (SAF) consisted of all enrolled subjects who received at least one dose of study drug. The SAF was used for summaries of demographic and baseline characteristics as well as efficacy data.

The MFAS included neonates in the SAF who were affected by systemic candidiasis and/or *Candida* infection at baseline. The MFAS was used for summaries and analyses of the efficacy data as well as selected demographic and baseline characteristics.

Sample Size Calculation and Analysis Methods

The sample size was to be at least 30 neonates up to 180 days old. It was not based on statistical considerations. Data was to be summarized using descriptive statistics including percentages and exact 95% confidence intervals.

Protocol Amendments

The original study protocol v 1.0 dated August 1, 2014 was not implemented. Study protocol v 2.0 dated September 10, 2014 was implemented and amended twice. Changes made in study protocol v 3.0 dated May 25, 2015 included changing the cutoff for positive mannan antigen test results from 250 to 125 pg/ml, specified that absence of *Candida* growth in case of *Candida*

meningitis could be based on 2 instead of 3 consecutive CSF cultures, increased the age from up to 90 days to up to 180 days, and specified that at least 4 neonates with *Candida* meningitis were to be enrolled. Changes made in study protocol v 4.0 dated September 13, 2017 included changing the sponsorship to Astellas, clarified that neonates with *Candida* meningitis would only be included if available during the enrollment period, and extended the study end date. Two subjects were enrolled under study protocol v 2.0, 32 subjects were enrolled under v 3.0, and 1 subject was enrolled under v 4.0.

Results

Patient Disposition

A total of 35 subjects were enrolled in the study. All subjects received at least one dose of study drug and were included in the SAF. Of these subjects, 21 (60%) were determined to have a diagnosis of proven or probable systemic candidiasis and/or *Candida* infection at baseline and were included in the MFAS.

Overall, 20 (57.1%) subjects completed study treatment which required a minimum of 14 days of study drug. Study drug was discontinued early in 15 (42.9%) subjects. Reasons for early discontinuation of study drug included lack of efficacy in 4 subjects, lack of confirmation of fungal infection in 4 subjects, and death in 3 subjects. Other reasons for early discontinuation of study drug included subject transferred hospital and negative cultures leading to antifungal treatment discontinuation prior to 14 days of treatment. Only 2 subjects discontinued the study prematurely, 1 due to death and 1 due to clinical worsening in the absence of detectable *Candida* infection.

Table 8-8: Patient Disposition- Study 9463-CL-6001

	Micafungin
Enrolled	**35 (100.0)**
Completed Treatment	20 (57.1)
Discontinued Treatment Prematurely	15 (42.9)
Lack of efficacy	4 (11.4)
Death	3 (8.6)
Infection not confirmed	4 (11.4)
Other	4 (11.4)
Completed Study	33 (94.3)
Discontinued Study Prematurely	2 (5.7)
Death	1 (2.9)
Other	1 (2.9)

Demographic and Other Baseline Characteristics

The following table summarizes demographic and baseline characteristics of subjects in the SAF and the MFAS. The populations were generally comparable. Slightly more than half were males and the majority were white. The mean age was approximately 2.5 months. Overall, 28

subjects in the SAF were ≤ 120 days and of those 17 were in the MFAS. The mean baseline weight was 2.3 kg for the SAF and 2.6 kg for the MFAS. The diagnosis of *Candida* infection was confirmed in 21 (60%) of the SAF subjects. The diagnosis was suspected but not confirmed in the remaining 14 (40%) subjects.

Table 8-9: Demographic and Baseline Characteristics- Study 9463-CL-6001

Parameter	SAF (n=35)	MFAS (n=21)
Sex		
Male	20 (57.1)	14 (66.7)
Female	15 (42.9)	7 (33.3)
Race		
White	32 (91.4)	20 (95.2)
Black	2 (5.7)	1 (4.8)
Other	1 (2.9)	0
Age (months)		
Mean (sd)	2.5 (2.1)	2.6 (2.3)
Median	1.9	1.5
Min, Max	0.3, 8.1	0.6, 8.1
Age Group		
0 to ≤ 4 weeks	8 (22.9)	5 (23.8)
> 4 weeks to ≤ 4 months	20 (57.1)	12 (57.1)
> 4 months to ≤ 6 months	3 (8.6)	1 (4.8)
> 6 months to < 2 years	4 (11.4)	3 (14.3)
Baseline Weight (kg)		
Mean (sd)	2.3 (1.2)	2.6 (1.3)
Median	2	2.4
Min, Max	0.5, 5.1	0.7, 5.1
Diagnosis		
Proven/Probable	21 (60.0)	21 (100.0)
Suspected/Not confirmed	14 (40.0)	N/A

The majority of the MFAS subjects had candidemia (blood) as the site of the infection. The most common *Candida* organisms isolated at baseline were *C. albicans* (52.4%) and *C. parapsilosis* (28.6%).

Table 8-10: Fungal Infection Characteristics (MFAS)- Study 9463-CL-6001

Parameter	Micafungin (n=21)
Site of Fungal Infection	
Blood	16 (76.2)
Lung	1 (4.8)

Parameter	Micafungin (n=21)
Lung and Skin	1 (4.8)
Urinary Tract	3 (14.3)
Organism	
C. albicans	11 (52.4)
C. glabrata	1 (4.8)
C. krusei	1 (4.8)
C. lusitaniae	1 (4.8)
C. parapsilosis	6 (28.6)
C. tropicalis	1 (4.8)

Efficacy Results

The primary endpoint(s) of the study were related to PK. Therefore, all efficacy endpoints were considered secondary.

The secondary efficacy endpoint of treatment response at EOT was assessed as success or failure by the Investigator for only those subjects who completed a minimum of 14 days of study drug therapy. For the 20 subjects in the SAF that completed a minimum of 14 days of study therapy, the successful treatment response rate was 80% (exact 95% confidence interval: 56.3%, 94.3%). For the 15 subjects in the MFAS that completed a minimum of 14 days of study treatment, the successful treatment response rate was 86.7% (exact 95% confidence interval: 59.5%, 98.3%). Treating those who were not assessed since they did not complete a minimum of 14 days of study therapy as failures, the successful treatment response rate is 45.7% with an exact 95% confidence interval of (28.8%, 63.4%) for the SAF and 61.9% with an exact 95% confidence interval of (38.4%, 81.9%) for the MFAS.

Table 8-11: Treatment Response at End of Treatment- Study 9463-CL-6001

Analysis Population-Cohort Treatment Response	Micafungin	Exact 95% Confidence interval
SAF-Overall	(n=35)	
Success	16 (45.7)	(28.8, 63.4)
Failure	4 (11.4)	
Not assessed*	15 (42.9)	
SAF-Completed	(n=20)	
Success	16 (80.0)	(56.3, 94.3)
Failure	4 (20.0)	
MFAS-Overall	(n=21)	
Success	13 (61.9)	(38.4, 81.9)
Failure	2 (9.5)	
Not assessed*	6 (28.6)	
MFAS-Completed	(n=15)	
Success	13 (86.7)	(28.8, 63.4)

Analysis Population-Cohort Treatment Response	Micafungin	Exact 95% Confidence interval
Failure	2 (13.3)	

*Not assessed by Investigator since did not complete a minimum of 14 days of study drug.

Fungal free survival at the EOT and the end of study was evaluated for those subjects with a confirmed diagnosis of systemic candidiasis and/or *Candida* infection at baseline (i.e. the MFAS). In the MFAS, fungal free survival at EOT was observed for 13 (61.9%) subjects. Of the 8 failures at EOT, 6 subjects did not have mycological eradication and 2 were not assessed. At the end of the study, fungal free survival was reported for 18 (85.7%) subjects. The 3 failures were due to death (1), lack of eradication (1), and not assessed (1). It should be noted that for the majority of the subjects, the end of treatment assessment was also the end of study assessment. Additionally, 5 of the subjects who did not have mycological eradication at the EOT but were considered to have mycological eradication at the end of study received micafungin with the addition of Ambisome or an increased dose of micafungin with or without the addition of Ambisome after the EOT assessment. Therefore, the assessment of mycological eradication after EOT in these subjects cannot be fully attributed to the protocol-specified dose of micafungin and the interpretation of the results at end of study must be made with caution.

Table 8-12: Fungal Free Survival at End of Treatment and End of Study (MFAS)- Study 9463-CL-6001

Timepoint Response	Micafungin (n=21)	Exact 95% Confidence Interval
End of Treatment		
Success	13 (61.9)	(38.4, 81.9)
Failure	8 (38.1)	
Did not have mycological eradication	6	
Not assessed	2	
End of Study		
Success	18 (85.7)	(63.7, 97.0)
Failure	3 (14.3)	
Died	1	
Did not have mycological eradication	1	
Not assessed	1	

For the purposes of this sNDA, subjects < 120 days of age are the most relevant patient population. In the 17 subjects in the MFAS who were < 120 days of age, fungal free survival at EOT was noted for 10 (58.8%) subjects.

A single emergent *Candida* infection was noted during the treatment period in a subject < 120 days of age who enrolled with candidemia. The emergent infection was reported based on a single positive stool culture without additional cultures to confirm invasive disease. The

subject's initial candidemia resolved on therapy with micafungin. There were no recurrent fungal infections noted during the study.

Overall, the all-cause mortality rate during the study was 14.3% (5/35) with an exact 95% confidence interval of (4.8%, 30.3%). All 5 deaths were of subjects < 120 days of age. Two deaths were from subjects with a proven *Candida* infection (in MFAS) and three of the deaths were in subjects without a confirmed fungal infection

8.1.3. Study 9463-CL-6002

Trial Design

Study 9463-CL-6002 was a retrospective review of the medical records of all newborns and small infants treated with micafungin because of sepsis and/or meningitis due to *Candida* during 2012-2015 at the Department of Neonatology of OPBG in Rome. The primary objective of the study was to collect data on plasma and CSF levels of micafungin to provide evidence for choosing the best dose of micafungin for treating neonates and small infants. The results of the study were originally published in 2015. In 2017, the Applicant (Astellas) entered into an agreement with the investigative site to gain access to the data from this study. The original study site provided their datasets to Astellas. Astellas, however, was not able to verify the data from the source records to perform data quality assurance.

In addition to summarizing micafungin plasma and CSF concentrations, the Applicant added treatment response as assessed by the investigator, 30 day all-cause mortality and overall all-cause mortality as objective efficacy endpoints to be summarized. The Safety analysis set included all subjects meeting the criteria for data collection. The MFAS included those subjects who had proven or probable systemic candidiasis and/or *Candida* meningitis at baseline (prior to first treatment). All endpoints were summarized with descriptive statistics.

Trial Results

A total of 18 neonates and young infants were treated with micafungin during the period of 2012-2015 in OBPG and make up the safety analysis set. Two of these subjects were determined to only have a possible diagnosis of systemic candidiasis. Therefore, 16 subjects were included in the MFAS.

The following table summarizes the demographic and baseline characteristics of the subjects by the average daily dose of micafungin received. It should be noted that 1 subject included in the 8 mg/kg/day group received 3 days of micafungin at a dose of 10 mg/kg/day before dropping to 8 mg/kg/day for 12 additional days. Additionally, 1 subject included in the 10 mg/kg/day group received 4 days of micafungin at a dose of 15 mg/kg/day before dropping to 10 mg/kg/day for 70 additional days. Overall, most of the subjects were male and white. Two-thirds of the subjects were ≤ 120 days old.

Table 8-13: Demographic and Baseline Characteristics (SAF)- Study 9463-CL-6002

Parameter	Micafungin < 8 mg/kg/day (n=2)	Micafungin 8 mg/kg/day (n=10)	Micafungin 10 mg/kg/day (n=6)
Sex			
Male	2 (100.0)	7 (70.0)	4 (66.7)
Female	0	3 (30.0)	2 (33.3
Race			
White	2 (100.0)	9 (90.0)	6 (100.0)
Black	0	1 (10.0)	0
Age (days)			
Mean (sd)	27.5 (10.6)	71.5 (55.1)	97.7 (74.1)
Median	27.5	61	106
Min, Max	20, 35	4, 150	15, 180
Age Group			
≤ 120 days	2 (100.0)	7 (70.0)	3 (50.0)
> 120 days	0	3 (30.0)	3 (50.0)
Baseline Weight (kg)			
Mean (sd)	2.1 (1.0)	2.8 (0.9)	4.4 (2.1)
Median	2.05	2.6	4.1
Min, Max	1.37, 2.73	1.7, 4.5	1.3, 6.8
Diagnosis			
Proven/Probable	2 (100.0)	8 (80.0)	6 (100.0)
Possible	0	2 (20.0)	0

The majority of the MFAS subjects had candidemia (blood) as the site of the infection. A single subject (> 120 days old) had positive blood and CSF cultures. The remaining were urinary tract infections. The most common *Candida* organisms isolated at baseline were *C. albicans* and *C. parapsilosis*.

Table 8-14: Fungal Infection Characteristics (MFAS)- Study 9463-CL-6002

Parameter	Micafungin < 8 mg/kg/day (n=2)	Micafungin 8 mg/kg/day (n=8)	Micafungin 10 mg/kg/day (n=6)
Site of Fungal Infection			
Blood	1 (50.0)	5 (62.5)	3 (50.0)
Urinary Tract	1 (50.0)	3 (37.5)	2 (33.3)
Blood and CSF	0	0	1 (16.7)
Organism			
C. albicans	0	5 (62.5)	3 (50.0)
C. krusei	0	1 (12.5)	0
C. parapsilosis	2 (100.0)	2 (25.0)	3 (50.0)

Successful treatment response was observed for all but 3 subjects. The 3 subjects that were considered to have failed therapy were all more than 120 days old and died after documented mycological eradication of the *Candida* infection. None of the deaths occurred within 30 days of starting treatment with micafungin. It should be noted that in addition to micafungin Ambisome use was noted for 5 subjects (1 who received < 8 mg/kg/day, 3 who received 8 mg/kg/day, and 1 who received 10 mg/kg/day of micafungin). Therefore, successful treatment response cannot be fully attributed to micafungin in these subjects.

Table 8-15: Treatment Response and All-Cause Mortality- Study 9463-CL-6002

Parameter	Micafungin < 8 mg/kg/day	Micafungin 8 mg/kg/day	Micafungin 10 mg/kg/day
Treatment Response-SAF	(n=2)	(n=10)	(n=6)
Success	2 (100)*	8 (80.0)**	5 (83.3)***
95% Confidence Interval	(15.8, 100)	(44.4, 97.5)	(35.9, 99.6)
Treatment Response-MFAS	(n=2)	(n=8)	(n=6)
Success	2 (100)*	6 (75.0)**	5 (83.3)***
95% Confidence Interval	(15.8, 100)	(34.9, 96.8)	(35.9, 99.6)
All-Cause Mortality-SAF	(n=2)	(n=10)	(n=6)
Deaths	0	2 (20.0)	1 (16.7)
95% Confidence Interval	(0, 84.2)	(2.5, 55.6)	(0.4, 64.1)

*****Includes 1 subjects who also received Ambisome
**Includes 3 subjects who also received Ambisome
***Includes 1 subject who also received Ambisome

8.2. Exploratory Efficacy Analysis

As an exploratory analysis, the review team attempted to assess the efficacy of micafungin at different dose groups and infection sites. Conclusions are limited by small sample size, missing data on dose and site of infection, non-random assignment to dose, and differences in study design among the 9 studies from which these data are gathered. Based on the available data as displayed in the table below, a dose-response relationship for efficacy is not discernible. It also does not appear that efficacy differed by infection site.

Table 8-16: Efficacy of Micafungin for Candidemia, Disseminated and CNS Disease in the ISSNEO Population Stratified by Dose of Micafungin Received

Dose (average dose received in mg/kg/day)	Infection Site; Number of neonates who received micafungin alone/total number	Treatment Duration (days, range)*	Survival at EOT (%)*	Mycological Response at EOT*	Recurrent Infection*
≤2	Blood; 13/14	5-28	**12/13 (92.3)**	13/13 (100)	0
	Blood/CNS; 1/1	36	**1/1 (100)**	1/1 (100)	1/1 (100)
	Disseminated**; 1/6	5	**1/1 (100)**	0	0

Dose (average dose received in mg/kg/day)	Infection Site; Number of neonates who received micafungin alone/total number	Treatment Duration (days, range)*	Survival at EOT (%)*	Mycological Response at EOT*	Recurrent Infection*
>2<6	Blood; 9/12	14-35	**6/9 (66.7)**	6/9 (66.7)	0
	Disseminated**; 0/1	N/A	**N/A**	N/A	N/A
≥6<8	Blood; 4/7	15-25	**4/4 (100)**	4/4 (100)	0
≥8<10	Blood; 10/19	1-21	**10/10 (100)**	7/10 (70)	0[1]
≥10<11	Blood; 14/15	2-28	**10/14 (71.4)**	7/14 (50)	0[2]
≥11	Blood; 0/1	N/A	**N/A**	N/A	N/A
	Blood with source***; 2/5	34-48	**2/2 (100)**	1/2 (50)	0
Total	54/81 (66.7%)		46/54 (85.2%)	39/54 (72.2%)	1/54 (1.9)

Source: Reviewer generated from data provided by the Applicant in response to an IR
*Includes only babies who received micafungin alone
**Not further specified by site
***Sources for the 5 patients were catheter tip/skin, lungs/urine, urinary tract, urinary tract, and wound respectively

8.3. Dosing Considerations for Candida Meningoencephalitis

Concerted efforts were made by the Applicant and by the review team to determine whether a dose of 10 mg/kg/day was optimal for treatment of neonatal candidiasis complicated by ME and/or ocular involvement in infants younger than 4 months of age. However, upon review of the data, it became apparent that although the dose was likely at least 10 mg/kg/day, the optimal dose for ME could not be established. These conclusions are based on the review of the individual animal data in a rabbit model of HCME which is considered pathophysiologically relevant to neonatal ME in humans. Section 9 presents full details of these studies, and clinically relevant details are discussed here. See the Clinical Pharmacology Section 6.2.1 in this review for further discussion on the PK and PD implications of these studies.

In the 2008 paper by Hope et al.[3], highest micafungin concentrations were seen in the meninges and choroid, but micafungin was not consistently detected in the CSF. The authors concluded that an $AUC_{0\text{-}24}$ target of 166.5 mg *h/L in the rabbit was associated with near-maximal reduction in fungal burden achieved at doses 8-16 mg/kg. When bridging this micafungin exposure to neonates using PK simulations, a dose of 9-15 mg/kg was suggested.

In a later paper by Hope et al.[7], 47 infants with suspected or proven candidiasis were given micafungin at 0.75, 1.5, 3, 7, 10 and 15 mg/kg/day. Serum micafungin concentration was measured using high-performance liquid chromatography. Using simulations, they determined that doses of 10 mg/kg/day would achieve an $AUC_{0\text{-}24}$ target of 166.5 mg *h/L thought to be

[7] Hope W, Smith P, Arrieta A, et al. Population pharmacokinetics of micafungin in neonates and young infants. Antimicrobial Agents and Chemotherapy. 2010;54(6):2633-2637.

associated with near-maximal decline in fungal burden in the majority (>90%) of pediatric patients younger than 4 months of age. In a 2008 paper by Petraitiene et al.[4], micafungin doses between 16 to 32 mg/kg were reported to achieve reduction in fungal burden greater than in untreated controls in various CNS compartments (combined cerebrum, cerebellum, spinal cord). Analysis by the Clinical Pharmacology reviewer Dr. Jason Moore, and Pharmacometrics reviewer Dr. Justin Earp showed that corresponding estimated neonatal doses would be approximately 10-25 mg/kg/day.

There are potential limitations to the rabbit model. First, although considered to be relevant to neonatal CNS infection, it is unclear how comparable the disease itself and CNS penetration of micafungin are between neonates and rabbits. Second, the rabbits were sacrificed after only 7 daily doses of micafungin, so outcome data (e.g. seizures, death) were not available and the duration of dosing for a CNS infection might have been suboptimal. Third, it is unclear how the decrease in fungal burden in different CNS compartments in general correlates with clinical efficacy in humans. Finally, equivalent neonatal doses of 10-25 mg/kg/day found after analysis of the Petraitiene study data raise concern that the use of 10 mg/kg/day may result in suboptimal-dosing of the neonates with *Candida* ME.

The maximum dose used in the 9 studies submitted to this sNDA was 15 mg/kg/day in 5 patients; *Candida* ME was not diagnosed in any of these patients and no conclusion regarding efficacy could be drawn.

Reviewer comment: Sections of labeling approved by the European Medicines Agency (EMA)[8] for micafungin pertaining to infants younger than 4 months are reproduced below:

[8] https://www.ema.europa.eu/en/documents/product-information/mycamine-epar-product-information_en.pdf

The Hope study referenced in the section above formed the basis of EMA's decisions on dosing regimens in infants younger than 4 months.

8.4. Integrated Review of Effectiveness

The pathophysiology of invasive candidiasis in neonates and infants younger than 4 months of age is distinct from that of adults or older children because of the risk of ME that can lead to significant early and delayed morbidity including neurodevelopmental abnormalities, and mortality. Thus, efficacy of micafungin for the treatment of neonatal candidiasis, i.e. candidemia and acute disseminated candidiasis with ME cannot be extrapolated from adult or older pediatric patients with candidemia. Micafungin exposure at the approved dose regimens for the treatment of candidemia in adults and pediatric patients older than 4 months of age may be insufficient for effective treatment of CNS disease in neonates and infants younger than 4 months of age.

The Applicant used a rabbit model of HCME (Hope et al) to determine a PD target of log reduction in fungal burden in CNS compartments (described in Sections 6.2.1, 9.3.2, and 17.2.3). In this model, micafungin exhibited linear plasma PK in the range of 0.25-32 mg/kg and penetrated most CNS compartments at doses ≥2 mg/kg, although it was not reliably detected in the cerebrospinal fluid (CSF). A dose-dependent reduction in fungal burden in various CNS compartments was observed: in the cerebrum and cerebellum, fungal burden reduction relative to untreated controls was observed at 8 mg/kg, while in spinal cord, fungal clearance

was achieved at 24 mg/kg. Significant fungal burden reduction in cerebrum, cerebellum and spinal cord relative to untreated controls was achieved at rabbit doses ranging from 16 to 32 mg/kg which correspond to approximate human neonatal doses of 10-25 mg/kg based on AUC comparison. Because animals were sacrificed on Day 7, survival was not assessed in this study; thus, the correlation between reduction in fungal burden and disease-free survival is unclear. Although the rabbit model appears pathophysiologically similar to human neonatal ME, the lack of outcome data, use of a single *Candida* strain and other limitations limit its generalizability to the neonatal population.

Based primarily on this rabbit model, a neonatal dose of 10 mg/kg was evaluated in the randomized Phase 3 trial (Study 9463-CL-2303) comparing micafungin to amphotericin B (both administered for at least 21 days) for invasive candidiasis including ME in neonates younger than 4 months of age. A sample size of 225 was targeted, but the Applicant was only able to enroll 30 infants, 20 of whom were exposed to micafungin. This sample size was insufficient to provide statistical inferences for efficacy. The Applicant therefore attempted to gather more data for evidence of efficacy of micafungin for treatment of neonatal candidiasis including ME, from 2 investigator-initiated studies conducted in Italy to which the Applicant obtained right of reference. Study 9463-CL-6001 was a prospective observational study using micafungin 8 mg/kg for treatment of neonatal candidiasis in neonates (28 infants were 4 months of age or younger; 7 infants were older than 4 months), while Study 9463-CL-6002 was a retrospective observational study in 18 neonates (12 infants 4 months of age or younger and 6 older than 4 months) with invasive candidiasis treated with micafungin at doses between 5 and 15 mg/kg. The Applicant also collected additional observational data from the Pediatrix consortium database (study 9463-CL-7001) containing data from more than 350 NICUs across the U.S. Because information on these neonates was collected by retrospective chart review, key data elements were often missing, including dosing regimens of micafungin in many patients. Further efficacy data were obtained by identifying neonates younger than 4 months of age from previously conducted Phase 1, 2 and 3 studies –9463-CL-2104, 98-0-046, 98-0-047, 99-0-63, and FG-463-21-08. These 6 studies are described in Section 10.1; due to the small sample sizes from disparate sources of data, no inferential statistical analyses were possible.

Across all 9 studies, only 6 pediatric patients with documented CNS infection were identified, 1 of whom was >4 months of age. Among 3/6 patients who received micafungin doses of 10 mg/kg, one survived to EOT with mycological response. One neonate from Study FG-463-21-08 who received a dose regimen of 2 mg/kg survived with mycological response at EOT but had recurrent infection; one from study 6001 received a concomitant antifungal agent, and another from study 7001 achieved survival and mycological response at EOT, but the dose of micafungin was unknown. Pharmacokinetic information generated from 4 pediatric patients showed variable micafungin concentration in the CSF following single and multiple doses of micafungin. Thus, no conclusions regarding micafungin effectiveness in documented CNS disease can be drawn from these data.

As detailed in section 6, extrapolation of efficacy for the treatment of candidemia, acute disseminated candidiasis, Candida peritonitis and abscesses without ME in pediatric patients younger than 4 months is supported by evidence from adequate and well-controlled studies in adult and pediatric patients 4 months of age and older with additional pharmacokinetic data in patients younger than 4 months. A dose regimen of 4 mg/kg/day in pediatric patients younger than 4 months of age achieves plasma exposure (AUC) comparable to the AUC estimates in adults at the approved dose regimen of 100 mg QD.

When choosing an antifungal drug to treat neonates with disseminated candidiasis, and candidemia with ME, clinicians must weigh the potential risks and benefits of available treatment options in light of individual patient factors such as comorbidities, concomitant medications, toxicities, and resistance of the isolate. In a population of premature and clinically unstable infants with serious Candida infections at risk for ME and/or ocular involvement, a micafungin dose of 4 mg/kg is unlikely to be sufficient and should be used only when ME and/or ocular involvement can be ruled out. Based on data from the rabbit and other nonclinical models as discussed in previous sections, the optimal neonatal dose for treatment of neonatal candidiasis with ME and/or ocular involvement may be higher than 10 mg/kg/day. A description of relevant nonclinical data showing micafungin doses that achieved significant CNS fungal burden reduction and corresponding neonatal doses are included in labeling. Statistical Issues The submission does not contain an adequate and well controlled study in a neonatal candidiasis population in order to draw statistical conclusions regarding the efficacy of a specific dose of micafungin. Study 9463-CL-2303 was designed to be such a study. However, due to feasibility issues of enrolling subjects, the study was stopped well before the planned sample size. Given the limited sample size, the study was underpowered and not able to achieve its stated objective of showing non-inferiority of micafungin to amphotericin B.

Studies 9463-CL-6001 and 9463-CL-6002 are limited by the fact that they are uncontrolled. 9463-CL-6002 has a further limitation of being a retrospective review of medical records.

Analyses of the data pooled across all studies or cross study comparisons should be interpreted with caution for a few reasons:

- Doses vary across the studies. While the dose was prespecified for Studies 9463-CL-2303 and 9463-CL-6001, the dose in 9463-CL-6002 was not. The dose used for a given subject in 9463-CL-6002 may have been based on unknown factors that could have had an impact on the response observed.
- Assessment of efficacy was not the primary goal for Studies 9463-CL-6001 and 9463-CL-6002. As such, there were differences in the definition of the treatment response.

8.5. Conclusions and Recommendations

Extrapolation of the efficacy of micafungin at a dose of 4 mg/kg in pediatric patients younger than 4 months of age for treatment of candidemia, acute disseminated candidiasis, Candida peritonitis and abscesses without ME was supported by evidence from adequate and well-controlled studies in adult and pediatric patients 4 months of age and older with additional pharmacokinetic and safety data in pediatric patients younger than 4 months of age. There were insufficient data in this sNDA to support a micafungin dose of 10 mg/kg for treatment of invasive candidiasis including candidemia and suspected ME in pediatric patients younger than 4 months of age. Given the difficulty of definitively ruling out *Candida* ME in premature and often clinically unstable patients < 4 months of age with candidemia and the potential adverse consequences of under-treatment with a dose of 4 mg/kg/day, relevant information on fungal burden reduction obtained from the rabbit model of HCME as well as a brief summary of existing neonatal safety data for micafungin doses from 5-15 mg/kg/day is included in labeling. A limitation of use informs providers that micafungin is not approved for the treatment of Candida meningoencephalitis and/or ocular disease.

9 Clinical Microbiology Review

9.1. Mechanism of Action

No new information provided.

9.2. Activity in vitro

No new information provided.

9.3. Activity in vivo (animal models of *Candida* infection)

Some of the studies supporting activity of micafungin in mice and rabbits with disseminated *Candida* infection are summarized below.

9.3.1. Murine model

Ikeda *et al*. (2000)[9] reported the activity of micafungin in Slc-ICR immunosuppressed mice infected with different *Candida* species. On Day 4 after initiation of immunosuppression, mice were infected, by intravenous (IV) inoculation of micafungin sensitive strains of *C. albicans, C. glabrata, C. tropicalis, C. krusei, C. parapsilosis*, or *C. guilliermondii*; inoculum concentration varied for different *Candida* species (Table 9-1). IV treatment with different doses of micafungin

[9] Ikeda F, Wakai Y, Matsumoto S, Maki K, Watabe E, Tawara S, Goto T, Watanbe Y, Matsumoto F, and Kuwahara S (2000) Efficacy of FK463, a new lipopeptide antifungal agent, in mouse models of disseminated candidiasis and aspergillosis. *AAC* 44: 614-618.

and other antifungal drugs was initiated 1 hour post-infection, for 4 days, and animals were followed for 15 to 20 days post-infection. Untreated mice infected with 4×10^5 colony-forming units (CFU) of *C. albicans* 16010 strain died within 11 days of infection; survival time for mice infected with other *Candida* species was not specified. The results show that the 50% effective doses (ED_{50}) of micafungin, against the various *Candida* species, were slightly higher than or comparable to amphotericin B and lower than fluconazole (Table 9-1).

Table 9-1: Activity of micafungin in mouse model of disseminated candidiasis*

***Candida* species**	**Strain****	**Inoculum (CFU)**	**Treatment regimen**	**ED_{50} (mg/kg/day)[a]**		
				Micafungin	**Fluconazole**	**Amphotericin B**
C. albicans	FP633	1.0×10^4	UID[b]	0.14 (0.10-0.19)	2.15 (1.32–3.23)	0.08 (0.05–0.10)
			BID[c]	0.19 (0.14–0.26)	1.82 (1.26–2.50)	0.11 (0.04–0.16)
C. albicans	16010	4.0×10^5	UID	0.21 (0.14–0.31)	4.51 (3.04–8.14)	0.12 (0.08–0.18)
C. albicans	FP1839 [d]	4.6×10^4	UID	0.26 (NE)	>20.0 (NE)	0.18 (NE)
C. glabrata	13002	3.5×10^7	UID	0.30 (0.22–0.42)	6.27 (4.08–10.1)	0.11 (0.08–0.16)
C. tropicalis	16009	1.6×10^4	UID	0.28 (0.20–0.39)	3.71 (2.47–6.06)	0.09 (0.06–0.12)
C. krusei	FP1866	6.0×10^7	UID	0.77 (0.55–1.08)	9.52 (6.12–17.4)	0.26 (0.12–0.42)
C. parapsilosis	FP1946	8.6×10^7	UID	1.00 (0.70–1.43)	10.9 (7.62–17.5)	0.06 (0.04–0.08)

[a] Values in parentheses are 95% confidence intervals. NE, confidence interval could not be estimated.
[b] Once daily treatment for 4 days, starting at 1 h (hour) after infection.
[c] Twice daily treatment for 4 days, starting at 1 h after infection.
[d] Fluconazole resistant.
*Mice were immunosuppressed by intraperitoneal (IP) administration of cyclophosphamide, 4 days before and 1 day after infection for all *Candida* species except *C. glabrata*. For *C. glabrata*, additional dose of cyclophosphamide was administered on Day 6 PI. The activity of antifungal agents was assessed as the 50% effective doses (ED_{50}), calculated by probit analysis or normal probability plot based on the survival rate at 15 days after infection.
**MIC values ≤0.125 µg/mL for all strains except *C. parapsilosis* (MIC 0.5 µg/mL); all strains were micafungin sensitive.

In another experiment, the effect of micafungin treatment on survival was compared in immunocompetent and immunosuppressed mice; mice were immunosuppressed with either hydrocortisone or cyclophosphamide. Experimental design was similar to that summarized above except that mice were infected with FP633 strain of *C. albicans*. The ED_{50} values in immunosuppressed mice show a trend towards higher values compared to immunocompetent mice (Table 9-2). It is noted that the inoculum concentrations used for infection were different in different groups of mice.

The micafungin ED_{50} values were slightly increased when the initiation of treatment was delayed by 24 hours compared to 1 hour (Table 9-2).

Table 9-2: Influence of immunosuppression and starting time of treatment on activity of micafungin in mouse model of disseminated candidiasis (*C. albicans*)

Immunosuppression*	Starting time of treatment after infection (h)	Inoculum (CFU)*	ED_{50} (mg/kg/day)[a]		
			Micafungin	Fluconazole	Amphotericin B
None	1[b]	1.9×10^6	0.13 (0.09–0.18)	1.5 (1.10–2.15)	0.04 (0.03–0.06)
Hydrocortisone	1[b]	1.3×10^5	0.45 (0.32–0.64)	14.9 (9.91–38.3)	0.23 (0.16–0.32)
Cyclophosphamide	1[b]	3.1×10^4	0.28 (NE)	≥4.0[d] (NE)	0.13 (NE)
	1[b]	1.2×10^4	0.25 (NE)	2.0 (1.40–2.85)	0.07 (0.05–0.10)
	24[c]	1.2×10^4	0.32 (0.24–0.45)	6.2 (4.49–8.43)	0.21 (0.15–0.29)

[a] Values in parentheses are 95% confidence intervals. NE, confidence interval could not be estimated.
[b] Once daily for 4 days, starting at 1 h (hour) after infection.
[c] Once daily for 3 days, starting at 24 h after infection.
[d] Fifty-percent survival was observed at 4.0 mg/kg of FLCZ.
*Mice immunosuppressed with either cyclophosphamide at 200 mg/kg administered intraperitoneally 4 days before and 1 day after infection or hydrocortisone at 100 mg/kg administered subcutaneously 1 day before and 3 h, 1 day, and 2 days after infection to induce a continuously immunosuppressed condition in the host. Mice were challenged intravenously with the FP633 strain of *C. albicans*.

A dose-dependent reduction in residual fungal burden in kidney, measured 1 day post-infection, was reported in immunocompromised mice infected with the FP633 strain of *C. albicans* and treated with micafungin 1 hour post-infection. Fungal burden in organs other than kidneys was not assessed.

Warn *et al*. (2002)[10] reported the effect of micafungin on fungal burden in CD1 mice with persistent neutropenia and inoculated IV with 1.2×10^6 CFU of a fluconazole and amphotericin B resistant strain (MY1012) of *C. tropicalis*; the inoculum concentration selected, based on initial experiments, was the highest concentration that could be administered without rapid death. Treatment was initiated 6 hours post-infection; micafungin was administered IV for 7 days, animals sacrificed on Day 11 post-infection, and residual fungal burden assessed in some of the organs (kidneys, lung, liver and brain). Mortality rate in the different groups of mice was comparable (Table 9-3). The surviving mice gradually improved; by Day 11, most mice showed few signs of severe disease. The authors state that mice treated with micafungin (particularly the higher doses) tended to improve and regained weight lost at an earlier stage of infection; however, the data were not shown. The activity of micafungin was dose-dependent: at micafungin doses of 5 and 10 mg/kg, lungs, liver, and kidneys were culture negative, i.e., below the level of detection (≤30 CFU/organ). However, amphotericin B or fluconazole were not

[10] Warn PA, Sharp A, Morrissey G, and Denning DW (2002) In vivo activity of micafungin in a persistently neutropenic murine model of disseminated infection caused by *Candida tropicalis*. *J Antimicrob Therapy* 50: 1071-1074.

effective in reducing fungal burden; this may be due to the fact that the *C. tropicalis* strain used was resistant to amphotericin B and fluconazole. The reason for low fungal burden in the liver and lungs of untreated control animals is unclear.

In brain, micafungin was effective in reducing fungal burden; however, amphotericin B and fluconazole were ineffective (Table 9-3).

Overall, the number of animals which remained culture positive was lower in the micafungin treated groups compared to the comparator antifungals.

Table 9-3: Effect of treatment on fungal burdens in different organs and survival in mice infected with *C. tropicalis*

Parameter	Drug mg/kg							
	Micafungin				Amphotericin B		Fluconazole	Control Regime
	10.0	5.0	2.0	1.0	5.0	0.5	50	
Residual fungal burden (Geometric mean) CFU/Organ								
Lungs	0[a]	0[a]	<1	17	349	132	14	4
Liver	0[b]	0[b]	0[b]	8	5300	35	18	5
Kidneys	0[c]	0[c]	32[c]	5212	530000	189000	107700	141800
Brain	189[d]	357[d]	263[d]	378	6830	488	21400	4160
Number of animals without residual fungal burden*								
No. (%)	5/17 (30)	3/17 (18)	6/18 (33)	0/16 (0)	1/15 (7)	0/16 (0)	0/17 (0)	0/32 (0)
Survival to Day 11								
No. (%)	17/20 (85)	17/20 (85)	18/20 (80)	16/20 (80)	15/20 (75)	16/20 (80)	17/20 (85)	32/40 (80)

[a] $P < 0.0001$ versus amphotericin B 0.5 mg/kg.
[b] $P < 0.001$ versus amphotericin B (both doses).
[c] $P < 0.001$ versus micafungin 1 mg/kg, amphotericin B (both doses), fluconazole and controls.
[d] $P < 0.0001$ versus amphotericin B and controls, and $P < 0.01$ versus fluconazole.
* Culture negative i.e., below the level of detection (≤30 CFU/organ)

9.3.2. Rabbit model

Several studies reported the activity of micafungin in the neutropenic (Petraitis *et al*., 2002[11]) and nonneutropenic (Hope *et al*., 2008[3]; Petraitiene *et al*., 2008[4]) hematogenous *Candida* meningoencephalitis (HCME) New Zealand White rabbit model. A micafungin sensitive strain (ATCC MYA-1237; NIH 8621) of *C. albicans* was used for IV inoculation.

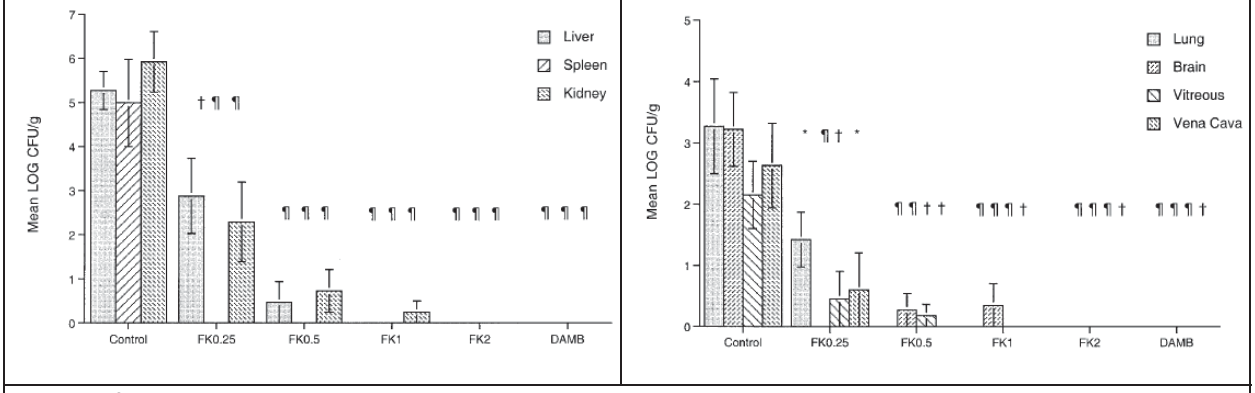
[11] Petraitis V, Petraitiene R, Groll AH, Roussillon K, Hemmings M, Lyman CA, Sein T, Bacher J, Bekersky I, and walsh TJ (2002) Comparative antifungal activities and plasma pharmacokinetics of micafungin (FK463) against disseminated candidiasis and invasive pulmonary aspergillosis in persistently neutropenic rabbits. *AAC* 46: 1857-1869.

- **Neutropenic rabbits**

Petraitis *et al*. (2002)[10] reported the activity of micafungin in neutropenic rabbits immunosuppressed with cytarabine for 5 days prior to IV infection with 10^3 CFU of *C. albicans*. Immunosuppression was maintained by administering cytarabine at a 2-day interval during the experiment. The IV treatment with micafungin (0.25 to 2 mg/kg) or amphotericin B (1 mg/kg) was initiated, 24 hours post-infection for up to 10 days in surviving rabbits. Tissues (lungs, liver, spleen, kidneys, brain and anterior vena cava) were processed for fungal culture and histopathology. It appears that the survival rate was not measured. The rabbits treated with micafungin showed dose-dependent decrease in fungal burden in all the tissues tested compared to untreated animals; the activity of the highest dose (2 mg/kg/day) of micafungin appears to be comparable to amphotericin B (1 mg/kg) (Figure 9-1).

There was no histologic evidence of organisms in rabbits treated with micafungin at doses of ≥0.5 mg/kg/day. At a lower dose of 0.25 mg/kg/day, a predominance of yeast-like structures was observed whereas in untreated controls, a transition from a predominance of hyphae and pseudohyphae was reported.

Figure 9-1: Effect of treatment with different doses of micafungin or amphotericin B on fungal burden in different organs in persistently neutropenic rabbits.



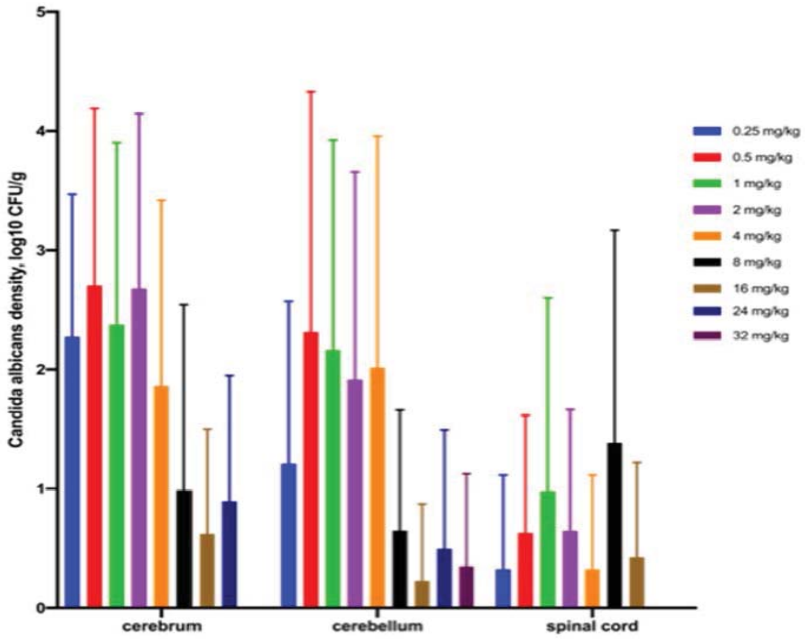
FK=micafungin
FK0.25 (*n* =8), FK0.5 (*n* = 8), FK1 (*n* = 8), FK2 (*n*= 6), and DAMB at 1 mg/kg/day (*n*= 6). Values are means ± SEMs. *, P <0.05; †, P < 0.01; ¶, P < 0.001. P values are for the results for treated rabbits in comparison to those for the untreated controls (UCs), as determined by ANOVA with Bonferroni's correction for multiple comparisons.

- **Nonneutropenic rabbits**

Another study (Hope *et al*., 2008[3]), reported the activity of micafungin in immunocompetent (nonneutropenic) rabbits. The experimental design was similar to that summarized above except that immunocompetent rabbits were infected IV with 10^6 CFU; the inoculum

concentration selected was based on pilot studies[12]. Treatment, with different doses (0.25 to 16 mg/kg; specified in the publication) of micafungin, was initiated 48 hours post-infection, for 7 days; however, it appears that micafungin doses >16 mg/kg were tested (Figure 9-2). Rabbits were sacrificed 30 minutes after the last dose and some of the tissues (cerebrum, cerebellum, and spinal cord) processed for assessing fungal burden. The results in Figure 9-2 show a decrease in fungal burden in treated animals compared to untreated animals; however, there is wide range of variability in fungal burden of treated animals; it is unclear if this is due to variability in response to treatment or a small number of animals in each group.

Figure 9-2: Effect on fungal burden



Source: Applicant submission
Note: Results for micafungin doses ≥16 mg/kg shown; the publication specified doses of 0.25-16 mg doses

Petraitiene *et al*. (2008)[4] reported the activity of micafungin in an immunocompetent (nonneutropenic) rabbit model; experimental design was same as summarized above for the nonneutropenic rabbit study except that microbiological evaluations included measurement of β-D-glucan levels, a component of the cell wall, by the (b) (4) assay (b) (4)

[12] It appears that inoculum concentration used was based on previous studies by the same group of investigators (Groll *et al*., 2000, *JID* 182: 274-282). The authors state that "pilot studies revealed that an IV inoculum of 10^5 CFU of *C. albicans* did not result in CNS infection, even in untreated animals; an inoculum of 10^7 CFU, on the other hand, led to early infectious deaths despite treatment, and an inoculum of 10^8 was precipitously lethal within 48 hours. However, the IV administration of 10^6 CFU resulted in consistent infection of brain tissue at 48 hours after inoculation and survival of amphotericin B treated and -untreated animals until the end of the experiment; this level was therefore selected."

(b) (4) in cerebrospinal fluid (CSF) and plasma. Also, several organs including meninges, cerebrum, cerebellum, spinal cord and eye were processed for culture. Histopathologic evaluation was conducted on representative sections of the cerebrum, cerebellum, and spinal cord.

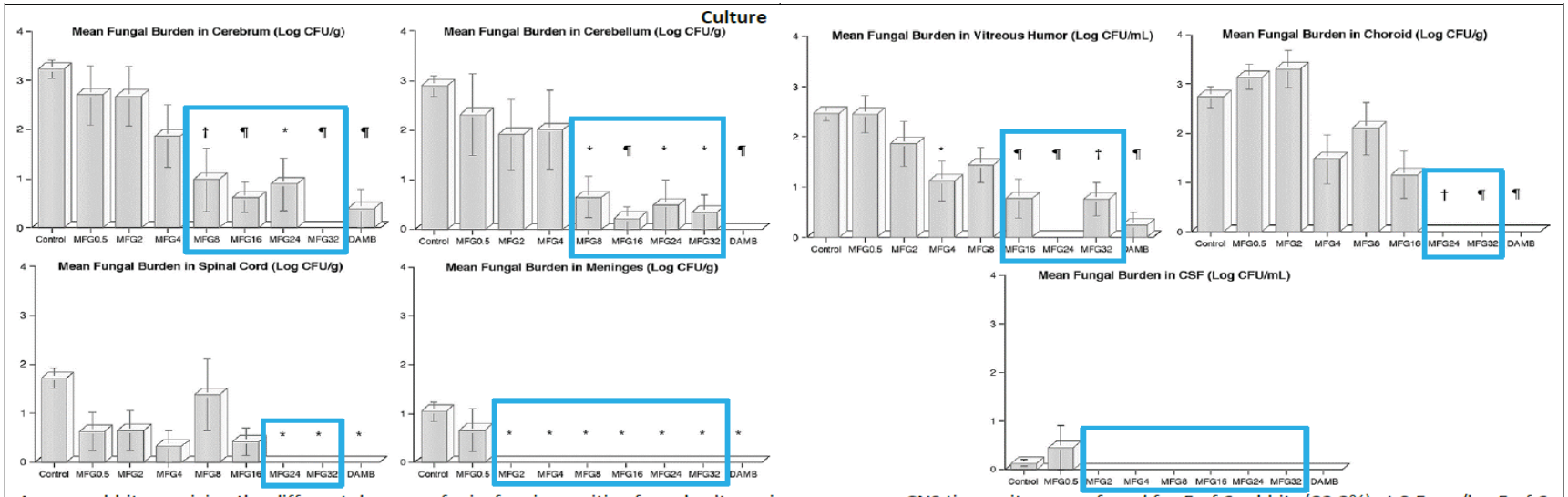
All infected animals were blood cultures positive at both 24 (Day 1) and 48 (Day 2) hours after inoculation; all untreated control animals remained culture positive for the duration of the experiment. The results show that, one day after initiation of treatment, all blood cultures were negative in rabbits treated with either micafungin (doses 0.5 to 32 mg/kg) or amphotericin B (1 mg/kg); also, all animals remained culture negative for the duration of the experiment.

Micafungin was effective in reducing fungal burden in the different tissues tested; however, the activity varied in different tissues. For example, in cerebrum and cerebellum, micafungin doses of ≥8 mg/kg were effective in significantly reducing fungal burden compared to untreated animals; spinal cord, meninges, vitreous humor, and choroid, however, were culture negative at micafungin doses of ≥24 mg/kg, ≥2 mg/kg, 4 mg/kg as well as ≥16mg/kg, and ≥24 mg/kg, respectively (Figure 9-3). Overall, the fungal burden in the CSF and the number of animals that were culture positive was low; only 8.1% of untreated CSF cultures were positive.

β-glucan was detected in the CSF specimens from all the untreated animals; β-glucan levels were lower in the plasma compared to CSF. Treatment with micafungin reduced β-glucan levels; such an effect was dose-dependent (Figure 9-3). There was a positive correlation between β-glucan levels in CSF and fungal burden in the cerebrum ($r = 0.842$; $p < 0.001$).

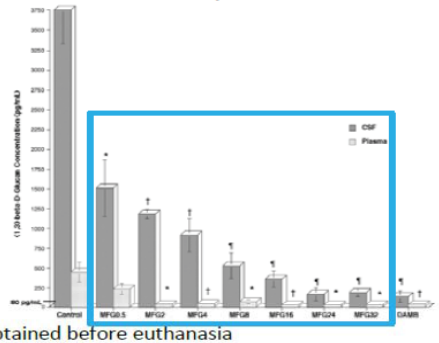
Overall, the micafungin activity in the CNS appears to be site- and dose-dependent.

Figure 9-3: Effect of treatment with micafungin or amphotericin B on mycological burden (culture) in different parts of the brain and eye, β-glucan levels in CSF and plasma, and histology



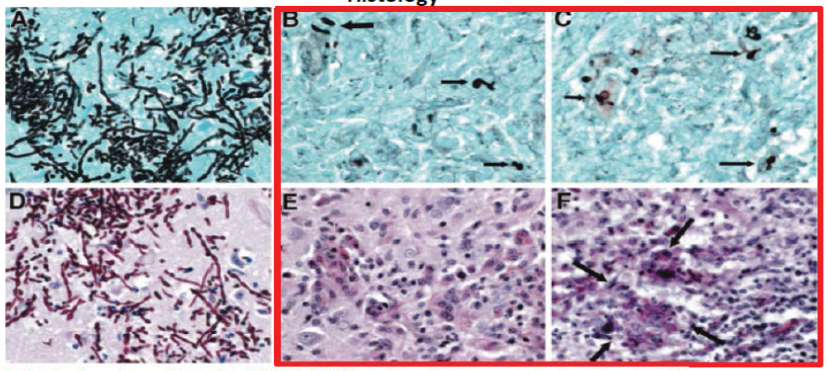
Among rabbits receiving the different dosages of micafungin, positive fungal cultures in one or more CNS tissue sites were found for 5 of 6 rabbits (83.3%) at 0.5 mg/kg, 5 of 6 (83.3%) at 2 mg/kg, 5 of 6 (83.3%) at 4 mg/kg, 3 of 6 (50%) at 8 mg/kg, 4 of 8 (50%) at 16 mg/kg, 3 of 4 (75%) at 24 mg/kg, and 2 of 5 (40%) at 32 mg/kg. Among amphotericin B-treated rabbits, 1 of 6 (16.7%) also had positive fungal cultures from the cerebrum samples.

β-glucan concentrations in CSF and the last plasma sample**



*Obtained before euthanasia

Histology***



***Antifungal effect of micafungin on microscopic morphology of the cell structure of *C. albicans* in cerebral tissue. (A) untreated control (original magnification, X400) (GMS), extensive infiltration of tissue by hyphae, pseudohyphae, and blastoconidia; (B) micafungin at 4 mg/kg (X400) (GMS), distorted blastoconidia (thin arrows) and hyphal fragments (thick arrow); (C) micafungin at 16 mg/kg (X400) (GMS), distorted blastoconidia (thin arrows); (D) untreated control (X400) (PAS); (E) micafungin at 4 mg/kg (X400) (PAS), microabscess consisting mononuclear cells and scatted polymorphonuclear leukocytes; (F) micafungin at 16 mg/kg (X400) (PAS), microabscesses consisting of mononuclear cells, macrophages, polymorphonuclear leukocytes, and necrotic foci (thick arrows).

Values are given as means ± standard errors of the means.
(P values were <0.05 [*], <0.01 [†], or <0.001 [¶] in comparison to untreated controls using ANOVA with Bonferroni's multiple comparisons test).

Overall, the studies show that micafungin is active in both murine and rabbit models of disseminated candidiasis. Micafungin administered to immunocompetent or immunosuppressed mice or rabbits with disseminated candidiasis prolonged survival and/or decreased the mycological burden in different organs including brain and eye. The effective dose may vary depending on the severity of infection, host immune status, and different organs. The activity of micafungin, against micafungin sensitive strains of *Candida* species, appears to be comparable to amphotericin B.

10 Review of Safety

10.1. Safety Review Approach

The safety review will focus on the 3 main studies submitted by the Applicant in support of this sNDA - Studies 9463-CL-2303, 9463-CL-6001, and 9463-CL-6002. These studies are fully described in Section 8, but an overview is provided in the Table 10-1.

Table 10-1: Primary Studies for Safety Analysis

	Design	Indication	Micafungin Dose	Patients (n) and age range
9463-CL-2303	Phase 3 Randomized, Double-Blind, Multi-center noninferiority study comparing efficacy and safety of Micafungin and Amphotericin B	Invasive candidiasis and candiduria, including *Candida* meningitis	10 mg/kg/day	Micafungin n=20 Amphotericin B n=10 Ages 9-117 days
9463-CL-6001	Prospective, open-label, multicenter study comparing plasma and CSF levels of micafungin	Systemic candidiasis and/or *Candida* meningitis	8 mg/kg/day	Micafungin n=35* No comparator Ages 0.3-8.1 months
9463-CL-6002	Retrospective multicenter study to determine plasma and CSF levels of micafungin	Invasive Candidiasis	<8 to 15 mg/kg/day^	Micafungin n=18** No comparator Ages 4-180 days

*There were 28 infants up to age 4 months in Study 9463-CL-6001
**There were 12 infants up to age 4 months in Study 9463-CL-6002
^In Study 9463-CL-6002, 2 infants got <8 mg/kg/day and the remaining got ≥8-15 mg/kg/day
Source: Table adapted from Applicant table 1 in Summary of Clinical Safety (Module 2.7.4)

Enrollment was limited in each of these studies, but because they differed significantly in design, endpoints and scheduled assessments, safety results could not be pooled for analysis. Due to the limited safety database, additional data from patients younger than 4 months enrolled in 6 supportive studies previously conducted by the Applicant were gathered for evaluation of safety and exploration of a possible dose-response relationship; details of these studies are provided in Table 10-2.

Table 10-2: Supportive Safety Studies

Study	Design	Micafungin Dose	Micafungin-treated patients <120 days of age (n)
9463-CL-7001	Retrospective analysis of patients treated with micafungin in 382 NICUs	2-15 mg/kg/day	n=116 (only 46 courses with available dose information)

Study	Design	Micafungin Dose	Micafungin-treated patients <120 days of age (n)
	(Pediatrix database)		
9463-CL-2104	Phase 1 open-label study to evaluate safety and PK of micafungin	7 mg/kg/day (weight >1000g) 10 mg/kg/day (weight <1000g)	n=13
FG-463-21-08	Phase 3 randomized, double-blind, active control PK study of micafungin and amphotericin B	2 mg/kg	n=20
98-0-047	Phase 2 open-label, non-comparative study to evaluate efficacy and safety of micafungin	1 mg/kg, increased at investigator's discretion	n=20
99-0-063	Phase 1 open-label dose-escalation study to evaluate PK and tolerance of micafungin	0.75, 1.5, 3.0 mg/kg doses each given once	n=13
98-0-046	Phase 2 open-label, non-comparative	1.5 mg/kg, could be increased in 1.5mg/kg increments	n=2

Source: Reviewer generated using information from Module 5.2

Studies 9463-CL-7001 and 9463-CL-2104 are described in further detail in Section 10.2. While safety analyses in this section focus on patients younger than 120 days, patients older than 120 days from study 9463-CL-6001 (n=7) were considered for evaluation of dose-response for safety and for central nervous system infections because there was one patient with CNS infection who was older than 120 days.

The following terms and definitions are used throughout the review. Candidemia is the finding of *Candida* spp. in the bloodstream. Disseminated/invasive candidiasis is generally used to describe the dissemination of candidemia to another body site. Neonatal candidiasis is a subset of disseminated/invasive candidemia occurring in young infants that implies a high risk of meningoencephalitis and ocular disease and is associated with significant morbidity including neurodevelopmental abnormalities and mortality.

10.2. Review of the Safety Database

Overall Exposure

There were 244 patients aged less than 120 days who got at least 1 dose of micafungin among the 9 studies submitted.

Table 10-3: Patients <120 days of age exposed to micafungin

Study ID	n
9463-CL-2104	13
9463-CL-2303	20
9463-CL-6001	28
9463-CL-6002	12
9463-CL-7001	116
98-0-046	2
98-0-047	20
99-0-063	13
FG-463-21-08	20
All Studies	244

Although 116 neonates were identified for inclusion in the safety database from study 9463-CL-7001, dosing regimens for micafungin were not specified in 76 of them resulting in their exclusion for purposes of safety analyses; thus, 168 patients were included in the safety database. Details are provided below.

Study 9643-CL-2303

Due to inability to enroll study subjects, there were only 20 patients randomized to the micafungin group and 10 patients randomized to the amphotericin B group. Most patients (25/30) were born at >27 weeks gestational age (83.3%) and 5/30 (16.7%) were born at <27 weeks. There were 7/30 (23.3%) patients with a baseline weight of <1000g, 5/30 (16.7%) with a baseline weight of 1000-1500g, and 18/30 (60%) with a baseline weight >1500g. See Section 8.1.1 for full details of study design and demographics.

Study 9643-CL-6001

As described in Section 8.1.2, this study was a prospective, open-label study to examine plasma and CSF PK and safety of micafungin at 8 mg/kg/day. Of 35 patients included in the Applicant's analysis, 28 were 4 months or younger. Fourteen of 35 (40%) patients were born at less than 27 weeks gestation and 21/35 (60%) born at >27 weeks gestation. Most patients (25/35, 71.4%) had a baseline weight of >1500g, 7/35 (20%) had a baseline weight of 1000-1500g, and 3/35 (8.6%) had a baseline weight of <1000g. See section 8.1.2 for a full description of study design and demographics.

Study 9643-CL-6002

This study was a retrospective medical records analysis of patients who were treated with micafungin at Ospedale Pediatrico Bambino Gesù, a Children's hospital in Italy. Astellas assumed sponsorship after the study was completed and gained access to the data from the study site. Of 18 patients in the study, 12 were 4 months of age or less. Patients were treated with doses ranging from 5 to 15 mg/kg/day. All patients were at least 27 weeks gestation. Most patients (16/18, 89%) weighed >1500g and 2/18 (11%) weighed 1000-1500g at baseline. See section 8.1.3 for full details of study design, demographics, and disposition.

Reviewer comment: Most patients (16/18, 89%) received doses of at least 8 mg/kg/day, but there were two patients who received doses <8 mg/kg/day: a 35-day-old who was treated with 5 mg/kg/day and a 20-day-old who received 7.84 mg/kg/day.

Study 9463-CL-7001

This was a retrospective analysis of neonates and young infants younger than 4 months identified in the Pediatrix database. Records of over 1 million infants who were discharged from 382 NICUs over 17 years were analyzed to identify patients diagnosed with either definite or possible invasive candidiasis and treated with micafungin. Their definition of invasive candidiasis was a culture positive for *Candida* from a normally sterile body site. There were 124 infants exposed to 139 courses of micafungin with a median duration of therapy of 10 days. Dosing information was available for 41 infants who received 48 courses of micafungin; 40 infants were 120 days or younger while 1 additional infant was 130 days of age. The average daily dose of micafungin in these 41 infants was 9.4 mg/kg/day, but the range of doses varied from 2-15 mg/kg/day

Study 9463-CL-2104

This was a multi-center, open-label study to evaluate PK and safety of micafungin in neonates greater than 48 hours of age up to 120 days of life with suspected candidemia or invasive (neonatal) candidiasis. Of 13 neonates enrolled, those weighing <1000g (n=6) received 10 mg/kg/day and those >1000g (n=7) received 7 mg/kg/day. One of the patients assigned to receive 7 mg/kg/day inadvertently received 10 mg/kg/day. Infants who received at least 4 consecutive days of micafungin were considered to have completed the course of study drug. There were no deaths or TEAEs leading to discontinuation.

Study FG-463-21-08

This was a phase 3 RCT comparing amphotericin B and micafungin that was submitted as part of the sNDA for pediatric approval in 2012. Out of 109 patients enrolled, 20 were <120 days of age and were included in some analyses for this review.

Reviewer comment: Study 9463-CL-7001 was limited because it was a retrospective study of

patients under varying conditions with little detail about their courses or outcomes. Information regarding TEAEs, deaths and discontinuations was not provided. Most patients were missing dosing information. Study 9463-CL-2104 was limited by small sample size and short courses of micafungin, making assessments of safety difficult. Study FG-463-21-08 used micafungin doses of 2 mg/kg/day, which does not contribute helpful information for safety assessments at the higher proposed doses. Brief relevant details of the other 3 studies (98-0-046, 98-0-047, and 99-0-063) are provided in Table 10-2.

Adequacy of the safety database:

The safety database for micafungin at the Applicant's proposed dose of 10 mg/kg in neonates and infants younger than 4 months with neonatal candidiasis consisted of 40 patients who received at least one 10 mg/kg dose of micafungin – 19, 12, 6 and 3 neonates were from studies 2303, 7001, 2104 and 6002 respectively. Of these 40 patients, 27 (67.5%) and 21 (52.5%) patients received ≥7 days and ≥14 days duration respectively. Because treatment of neonatal candidiasis would require a minimum of 7 days of micafungin, safety assessments at all doses included patients who received ≥7 days duration. Nine patients from study 7001 (Pediatrix database) received >11 mg/kg – 5 received 15 mg/kg, while 4 received doses of 11-14 mg/kg/day – 8/9 (88.9%) received durations ≥7 days.

Across all 9 studies, only 6 patients had proven CNS disease based on culture, PCR or imaging. Their dosing regimens were inconsistent – 1 neonate was treated with <2 mg/kg micafungin in study 2108, 1 received 8 mg/kg in study 6001, 3 received 10 mg/kg (1 was in study 6002 and was 161 days old, and 2 were in study 2303), and the dose of micafungin was unknown in a neonate with meningoencephalitis from study 7001. These patients will be discussed in further detail in Section 10.9, but they constituted a very limited database of neonates with meningoencephalitis.

In an effort to bolster patient numbers for analysis of safety, the Applicant included patients from their own previously-completed Phase 3 trial (FG-463-21-08), Phase 2 (98-0-047, 98-0-046) and Phase 1 trials (9463-CL-2104, 99-0-063), as well as from the observational Pediatrix database (9463-CL-7001). As mentioned previously, of 244 patients identified in these 9 studies, only 168 patients had specified micafungin dosing regimens and were included in safety analyses.

Aside from limited numbers of patients receiving relevant doses and durations of micafungin, adequacy of the safety database was further hampered by lack of consistency in study design, endpoints, and dosing regimens (0.75-15 mg/kg). Although study populations generally consisted of ill neonates with invasive candidiasis, multiple comorbidities and concomitant medications, a direct comparison of their characteristics across all 9 studies was not possible. Further, because all except the Phase 3 studies were observational, study 6002 was retrospective and study 7001 consisted of real-world data, assessments of safety varied widely and were often confounded by the concomitant use of other antifungal drugs. Safety conclusions must therefore be interpreted with caution.

10.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The quality and integrity of data varied widely among the 3 main studies submitted to this sNDA. Safety assessments in Study 2303 were conducted prospectively according to a pre-defined schedule of assessments (Table 10-4) with standard definitions of adverse events, treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs). Adverse events were coded using MedDRA v20.1**.** The Applicant ensured that data was generated and reported in compliance with the protocol, GCP and regulatory requirements.

Study 6001 was also conducted prospectively, and adverse events were coded using MedDRA v20.1 and standard definitions. A schedule of assessments (Table 10-5) was implemented. The Applicant assumed sponsorship of the study during its conduct, had access to source data and audited a sampling of reconsented subjects to verify compliance with the protocol and regulations. The Applicant had patient data recorded in an electronic database provided by the (b) (4) and conducted several data reviews and audits.

Study 6002 was completed and published before Astellas assumed sponsorship, and they were unable to verify source data. No schedule of assessments was used to collect safety data in this study. Adverse events were coded using MedDRA v20.1; existing laboratory data were provided.

In addition to the heterogeneity of available safety data in the 3 main studies as noted above, the following additional deficiencies in aggregate safety data were noted (see Section 8 for additional concerns noted by the Statistical Reviewer, Dr. Cheryl Dixon):

- Many patients (primarily from the Pediatrix database) were missing dosing information
- Many patients were missing information about site of infection
- Study 9463-CL-6002 did not include CBC data, nor standard safety evaluations
- Dosing regimen and treatment duration was inconsistent across studies
- Safety evaluations were done at inconsistent time points
- Units used for certain laboratory evaluations were not consistent among studies
- Terminology defining disease states (candidemia, invasive candidiasis, acute disseminated candidiasis, neonatal candidiasis) were used inconsistently and added confusion.

In an attempt to clarify some of these details, the following information requests (IRs) were sent:

- July 19, 2019
    - Requesting clarifications and further details about discontinuations
    - Requesting additional death narratives
    - Confirming low numbers of AEs for study 9463-CL-6002
    - Clarification of lack of consistent endpoints for study 9463-CL-6002

    - Questioning the lack of an ISS document (none was prepared)
- August 5, 2019
    - Confirming numbers of suspected and proven CNS infections
    - Requesting additional safety and efficacy narratives
- September 17, 2019
    - Confirming lack of hematologic data for study 9463-CL-6002
    - Requesting additional outcome data and clarification of infection sites for many patients

Categorization of Adverse Events

Adverse events were categorized as treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), or adverse events of special interest (AESI). TEAEs were defined as AEs that emerged or worsened at any time during study drug administration until 72 hours after the last dose of study drug. AEs were considered SAEs if they were life-threatening or resulted in death, congenital anomaly, birth defect, inpatient hospitalization or prolongation of hospitalization, significant disability or disruption of the ability to conduct normal life functions. AESIs in study 9463-CL-2303 included hepatic events, renal events, hemolytic events, allergic reactions, injection site reactions and infusion related reactions. AESIs in study 9463-CL-6001 and study 9463-CL-6002 included any preferred terms that might be indicative of an infusion-related reaction based on terms used in a 2010 paper by Siena et al[13]. Causality in studies 2303 and 6001 was assessed as not related, possible or probable. Although safety assessments in study 2303 listed severity of AEs including abnormal laboratory values, measured as mild (no disruption of normal daily activities), moderate (affected normal daily activities) and severe (inability to perform daily activities, these definitions did not apply to this ill neonatal population.

Routine Clinical Tests

Routine clinical testing for Study 2303 was done only if clinically indicated for the patient. Ideally, blood, urine and CSF cultures would have been done at baseline and repeated later to document clearance or persistence, but very few CSF samples were obtained Similarly, while presence of end-organ dissemination should have been assessed with various imaging modalities (renal ultrasound, abdominal ultrasound or CT, echocardiogram, head ultrasound or MRI or CT) and ophthalmic exam, these were not always possible owing to the patient's clinical instability or other factor. PK samples were collected from blood and CSF; CSF samples were only collected if the patient was getting a lumbar puncture as part of their clinical management. Hematology and chemistry labs were to be obtained every other week, but if labs were done as part of the patient care and were within the time frame, they were accepted

[13] Siena S et al. Reduced incidence of infusion-related reactions in metastatic colon cancer during treatment with cetuximab plus irinotecan with combined corticosteroid and antihistamine premedication. *Cancer* 2010;116;1827-37.

so that additional manipulation could be avoided. ECGs were not required. Vital signs and weight were obtained at baseline; vital signs were recorded more frequently during the first 3 infusions of study drug. The schedule of assessments for Study 2303 is provided in table 10-4.

Table 10-4: Schedule of Assessments in Study 9463-CL-2303

Assessments	Screening/Baseline	Randomize	Treatment Period †				Post-Treatment Period ‡
			Every 48 h	7 Days After 1st Dose of Study Drug	Every4-7 Days	Day 1 - Last Dose of Study Drug	
Verification of Inclusion or Exclusion Criteria	X						
Informed Consent/Privacy Acknowledgement	X						
Randomization		X					
Demographics	X						
Pertinent Medical History	X						
Medical Baseline Conditions	X						
Physical Examination	Within 24 h§						
Body Weight	Within 24 h§'¶					X††	
Retinal Exam	X‡‡			X‡‡			X‡‡
LP	X§§				X§§		
Abdominal ultrasound	X‡‡			X‡‡			X‡‡
Echocardiogram	X‡‡			X‡‡			X‡‡
Head Ultrasound, CT, **or** MRI	X‡‡			X‡‡			X‡‡
Urine & Blood Fungal Culture	X¶¶		X§§				
Plasma PK Sampling						X¶¶¶¶	
CSF PK Sampling						X†††	
Vital signs	Within 24 hours§					X‡‡‡	
Catheter Status	Within 7 days§					X§§§	
Hematology and Serum Chemistry	Within 72 h§					X¶¶¶	X††††
Clinical Assessment	X					X X††††††	X‡‡‡‡,§§§§
Mycological Assessment	X						X‡‡,§§§§
Collection of Fungal Isolates	X					X¶¶	X¶¶
Emergent Fungal Infection Assessment						X†	X‡‡‡‡,§§§§
Recurrent Fungal Infection Assessment							X‡‡‡‡,§§§§
Prior and Concomitant Medications	X‡‡‡‡‡					X‡‡	Antifungal therapy only
Study Medication						X†	
AEs						X§§	SAE only§§
Non-Medication treatment (Surgery, etc.)	Within 7 days§					X	

AE: adverse event; CSF: cerebrospinal fluid; CT: computerized tomography; eCRF: electronic case report form; ESV: end of study visit; LP: lumbar puncture; MRI: magnetic resonance imaging; SAE: serious adverse event

†From the first dose of study drug therapy to the last dose of study drug therapy.

‡From the last dose of study drug therapy through 30 days after the last dose of study drug therapy. An ESV (post-treatment) occurred 30 days, ± 3 days, after the last dose of study drug.

§Prior to the first dose of study drug.

¶If not clinically feasible to obtain weight within 24 h, a weight within 72 h prior to the first dose was acceptable.

††Assessed weekly, ± 1 day, while on study drug therapy.

‡‡Obtained between 72 h prior to first dose of study drug and 7 days after starting study drug therapy, if clinically feasible. Follow-up exams should have been obtained any time during the post-treatment period.

In the abdominal ultrasound, the radiologist should have assessed the liver, spleen, and kidneys. Retinal exam should have been performed, if clinically feasible.

§§Obtained LP within 72 h prior to starting study drug therapy, **unless** already collected to diagnose enrolling fungal infection. However, when this was not possible due to subject instability, positive cultures from specimens drawn within the first 4 days of study drug initiation were acceptable for baseline diagnosis of meningitis. If CSF culture was positive, LP was to be repeated every 4 to 7 days until negative culture was documented. For infants who participated in the CSF pharmacokinetic portion of the study, reference is made to Appendix 3 of study protocol for procedures on collection of CSF.

¶¶Obtained blood and urine fungal cultures within 24 h prior to starting therapy, **unless** either has already been collected within 4 days prior to the first dose of study drug to diagnose the enrolling fungal infection. If cultures were positive, obtained blood and urine fungal cultures during the treatment period every 48 (± 3) h until 2 negative cultures were obtained, separated by ≥ 24 h. If cultures were negative, it was not necessary to repeat. All fungal culture results obtained for the subject were recorded in the eCRF.

†††Reference is made to Appendix 3 of the study protocol for CSF pharmacokinetic sample schedule and for handling/shipping guidelines.

‡‡‡Obtained blood pressure, temperature and heart rate within 15 (± 5) min prior to the start of the infusion, at least once during the infusion and at the end of the infusion for the first 3 study drug infusions.

§§§Recorded central and umbilical catheters present at the time of enrollment, inserted during study drug therapy, and removed during study drug therapy.

¶¶¶Hematology and serum chemistry panels were obtained every other week, ± 1 day, while on study drug therapy and at the end of study drug therapy. If additional laboratory values were obtained consistent with local standard of care, these were captured on a weekly basis in the eCRF; to minimize blood draws, these additional labs were not required per protocol. Any additional laboratory values obtained as a result of following or monitoring a specific abnormal laboratory value are also to be captured on the eCRF as appropriate. Standard of care assessments and evaluations should always have been considered adequate for inclusion in the eCRF (e.g. safety labs, LP, radiology, etc) when performed per protocol and during the protocol defined timeframes to reduce any unnecessary additional manipulation of this subject population.

††††Post-treatment hematology and serum chemistry panels were taken at 2 occasions: 3-7 (± 3) days after end of study drug therapy and at the ESV.

‡‡‡‡Reference is made to Section 5.3 of study protocol for definitions.

§§§§Recorded at one week (± 1 day) after last dose of study drug and at ESV (± 3 days).

¶¶¶¶Fungal isolates, from normally sterile site cultures, were collected for subjects with emergent and recurrent *Candida* infections anytime during the course of the study, and/or for mycological persistence at end of study drug therapy.

†††††Only anti-infectives or medications [e.g. steroids or immunosuppressants] associated with the defined risk factors for neonatal candidiasis (see Appendix 4 of study protocol) given within 7 days prior to the first dose of study drug therapy and all antifungal therapy within 28 days prior to the first dose of study drug therapy.

‡‡‡‡‡All medicines administered during the treatment period were recorded on the eCRF.

§§§§§AEs occurring during study drug therapy through 72 h after the last dose of study drug therapy were followed through 30 days after the last dose of study drug therapy. SAEs occurring during study drug therapy up to 30 days following the last dose of study drug were reported. SAEs occurring during study drug therapy up to 72 h after the last dose of study drug were captured on the eCRF.

¶¶¶¶¶Reference is made to Appendix 2 of the study protocol for plasma pharmacokinetic sample schedule and for handling/shipping guidelines.

††††††Clinical assessment done weekly (± 1 day) while on study drug.

Source: Table and footnotes taken from full clinical study report (Module 5.3.5.1)

The schedule of assessments for Study 9463-CL-6001 is provided in table 10-5. Despite the

detailed schedule, assessments varied based on patient condition, which limits the data available for analysis.

Table 10-5: Schedule of Assessments for Study 9463-CL-6001

Study Procedures	Screening/ Baseline[b]	(V1) Day 1[a]	PK	V2	V3	(V4) Day 14 (± 2 days)	V5[i]
Informed consent obtained	X						
Inclusion/exclusion criteria evaluation	X						
Medical history	X						
Vital signs	X			X	X	X	X
Physical examination	X			X	X	X	X
Septifast test	X[c]						
Blood culture	X[c]			X[e]			
CSF culture with pleocytosis evaluation	X[c]			X[e]			
Mannan antigen	X			X[e]			
Peritoneal fluid culture	X[c]						
Urine culture	X[c]						
Tracheal aspirate	X[c]						
Gastric aspirate	X[c]						
Stool culture	X[c]						
CBC with differentiation	X			X	X	X	X
PCR	X			X	X	X	X
Liver function tests	X			X	X	X	X
Coagulation	X			X	X	X	X
Blood gas analysis	X			X	X	X	X
Urine analysis	X			X	X	X	X
Renal function	X			X	X	X	X
12-lead ECG		X[d]		X	X	X	X
Micafungin infusion		X		X[h]			
Pharmacokinetics			X[f;g;]				
Concomitant Medications	X	X		X	X	X	X
AE/SAE Assessment		X		X	X	X	X
In vitro susceptibility testing (MIC)[l]	X[j]			X[k]			

AE: adverse event; CBC: complete blood count; CSF: cerebrospinal fluid; ECG: electrocardiogram; MIC: minimum inhibitory concentration; PCR: polymerase chain reaction; PK: pharmacokinetics; SAE: serious adverse event; spp.: species; V: visit.

a. The day 1 visit (visit 1) was to be conducted as soon as possible after the screening/baseline.

b. Provided that therapy with micafungin had not been already initiated, assessment results, already performed within 5 days before screening, could be recorded and evaluated for the confirmation of the diagnosis, for patients' eligibility and/or as baseline assessments.

c. Optional: could have been performed according to inclusion criterion 1.

d. 12-lead ECG was to be performed before the start of the first infusion and immediately after the end of the first infusion with the investigational product.

e. At least 2 blood cultures and/or at least 2 CSF cultures together with assessment of mannan antigen level, for assessment of infection and evaluation of secondary endpoint were performed starting at the day 1 visit (visit 1), at any time. It was recommended, though, to collect blood draws concomitantly with blood draws for other laboratory assessments, in accordance to the indicated timeframes.
f. Pharmacokinetic assessments were performed before infusion and at 1, 3 and 8 hours after the end of the intravenous infusion, on 1 of the treatment days between the third and the 10th treatment day.
g. In a subset of 5 patients, blood draws were collected simultaneously via capillary micromethod (withdrawal from the heel) and venous method (withdrawal from a peripheral vein).
h. Micafungin was administered via intravenous infusion at 8 mg/kg once a day for approximately 1 hour.
i. End of trial visit (visit 5) was performed if it occurred at least 3 days after the previous visit.
j. Results of in vitro susceptibility (MIC) testing performed at the investigative site was recorded for *Candida* spp. isolates collected from cultures used to diagnose the candidiasis.
k. During therapy, MIC testing was to be performed on *Candida* spp. collected from cultures of specimens persisting or new *Candida* spp. during the treatment period.
l. Fungal organisms isolated from cultures were further tested to confirm species identification and final MIC testing at a central laboratory at the end of the study. Procedures for shipping and handling of the fungal isolates were outlined in a separate laboratory manual. Results are provided in a separate report.

Source: Table and footnotes taken from full clinical study report (Module 5.3.5.2)

A detailed plan of assessments was not provided or carried out in Study 9463-CL-6002. The last laboratory values (AST, ALT, GGT, alkaline phosphatase, albumin, protein, bilirubin, direct bilirubin, urinalysis) prior to starting the drug were designated as baseline values which were then compared to values at end of treatment (the last value recorded between day 1 and termination) and the last recorded assessment. There was no hematologic data available.

10.4. Safety Results

10.4.1. Deaths

Study 9643-CL-2303

There were 3 deaths in the micafungin treatment arm and 1 death in the amphotericin arm. Narratives are summarized below. In all narratives provided in the safety analysis, Study Day is referenced to the day of micafungin initiation (Day 1). Gestational age (GA) at which the patient was born will be described using the convention "ex-36-week GA," which describes a patient born at 36 weeks gestation. Some narratives lacked relevant detail, so this reviewer supplemented them with information culled from various datasets and patient profiles whenever possible.

Micafungin

1. Patient (b) (6) was a 17-day old ex-26-week GA female randomized to micafungin 10 mg/kg/day for candidemia due to *Candida parapsilosis*. Comorbidities included hepatic failure, renal failure, and cardiorespiratory failure. Study drug was discontinued on Day 3 due to the SAE of cardiovascular insufficiency, although the Applicant did not think that the SAE was related to study drug. This patient died from cardiovascular insufficiency (bradycardia and hypotension) on Day 3.

Reviewer comment: While the role of micafungin cannot be definitively excluded, these patients all appeared to be very ill premature infants with multiple comorbidities that may have independently contributed to their deaths. This was likely the case for patient (b) (6) *who had multiorgan failure, including cardiac failure, and died of cardiovascular insufficiency.*

2. Patient (b) (6) was a 26-day old ex-22-week GA female randomized to micafungin 10 mg/kg/day for candidemia due to *Candida parapsilosis*. Comorbidities included anemia, *Acinetobacter sepsis* and total necrosis of the gut. Blood culture on Day 16 grew *Candida parapsilosis*, so study drug was discontinued on that day due to lack of efficacy, and voriconazole was started. Bacterial sepsis due to coagulase-negative *Staphylococcus* was also present from Days 15-19. This patient had a laparotomy on Day 31 during which no viable gut was found, so she was placed on comfort care and died on Day 32.

Reviewer comment: Patient (b) (6) *had recurrent candidemia while on study drug which may be viewed as a treatment failure that contributed to death, but also had bacterial sepsis and other comorbidities. The second positive culture was the same isolate (Candida parapsilosis) with the same MIC (1) as the initial isolate, indicating that resistance did not develop.*

3. Patient (b) (6) was a 35-day old ex-28-week GA female randomized to micafungin 10 mg/kg/day for candidemia due to *Candida albicans*. Comorbidities included bronchopulmonary dysplasia, intraventricular hemorrhage, sepsis, apnea and bradycardia. Signs of sepsis had been present since Day -11 and *C. albicans* grew on Day -5 and Day 3. No antifungals were given prior to Day 1. Study drug was discontinued on Day 2 due to the SAE of septic shock, although the Applicant did not think that the SAE was related to study drug. She died on Day 3 due to multi-organ failure and septic shock.

Reviewer comment: Patient (b) (6) *appeared to have candidemia at least 5 days prior to starting the study and did not get any treatment prior to Day 1, so it is possible that the disease was too invasive for any treatment to be effective by the time antifungals were started, although shock appeared to develop on Day 2.*

Amphotericin B

1. Patient (b) (6) was a 14-day old ex-24-week GA American female randomized to amphotericin B 1 mg/kg/day for candiduria with *Candida parapsilosis*. Comorbidities included jaundice, adrenal insufficiency, anemia, hypotension, necrotizing enterocolitis, metabolic acidosis, and low urine output. Study drug was discontinued on Day 11 for unspecified reason. The patient underwent exploratory laparotomy on Day 15 which revealed minimal healthy gut tissue. Clinical status continued to worsen with thrombocytopenia, respiratory failure, and bilious output from peritoneal drains; the patient died on Day 26 after being removed from the mechanical ventilator.

Reviewer comment: This patient had multiple comorbidities and died due to withdrawal of care secondary to severe necrotizing enterocolitis, which was not likely to be related to study drug.

Study 9643-CL-6001

There were 5 deaths during the study; narratives are summarized below. Two more deaths occurred after study completion but information about these patients was very limited.

1. Patient (b) (6) was a 2-month-old ex-25-week GA female who was treated with micafungin 8 mg/kg/day for suspected candidiasis (right lung BAL positive for Mannan antigen) for 4 days. This patient developed septic shock with positive blood and tracheal cultures with multi-drug resistant *Pseudomonas aeruginosa* on Day 3. Last dose of study drug was on Day 4 and no further antifungals were given. Vancomycin, amikacin, colistin and meropenem were administered. Death occurred on Day 5 from septic shock and coagulopathy.

Reviewer comment: Study drug was discontinued due to death. Death was due to bacterial sepsis which is unlikely to be related to micafungin.

2. Patient (b) (6) was a 1.2-month-old ex-26-week GA male who was treated with micafungin 8 mg/kg/day for suspected candidiasis (positive Mannan antigen from BAL) for 10 days. He had septic shock, hypotension and anuria on Day 5. Cultures of tracheal aspirate and stool were positive for multi-drug resistant *Pseudomonas aeruginosa*. Study drug was discontinued on Day 10 for unspecified reason. Ceftazidime, metronidazole, and meropenem were administered, along with a second course of micafungin from Day 15 to Day 17. Death occurred on Day 18 from septic shock.

Reviewer comment: *Study drug was discontinued on Day 10 in patient* (b) (6) *for unclear reasons, seemingly unknown to the Applicant, but they state, "it is possible that the micafungin treatment was discontinued on day 10 due to the lack of fungal disease observed in subsequent culture samples." The etiology of sepsis was unclear as there is no mention of bacteremia or fungemia; death was unlikely related to a micafungin-associated AE, but it is difficult to comment on the possibility of treatment failure contributing to death.*

3. Patient (b) (6) was a 1.9-month-old ex-27-week GA female who was treated with micafungin 8 mg/kg/day for suspected candidiasis (positive *Candida* ELISA on BAL) for 10 days. She had septic shock and ascites starting on Day 9. No further antifungals were given, but she received meropenem, amikacin, vancomycin and ciprofloxacin. Death was on Day 10 from ESBL *Klebsiella pneumoniae*-related septic shock and ascites.

Reviewer comment: Study drug was discontinued due to death, which appears due to bacterial

sepsis.

4. Patient (b) (6) was a 1.3-month-old ex-36-week GA male who was treated with micafungin 8 mg/kg/day for *C. albicans* candidemia for 16 days. On Days 13 and 14, stool cultures were positive for *Candida parapsilosis*. Patient completed treatment with study drug on Day 16. Vancomycin, meropenem, acyclovir, amoxicillin-clavulanate, gentamicin, cefoxitin were administered over the course of illness, as well as a second course of micafungin from Day 18 to Day 27. This patient had septic shock from *Klebsiella pneumoniae* and disseminated intravascular coagulation starting on Day 27 and died on Day 28.

Reviewer comment: Study drug was discontinued because the patient completed the desired course of treatment with resolution of fungemia. Rectal cultures were later positive for C. parapsilosis, which would not be an indication for continuation of antifungals. The reason listed for restarting micafungin was "flebitis" and there was no further explanation. The cause of death appeared to be bacterial sepsis.

5. Patient (b) (6) was a 0.6-month-old ex-23-week GA male who was treated with micafungin 8 mg/kg/day for *C. parapsilosis* candidemia for 7 days. Blood culture was positive for *Candida parapsilosis* (MIC = 1) on Day -1. Blood culture on Day 6 was positive for *Candida parapsilosis* (MIC = 2) and *Enterococcus faecium*. Study drug was stopped on Day 7 due to lack of efficacy. Blood cultures were reported as persistently positive for *Candida parapsilosis* on Day 14 despite treatment with fluconazole, micafungin, amphotericin B and flucytosine. Piperacillin-tazobactam, meropenem and vancomycin were also administered. This patient had peritonitis and multi-organ dysfunction starting on Day 15 and died that same day from respiratory failure, *Candida parapsilosis* sepsis, peritonitis, pneumothorax, intestinal perforation, multi-organ failure and prematurity.

Reviewer comment: These 5 patients were all very ill with multiple comorbidities including prematurity in 4/5 (80%), and it is likely that sepsis was significantly implicated in their deaths. In 4 out of the 5, a bacterial pathogen was identified, and it does not appear that micafungin is related to their deaths.

In patient (b) (6), Candida parapsilosis was repeatedly cultured from blood and likely contributed to the patient's death. The second isolate had an increased MIC compared to the first, which indicates developing resistance or a different isolate. Thus, treatment failure of micafungin likely contributed to death; of note, the patient also failed treatment with amphotericin B, fluconazole and flucytosine.

Limited information about the 2 patients who died after study completion was provided in response to an information request. Patient (b) (6) was a 2.2-month-old ex-24-week GA female who received micafungin 8 mg/kg/day for 15 days for C. parapsilosis isolated from skin and

lung; she died later that year due to lower respiratory tract infection. Patient (b) (6) *was a 5.8-month-old ex-25-week GA male who received micafungin 8 mg/kg/day for 14 days for suspected candidiasis based on positive Mannan antigen from BAL; he was later reported to have died but no further information was available.*

Study 9463-CL-6002

There were 3 deaths during the study, all in patients >120 days of age who received ≥8 mg/kg/day of micafungin. All 3 patients had documented eradication of their *Candida* infections prior to death.

1. Patient (b) (6) was a 161-day-old ex-29-week GA male who was treated with micafungin 15 mg/kg/day from Days 1 to 4 and micafungin 10 mg/kg/day from Days 5 to 74 for *C. albicans* isolated from CSF and blood cultures on Day -2. The reason for the dose change was not specified. Blood and CSF cultures were repeated twice to confirm clearance and were negative. Death occurred on Day 170, 96 days after stopping micafungin, from *Serratia* sepsis.
2. Patient (b) (6) was a 131-day-old ex-38-week GA female who was treated with micafungin 8 mg/kg for 16 days for candiduria due to *C. albicans* diagnosed on Day -1. Repeat culture on Day 16 was negative. This patient died on Day 59 due to heart failure.
3. Patient (b) (6) was a 140-day-old ex-37-week GA male who was treated with micafungin 8 mg/kg/day for 28 days for candiduria due to *C. krusei* diagnosed on day -2. Repeat cultures were negative on Days 4 and 9. This patient died due to cardiac arrest and respiratory failure on Day 48.

Reviewer comment: Given the long duration between treatment completion and death, it does not seem that these deaths were related to micafungin.

10.4.2. Serious Adverse Events

Study 9463-CL-2303

Eleven of 20 patients (55%) in the micafungin arm and 5/10 (50%) in the amphotericin arm had treatment emergent SAEs. Some patients had more than one SAE. There was one episode of acute kidney injury in the micafungin group and none in the amphotericin group; 4 patients in the micafungin group compared to 1 in the amphotericin group had anemia (some with multiple instances). Two patients in the micafungin arm had abnormal LFTs, including increased ALT, AST and bilirubin, compared to none in the amphotericin group. There was one episode of cardiovascular insufficiency in the micafungin group compared to none in the amphotericin group. One patient in the micafungin group experienced intraventricular hemorrhage and hydrocephalus, but none had these SAEs in the amphotericin group. There were 3 episodes of sepsis in the micafungin group and none in the amphotericin group. SAEs seen only in the amphotericin group consisted of a single episode each of hypertension, hypotension, hypothermia, intestinal perforation, oliguria, and obstructive airway disorder.

Table 10-6: Patients with SAEs in Micafungin treatment arm of Study 9463-CL-2303

Subject ID/ Site ID	Age (days)	Sex	SAE(s)	Day of onset	Action taken with study drug	Outcome at end of study	Reviewer assessment of relation to study drug
(b) (6)	12	M	Sepsis (*Klebsiella pneumoniae*)	11	Dose not changed	Resolved	Not likely
	18	M	LFT abnormal	27	Dose not changed (but stopped on day 28)	Resolving	Possible
	9	F	Anemia (multiple instances)	1, 4, 21, 40, 49, 58	Dose not changed	Resolved	Not likely
	26	F	Anemia (multiple instances)	7, 15, 18	Dose not changed	Resolved	Not likely
	17	F	Cardiovascular insufficiency	3	Drug withdrawn	Fatal	Not likely
	35	F	Septic shock	3	Drug withdrawn	Fatal	Not likely
	20	F	Intraventricular hemorrhage; hydrocephalus	14; 21	Dose not changed	Resolved with sequelae; Resolving	Not likely
	16	F	Anemia	7	Dose not changed	Resolved	Not likely
	14	F	Anemia (multiple instances)	7, 41	Dose not changed	Resolved	Not likely
	117	F	ALT increased; AST increased; bilirubin increased	22; 22; 22	Drug withdrawn	Resolving; Resolving; Resolved	Possible
	15	M	Septic shock (pre-existing bacterial sepsis); acute kidney injury	4; 4	Drug withdrawn (on day 3)	Not resolved; Resolved	Not likely

Source: Table generated by reviewer from Appendix 13.2.7.4 of 9463-CL-2303 study report (module 5.3.5.1)

Reviewer comment: The overall rate of SAEs was comparable between the amphotericin (50%) and micafungin (55%) groups. Anemia was the most common SAE in the micafungin group. Most of the infants in the study were premature and very ill and there could be many etiologies for anemia in this population. The episodes of anemia resolved without discontinuation of micafungin, but the role of micafungin in its etiology cannot be excluded.

Two SAEs of abnormal LFTs appeared to be resolving after discontinuation of micafungin, so those may have been related to micafungin, but again, there were many confounding factors that also could have contributed to increased LFTs.

SAE of sepsis was reported only in the micafungin-treated patients. This could be due to chance in such a small sample size. Bacterial sepsis is unlikely to be related to micafungin, but fungal

sepsis may be viewed as treatment failure. Patient (b) (6) *died of fungal sepsis and was discussed in section 10.4.1.*

Study 9463-CL-6001

Among 28 patients under 120 days of age, 11 (39%) experienced treatment emergent SAEs. All patients were treated with micafungin 8 mg/kg/day. The most common SAEs were sepsis (septic shock 10.7%, *Klebsiella* sepsis 7.1%, bacterial sepsis 7.1%), bradycardia (7.1%) and respiratory failure (7.1%). The following SAEs each occurred in a single patient (3.6%): neutropenia, ascites, acute kidney injury, anuria, and hypotension. Some patients experienced multiple SAEs as shown in the table below. Some events were fatal, and those cases were described in more detail in section 10.4.1.

Reviewer comment: There were 7 patients older than 120 days, and 6/7 had SAEs; 3/7 (42.8%) with elevated GGT, 1/7 (14.2%) with elevated AST, and 1/7 (14.2%) with elevated bilirubin.

Table 10-7: Patients with SAEs in Study 9463-CL-6001

Subject ID	Age in months	Sex	Preferred term(s)	Day of onset	Action taken on study drug	Outcome at end of study	Reviewer assessment of relation to study drug
(b) (6)	0.5	F	*Klebsiella* sepsis	17	Dose not changed	Resolved	Not likely
	2.0	F	Septic shock	3	Dose not changed	Fatal	Not likely
	1.2	M	Anuria, hypotension, septic shock	5	Dose not changed	Fatal	Not likely
	1.9	F	Ascites, septic shock	9	Dose not changed	Fatal	Not likely
	0.7	M	*Klebsiella* sepsis	13	Dose not changed	Resolved	Not likely
	1.3	M	Neutropenia	12	Dose not changed	Resolved	Possibly
	3.3	M	Bacterial sepsis	15	Dose not changed	Resolved	Not likely
	0.7	F	Respiratory failure	6	Dose not changed	Resolved	Not likely
	1.6	M	Bacterial sepsis	5	Dose not changed	Resolved	Not likely
	0.7	F	Bradycardia, pulmonary hypertension; Acute kidney injury	2; 2; 7	Dose increased	Resolved; Resolved; Resolving	Not likely
	1.3	M	Bradycardia, respiratory failure	11	Dose increased	Resolved	Not likely

Source: Reviewer generated

Reviewer comment: Patient (b) (6) *SAE of neutropenia was possibly related to micafungin. The*

neutropenia started on Day 12 and he was treated with filgrastim from Day 13 to 15. Study drug was stopped on Day 16 and the neutropenia was considered resolved on Day 18. Improvement in neutropenia was likely due to the treatment with filgrastim, but the contribution of micafungin to the event cannot be excluded. Many factors including sepsis and various drugs can lead to marrow suppression and neutropenia in this patient population.

Patient (b) (6) *had bradycardia on Day 2 which was treated with epinephrine and albumin. She also had pulmonary hypertension on Day 2 which may have been related to cardiac issues including bradycardia. The pulmonary hypertension was treated with sildenafil from Day 3 to Day 11 and was considered resolved on Day 13. Acute kidney injury on Day 7 occurred in the setting of oliguria which had started on Day -1. Micafungin dose was increased from 8 mg/kg/day to 11 mg/kg/day for only one day on day 7 for unclear reasons. The SAEs for this patient were likely related to pre-existing conditions.*

Patient (b) (6) *had bradycardia and respiratory failure on Day 11, both of which are common in premature infants. These events apparently resolved on Day 12, but respiratory failure was documented elsewhere as pre-existing and ongoing. Study drug was increased from 7.8 mg/kg/day to 8 mg/kg/day on Day 12, apparently in response to the events, but such an insignificant increase is unlikely to have impacted the patient's clinical status.*

The cases of septic shock, the most common SAE, were all bacterial in etiology, and seem more likely to be related to the patients' other risk factors such as prematurity, central lines and overall severity of illness than to the study drug.

Study 9463-CL-6002

No SAEs were reported for the 12 patients under 120 days of age in this study. In the 6 patients 120 days or older, the 3 reported SAEs resulted in the deaths described in section 10.4.1.

Reviewer comment: It seems unlikely that such an ill patient population younger than 120 days would not have had any SAEs, but none were reported. Because the Applicant did not have access to source data in study 9463-CL-6002, they were unable to verify the data or lack of SAEs.

10.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

Study 9463-CL-2303

There were 9 reported discontinuations in the micafungin group: 5 were due to adverse events (including 2 deaths), 1 was due to lack of efficacy, and 3 were due to physician decision. The 3 cases of micafungin discontinuation due to physician decision included one patient with persistent infection, one patient who did not fulfill inclusion criteria and for whom they felt it was in the patient's best interest to discontinue, and another who was switched to fluconazole at the attending physician's discretion after only 1 dose of micafungin. Two of the 5 discontinuations due to AEs in the micafungin group were deaths due to cardiovascular

insufficiency and septic shock and were described in further detail in section 10.4.1. The other patients are described below. There were 3 AEs leading to discontinuation in the amphotericin group which are also described below.

Reviewer comment: Micafungin was reported to be discontinued based on physician decision due to persistent infection (multiple positive cultures with Candida parapsilosis) in patient (b) (6) *on Day 19. In the opinion of the reviewer, the reason for discontinuation should be lack of efficacy rather than physician decision. The case of the patient who was switched to fluconazole after only one dose of micafungin likely reflects physician discomfort in treating the patient with micafungin, but the patient was not given enough time on the micafungin to make any assessments of its efficacy.*

Micafungin discontinuations due to AEs:

1. Patient (b) (6): See section 10.4.1

2. Patient (b) (6) 8: See section 10.4.1

3. Patient (b) (6) was a 117-day-old ex-35-week GA female who was treated with micafungin 10 mg/kg/day for 24 days for *C. albicans* candidemia. She had normal LFTs at baseline but had elevated bilirubin, AST and ALT on Day 22. She was on multiple medications including vancomycin, meropenem, omeprazole and furosemide. Micafungin was discontinued on Day 24. Elevated AST and ALT were resolving at the end of the study. Elevated bilirubin resolved on Day 50.

Reviewer comment: The elevated LFTs in patient (b) (6) *are possibly related to micafungin as they were resolving after discontinuation, but there may have been other causative factors for the elevated LFTs such as TPN and sepsis. Review of the medication list did not reveal any other hepatotoxic medications.*

4. Patient (b) (6) was a 15-day-old ex-40-week GA male who was treated with micafungin 10 mg/kg/day for 3 days for *C. famata* and *C. guillermondii* candidemia with liver abscess. He developed septic shock and acute renal failure on Day 4. The patient was on multiple other medications including vancomycin, piperacillin-tazobactam and furosemide. Micafungin was discontinued prior to the Day 4 dose; use of an alternative antifungal medication was not reported. Acute renal failure resolved on Day 35 and septic shock was reported as not resolved at the end of the study, but repeat blood cultures were negative for *Candida*.

Reviewer comment: Patient (b) (6) *had acute kidney injury in the setting of sepsis, which could have been related to poor perfusion or nephrotoxic medication, but the role of micafungin cannot be excluded.*

5. Patient (b) (6) was a 13-day-old ex-31-week GA male who was treated with micafungin 10 mg/kg/day for 16 days for *C. albicans* candidemia. He developed

Acinetobacter sepsis on Day 9 and was diagnosed with endocarditis on Day 15. Micafungin was discontinued on Day 16 as sepsis and endocarditis was thought to be bacterial. Amphotericin B was started on Day 19. Endocarditis was not resolved at the end of the study.

Reviewer comment: Patient (b) (6) *had Acinetobacter sepsis and endocarditis, which was the reported reason for discontinuing micafungin. Bacterial endocarditis is not likely to be related to micafungin, but if the endocarditis was suspected to be fungal, they may have discontinued therapy due to concern for failure of micafungin. Amphotericin B was started on Day 19 with reports of decreasing size of vegetation seen on echocardiogram on Day 39, so this may represent treatment failure of micafungin leading to fungal endocarditis.*

There was an additional patient identified by the reviewer that may represent a discontinuation. Patient (b) (6) *was an 18-day-old ex-32-week GA male with candiduria and presumed eye dissemination who had an abnormal liver test on Day 27. The investigator listed the action taken as "dose not changed," however the study drug was stopped on Day 28. Vancomycin and ceftazidime had been started on day 26 due to concern for neonatal sepsis. Candida blood cultures were negative and repeat eye exam was "not assessed by the investigator." Due to the timing of adverse event and discontinuation of micafungin the next day, this could be considered as a discontinuation due to an adverse event in the opinion of the reviewer, but the investigator did not categorize it as such.*

Amphotericin B

6. Patient (b) (6) was a 12-day-old ex-24-week GA male who was treated with 10 days of amphotericin B 1 mg/kg/day for *C. albicans* candidemia. He had intestinal perforation on Day 11 that resolved on Day 23. Study drug was discontinued prior to the Day 11 dose and he was switched to micafungin. He also had hypotension on Day 12 which resolved the same day. Cultures were negative on Day 19.

7. Patient (b) (6) was a 17-day-old ex-38-week GA female who was treated with 8 days of amphotericin B 1 mg/kg/day for *C. albicans* candidemia, which cleared on Day 4. She had hypothermia on Day 9 which resolved on Day 10. Study drug was discontinued prior to the Day 9 dose.

8. Patient (b) (6) was a 13-day-old ex-36-week GA male who was treated with 7 days of amphotericin B 1 mg/kg/day for *C. glabrata* candiduria. He developed hypertension on Day 3 that did not resolve by the end of the study. Study drug was discontinued on Day 7.

Study 9462-CL-6001

Other than the deaths discussed above, there were no discontinuations due to TEAEs.

Study 9462-CL-6002

There were no reported TEAEs leading to discontinuation of study drug.

Reviewer comment: *It seems unlikely that such an ill patient population would not have had any TEAEs leading to discontinuation of study drug, but none were reported. Because the Applicant assumed sponsorship of the study after it was completed, and did not have access to source data, they were unable to verify the data or lack of TEAEs leading to discontinuation of study drug.*

10.4.4. Treatment-Emergent Adverse Events

Study 9463-CL-2303

There were 14/20 (70%) patients in the micafungin group and 7/10 (70%) in the amphotericin B group with non-serious TEAEs. Similar preferred terms were combined to prevent splitting of potential safety signals (described in the footnotes of the Table 10-8). The most common TEAE was anemia which occurred in 10/20 (50%) of the micafungin patients and 4/10 (40%) of the amphotericin B patients. In the micafungin and amphotericin treatment arms respectively, neutropenia occurred in 3/20 (15%) and 0/10 (0%) of patients, thrombocytopenia in 2/20 (10%) and 3/10 (30%) of patients, abnormal LFTs in 6/20 (30%) and 2/10 (20%) of patients, and septic shock in 6/20 (30%) and 3/10 (30%) of patients. All other TEAEs occurred at a frequency of <10% in the micafungin patients. Table 10-8 displays TEAEs that occurred at a frequency of 5% or greater in the micafungin group.

Table 10-8: TEAEs occurring in ≥5% of Micafungin-treated patients in study 9463-CL-2303

Preferred Term	MICAFUNGIN (10 MG/KG/DAY) (N=20)	AMPHOTERICIN B (1 MG/KG/DAY) (N=10)
Anemia[1]	10 (50.0)	4 (40.0)
Neutropenia	3 (15.0)	0
Liver function test abnormal[2]	6 (30.0)	2 (20)
Septic shock[3]	6 (30.0)	3 (30)
Staphylococcal infection	2 (10.0)	0
Thrombocytopenia	2 (10.0)	3 (30.0)
Urinary tract infection bacterial	2 (10.0)	0
Hyperbilirubinemia[4]	2 (10.0)	1 (10)
Blood urea increased	1 (5.0)	0
Cardiovascular insufficiency	1 (5.0)	0
Dermatitis	1 (5.0)	0
Endocarditis	1 (5.0)	0
Hydrocephalus	1 (5.0)	0
Hypertension	1 (5.0)	1 (10.0)
Hypoalbuminemia	1 (5.0)	0
Hypothermia	1 (5.0)	1 (10.0)
Infusion site rash[5]	1 (5.0)	1 (10)
Intraventricular hemorrhage	1 (5.0)	1 (10.0)
Medical device complication	1 (5.0)	0
Neonatal infection	1 (5.0)	0

Preferred Term	MICAFUNGIN (10 MG/KG/DAY) (N=20)	AMPHOTERICIN B (1 MG/KG/DAY) (N=10)
Phlebitis[6]	1 (5.0)	1 (10)
Pneumonia	1 (5.0)	0
Post procedural hemorrhage	1 (5.0)	0
Pyrexia	1 (5.0)	2 (20.0)
Renal failure acute	1 (5.0)	0
Vomiting	1 (5.0)	0

[1]Anaemia, anemia neonatal
[2]Liver function test abnormal, hepatic function abnormal, hepatic enzyme abnormal, hepatic enzyme increased, ALT increased, AST increased
[3]Septic shock, sepsis, Staph sepsis, bacterial sepsis, sepsis neonatal, bacteria blood identified
[4]Hyperbilirubinemia, blood bilirubin abnormal, blood bilirubin increased
[5]Infusion site rash, infusion site reaction
[6]Phlebitis, thrombophlebitis

Reviewer comment: the most common TEAEs in the micafungin group were blood disorders such as anemia and thrombocytopenia, infections, and abnormal liver function tests. Considering the small sample sizes, the rates between the two arms were comparable. Attribution of causality is difficult because these AEs could all be comorbidities related to the severity of illness in the patient population, although the role of micafungin cannot be excluded. Other TEAEs occurred at rates of 5-10% each, which could easily be attributed to chance.

Study 9463-CL-6001

There were 25/28 (89%) patients who experienced 56 total TEAEs. Table 10-9 shows the TEAEs occurring in ≥5% of patients. The most common TEAEs were elevated GGT in 8 patients (28.6%) and edema in 5 patients (17.9%). Thrombocytopenia, cholestasis, and hyponatremia occurred in 3 patients (10.7%) each. Leukopenia, bradycardia, diarrhea, hypertransaminasemia, hyperbilirubinemia, increased CRP, hypokalemia, and hypotension occurred in 2 patients (7.1%) each. The following TEAEs only occurred in 1 patient each (3.6%) and are not displayed in Table 10-9: coagulopathy, leukocytosis, rectal hemorrhage, neonatal drug withdrawal syndrome, pyrexia, sepsis, urinary tract infection (bacterial), wound dehiscence, increased blood alkaline phosphatase, increased inflammatory marker, fluid retention, hypoalbuminemia, cerebral hemorrhage, oliguria, bronchopulmonary dysplasia, decubitus ulcer, hypertension, and phlebitis.

Table 10-9: TEAEs occurring in ≥5% of patients in Study 9463-CL-6001

System Organ Class	Preferred Term	MICAFUNGIN 8.0 mg/kg/day (n=28) N (%)
Blood and lymphatic system disorders	Leukopenia	2 (7.1)
	Thrombocytopenia	3 (10.7)
Cardiac disorders	Bradycardia	2 (7.1)
Gastrointestinal disorders	Diarrhea	2 (7.1)
General disorders and administration site conditions	Edema	5 (17.9)

System Organ Class	Preferred Term	MICAFUNGIN 8.0 mg/kg/day (n=28) N (%)
Hepatobiliary disorders	Cholestasis	3 (10.7)
	Hypertransaminasemia	2 (7.1)
	Hyperbilirubinemia[1]	2 (7.1)
Investigations	C-reactive protein increased	2 (7.1)
	Gamma-glutamyltransferase increased	8 (28.6)
Metabolism and nutrition disorders	Hypokalemia	2 (7.1)
	Hyponatremia	3 (10.7)
Vascular disorders	Hypotension	2 (7.1)

Table generated in JMP by reviewer using Applicant's ADAE dataset

1. The terms "hyperbilirubinemia" and "blood bilirubin increased" were combined into "hyperbilirubinemia"

Reviewer comment: The most common TEAE was abnormal LFTs including hypertransaminasemia, elevated GGT/cholestasis, and hyperbilirubinemia. These liver-related TEAEs could potentially be related to micafungin, although other factors such as sepsis, concomitant medications, TPN and prematurity may have played a role. Edema occurred in 5 patients but the type of edema – for example, local infusion reactions vs. generalized edema – could not always be distinguished. Two patients had generalized edema secondary to fluid retention, but edema was not further characterized in the other 3 patients.

Study 9463-CL-6002

There were 2/12 (16.7%) patients with TEAEs. Patient (b) (6), a 65-day-old ex-37-week GA female treated with micafungin 10 mg/kg/day, developed elevated AST (71 IU/L), ALT (45 IU/L) and GGT (606 IU/L) on Day 13 that was listed as resolved on Day 19 (AST 28 IU/L, ALT 17 IU/L, GGT 260 IU/L). Study drug was also stopped on Day 19 and the patient was discharged home on the same day. Patient (b) (6) was a 35-day-old ex-36-week GA male being treated with micafungin 5 mg/kg/day who had elevated GGT (538 IU/L) starting on Day 25 and ending on Day 185. Micafungin was stopped on Day 26. The only other available data point was a GGT of 1535 IU/L on Day 40.

Reviewer comment: Micafungin may have contributed to the increased transaminases in patient (b) (6), although they seem to have resolved before the drug was stopped, and the GGT was also trending down by the time of discontinuation. Patient (b) (6) had elevated GGT that continued to increase after drug discontinuation. This patient had liver disease listed as an admission diagnosis, and also had invasive candidiasis with dissemination to the kidneys and liver, so there were many other factors that could have contributed to elevated GGT; micafungin could have possibly played a role. Based on Applicant review of events, there was insufficient information provided by the site but "it appeared from the course of events that the increased GGT did not result in premature termination of study drug."

In such an ill population, it seems unlikely that there were so few TEAEs. The Applicant states that they were unable to independently verify the data because they assumed sponsorship after it was collected. There may have been events that are not reflected in the available data.

Adverse Events of Special Interest (AESI)

Study 9463-CL-2303

Hepatic and renal events are shown above. There were no hemolytic reactions reported. The Applicant identified 3/20 (15%) micafungin patients and 2/10 (20%) amphotericin B patients who may have had infusion related reactions as shown in table 10-10. One (5%) micafungin patient and 3/10 (30%) amphotericin B patients had possible allergic-type reactions as shown in Table 10-11.

Table 10-10: AESI - Infusion-Related Reactions

Treatment-Emergent Adverse Events of Interest (MedDRA v12.0) - Infusion-Related Reactions
Safety Analysis Set

Preferred Term	Micafungin (N=20)	Amphotericin B (N=10)
Overall	3 (15.0%)	2 (20.0%)
Anaemia	1 (5.0%)	0
Drug eruption	0	1 (10.0%)
Hypothermia	1 (5.0%)	0
Infusion related reaction	0	1 (10.0%)
Infusion site rash	1 (5.0%)	0

Source: Clinical Study Report (Module 5.3.5.1)

Table 10-11: AESI - Allergic-Type Reactions

Treatment-Emergent Adverse Events of Interest (MedDRA v12.0) - Histamine Release/Allergic-Type Reactions
Safety Analysis Set

Preferred Term	Micafungin (N=20)	Amphotericin B (N=10)
Overall	1 (5.0%)	3 (30.0%)
Cardiovascular insufficiency	1 (5.0%)	0
Drug eruption	0	2 (20.0%)
Hypotension	0	1 (10.0%)

Source: Clinical Study Report (Module 5.3.5.1)

Reviewer comment: Anemia may be an adverse reaction to the study drug but is not likely to be an acute infusion-related reaction. Cardiovascular insufficiency was not acute and therefore not likely to be an infusion reaction. Rash may have been related to micafungin.

Study 9463-CL-6001

The Applicant designated infusion-related reactions (IRRs) for studies 9463-CL-6001 and 9463-CL-6002 as AESI. They used preferred terms to identify these possible reactions based on terms provided in a 2010 paper by Siena et al.[12], shown in figure 10-1.

Figure 10-1: Preferred Terms for Possible Infusion-Related Reactions

Cardiac	Respiratory	Other
Acute myocardial infarction	Acute respiratory failure	Anaphylactic reaction[a]
Angina pectoris	Apnea	Anaphylactic shock[a]
Cardiac failure	Asthma	Anaphylactoid reaction[a]
Cardiopulmonary failure	Bronchial obstruction	Anaphylactoid shock[a]
Hypotension[a]	Bronchospasm	Blood pressure decreased
Myocardial infarction	Cyanosis	Chills
Myocardial ischemia	Dyspnea	Clonus
	Dyspnea at rest	Convulsion
	Dyspnea exacerbated	Drug hypersensitivity[a]
	Dyspnea exertional	Epilepsy
	Hypoxia	Hyperpyrexia
	Orthopnea	Hypersensitivity[a]
	Respiratory distress	Infusion related reaction
	Respiratory failure	Loss of consciousness
		Pyrexia
		Shock
		Sudden death
		Syncope

Source: Siena S et al. Reduced incidence of infusion-related reactions in metastatic colon cancer during treatment with cetuximab plus irinotecan with combined corticosteroid and antihistamine premedication. *Cancer* 2010;116;1827-37.

Three patients (10.7%) were found to have AESI, all of which were hypotension; 2 of these patients had septic shock at the time. The other patient developed hypotension on day 2 of micafungin, and also had pulmonary hypertension and bradycardia. Hypotension persisted for 5 days.

Reviewer comment: Hypotension in the setting of septic shock and cardiovascular collapse is not likely to be related to an infusion-related reaction. Based on our review, the occurrence of other AEs of interest outlined in the table are provided in the TEAE table.

Study 9463-CL-6002

There were no reported infusion-related reactions.

Reviewer comment: Anaphylaxis was not seen in any neonate younger than 4 months exposed to micafungin in the 9 studies considered in this sNDA.

Laboratory Findings

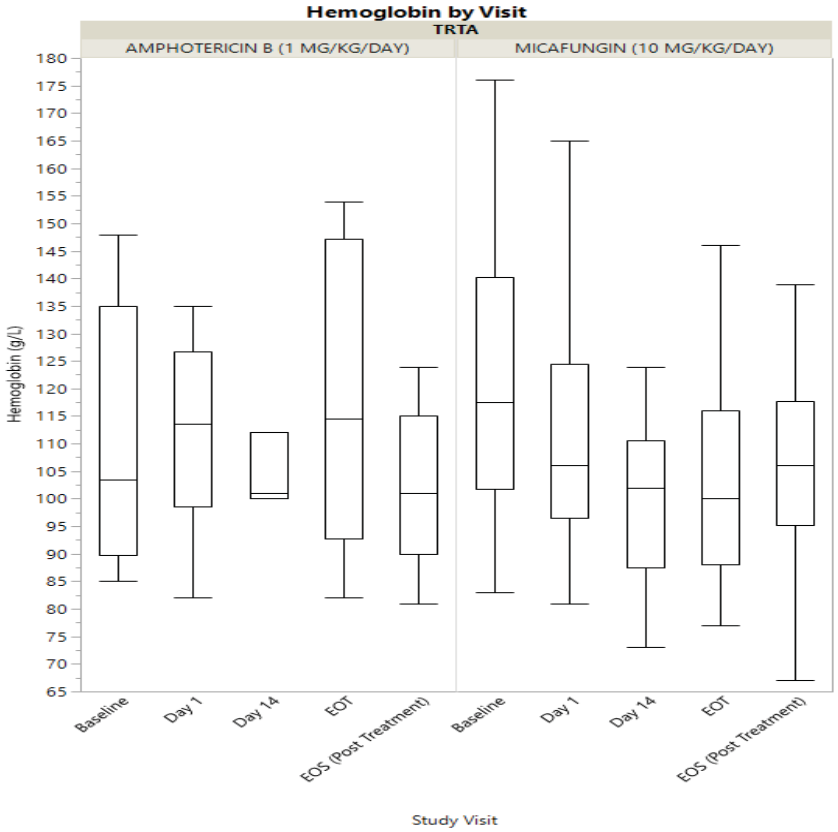
Based on labeled AEs related to micafungin, and patterns of SAEs and TEAEs observed during the review, analyses of hemoglobin, platelets, WBC, AST, ALT, creatinine, total bilirubin, and

GGT value changes in the 3 main studies submitted to the sNDA were conducted. Laboratory reference ranges were provided by age group for study 2303 and can be found in appendix 13.1.10 of the study report in module 5.3.5.1. Reference ranges for study 6001 were provided by age group and gender and can be found in appendix 13.1.10 of the study report in module 5.3.5.2. Reference ranges for study 6002 were taken from a textbook, Gregory's Pediatric Anesthesia, 5th edition which was published in 2012. LFT data were analyzed using Analysis Studio to create shift plots from baseline to maximum post-baseline values using multiples of the upper limit of normal (ULN). The interpretation of the results shown here is limited by small sample sizes.

Study 9463-CL-2303

Hemoglobin

Figure 10-2: Study 9463-CL-2303 Hemoglobin Trends over Time

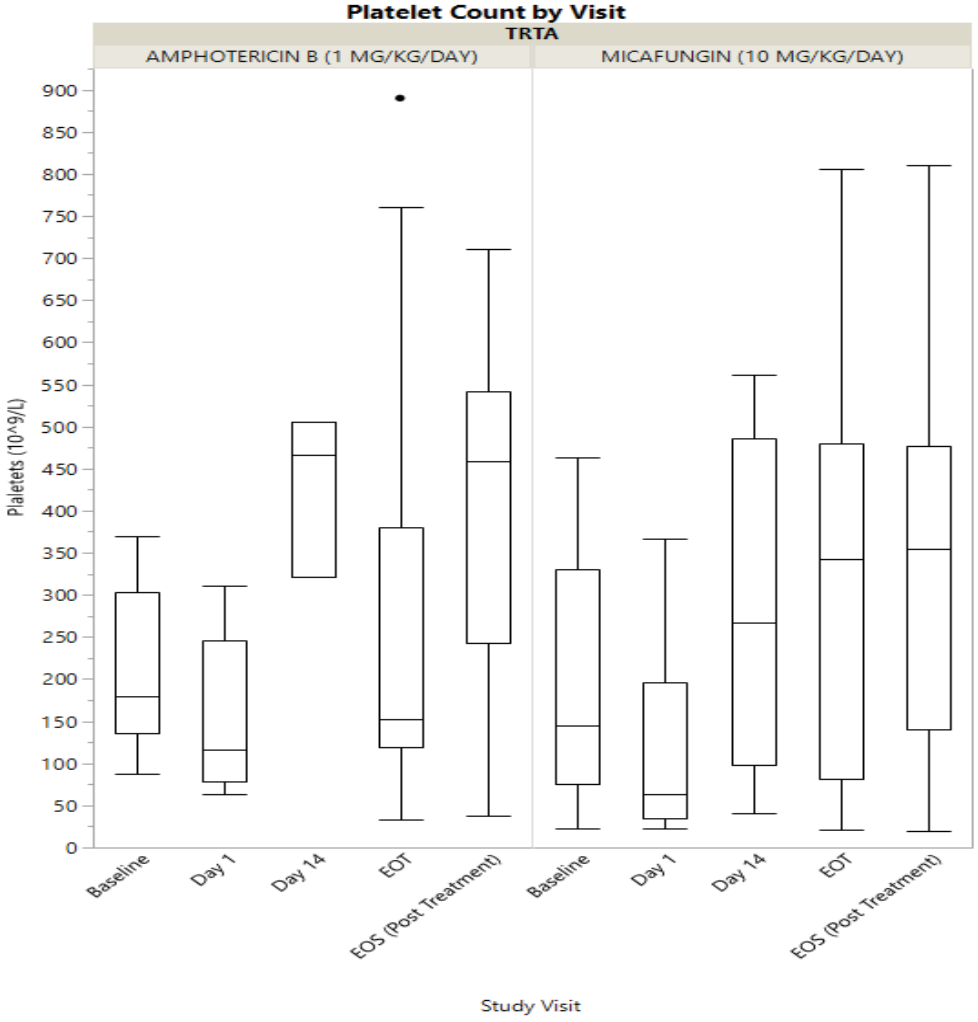


Source: Reviewer-generated in JMP using ADLB

Reviewer comment: There was a slight general trend towards decreasing hemoglobin throughout the study, almost equally so in both treatment arms. It is unclear in this ill patient population whether anemia was related to their overall condition, frequent blood draws, or study drug. This trend is consistent with the TEAE analysis; anemia occurred at a rate of 50% in the micafungin group and 40% in the amphotericin B group.

Platelets

Figure 10-3: Study 9463-CL-2303 Platelet Counts over Time



Source: Reviewer-generated in JMP using ADLB

Reviewer comment: There was no reliable trend towards thrombocytopenia or thrombocytosis based on this graph, although the dip in platelet count on Day 1 may have been related to sepsis. Some patients may have had thrombocytosis secondary to inflammation. Analysis of TEAEs showed that there were 2 patients (10%) in the micafungin group and 3 patients (30%) in the amphotericin B group with thrombocytopenia.

White blood cell count (WBC)

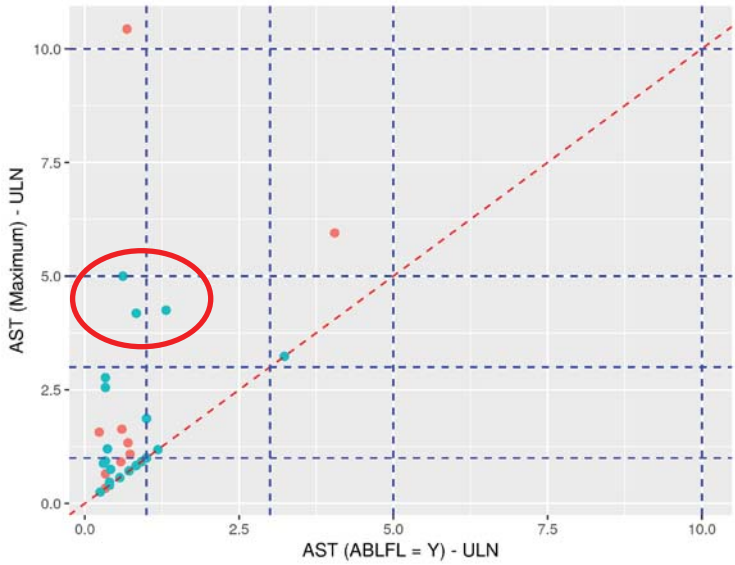
There was no reliable trend in WBC count (data not shown) throughout the study in either the micafungin or amphotericin treatment arms.

Reviewer comment: There were 3 patients (15%) in the micafungin group with neutropenia, but this could have been due to many other factors including sepsis, prematurity, and other drug effects. Outliers with leukocytosis may have been due to infection.

Liver Enzymes

Plots of baseline to maximum post-baseline changes in liver enzyme values are provided below. Causality was difficult to attribute given the underlying severity of illness in these neonates. Brief narratives are provided for neonates who had significant post-baseline elevations (>3x ULN) in liver enzyme values from a normal baseline. Red circles are used to highlight the patients being discussed in the narratives.

Figure 10-4: Study 9463-CL-2303: Maximum Post-Baseline AST Changes in the Two Treatment Arms (x ULN)



Legend: blue=micafungin treated patients; pink=amphotericin B-treated patients. X axis represents baseline AST in multiples of ULN. Y axis represents maximum AST in multiples of ULN.
Source: Reviewer-generated in Analysis Studio using ADLB

Reviewer comment: There were 3 micafungin-treated patients with normal to slightly elevated AST values at baseline (indicated in the red circle above) who developed post-baseline AST >3 x ULN:

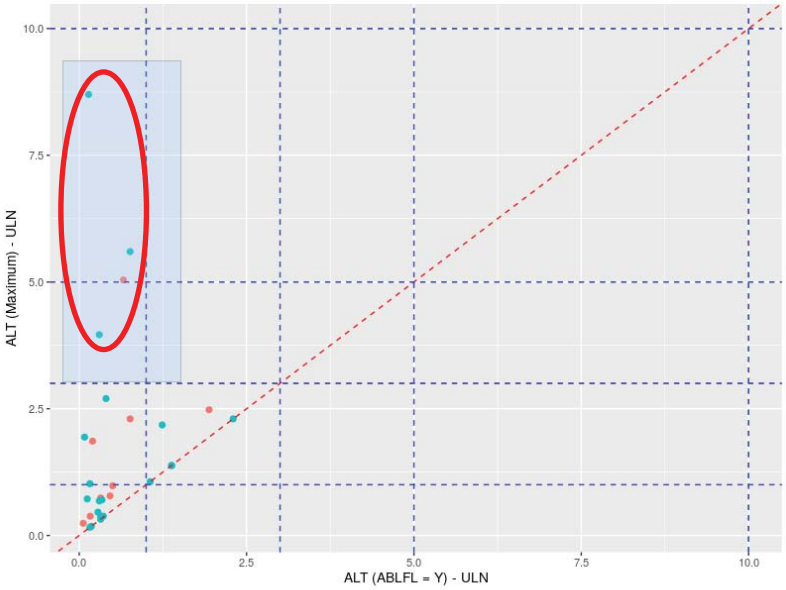
Patient (b) (6) *was a 26-day old ex-31-week male who was treated with micafungin 10mg/kg/day for 10 days. He had a baseline AST of 0.833 x ULN and a maximum AST of 4.183 x ULN. Baseline AST on Day -1 was 50 IU/L and the AST on Day 3 was 251 IU/L; no repeat values are available. Medical history included Listeria sepsis, hyperbilirubinemia, respiratory distress, and intraventricular hemorrhage. Micafungin could have contributed to AST elevation, but causality is unclear in the setting of comorbidities and multiple medications.*

Patient (b) (6) *was an 18-day old ex-32-week male who was treated with micafungin*

10mg/kg/day for 28 days. The patient reportedly had enlarged liver, hypocholic stool, direct hyperbilirubinemia and elevated transaminases of unspecified etiology on day -1. Baseline AST on Day 1 was 37 IU/L, increased to 107 IU/L on Day 14 and reached a peak of 300 IU/L (5x ULN) on Day 27. After micafungin was stopped on Day 28, AST began to decrease, and the last recorded measurement was 105 IU/L on Day 56. It is unclear whether the patient had underlying liver disease which predisposed him to increased AST, but micafungin likely played a role.

Patient (b) (6) *was a 12-day old ex-35-week male who was treated with micafungin 10mg/kg/day for 19 days. He had a medical history of gastroschisis, cystic fibrosis and ascites and. He developed Klebsiella sepsis on Day 11. His antifungal treatment was changed to amphotericin B for persistent candidemia on Day 19. AST on Day 1 was 79 IU/L (1.317 x ULN), rose to 97 IU/L on Day 14, and then to 136 IU/L on Day 19. Despite stopping micafungin on Day 19, AST stayed at 137 IU/L on Day 49 (4.25 x ULN). Increased AST may have been related to micafungin, but it would be unusual to have persistently elevated AST this long after discontinuing the offending agent.*

Figure 10-5: Study 9463-CL-2303 Maximum Post-Baseline ALT Changes in the Two Treatment Arms (x ULN)



Legend: blue=micafungin treated patients; pink=amphotericin B-treated patients. X axis represents baseline ALT in multiples of ULN. Y axis represents maximum ALT in multiples of ULN.
Source: Reviewer-generated in Analysis Studio using ADLB

Reviewer comment: Three micafungin-treated patients had normal ALT at baseline and went on to develop ALT > 3 x ULN:

Patient (b) (6) *was a 9-day-old ex-36-week female who was treated with micafungin 10*

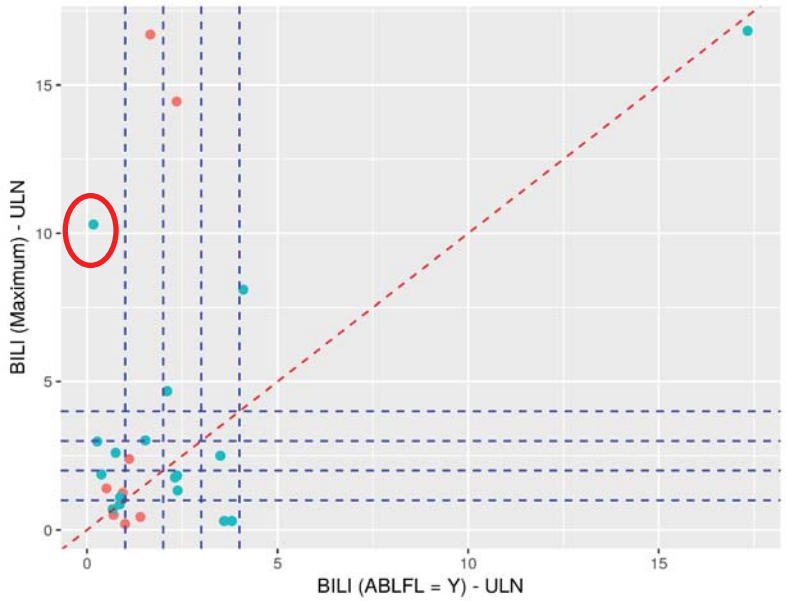
mg/kg/day for 42 days. Baseline ALT on Day 1 was 7 IU/L and it remained normal except for one level of 435 IU/L (8.7 x ULN) on Day 42. Other LFTs and repeat ALT were normal, therefore this may have been a lab error.

Patient (b) (6) *was a 26-day-old ex-22-week female who was treated with micafungin 10 mg/kg/day for 16 days. Underlying conditions included sepsis, respiratory distress and necrotizing enterocolitis (NEC). Baseline ALT on Day 1 was 15 IU/L. Maximum ALT was 198 IU/L (4 x ULN) on Day 19, after micafungin was stopped on Day 16 in the setting of persistent infection and worsening NEC. Micafungin may have been related to increasing ALT, but it is difficult to confirm causality in the setting of multiple comorbidities and medications.*

Patient (b) (6) *(discussed above in the AST section) had a baseline ALT of 38 IU/L, rose to 55 IU/L on Day 14, and to 109 IU/L (5.6 x ULN) on Day 19. After discontinuation of micafungin on Day 19, repeat ALT on Day 49 remained elevated at 119 IU/L. Micafungin may have been related to increased ALT, but the persistence of ALT elevation 30 days after stopping micafungin may indicate an additional etiology.*

Abdominal ultrasounds for these 3 patients did not show evidence of hepatosplenic candidiasis.

Figure 10-6: Study 9463-CL-2303 Maximum Post-Baseline Bilirubin Changes in the Two Treatment Arms (x ULN)



Legend: blue=micafungin treated patients; pink=amphotericin B-treated patients. X axis represents baseline total bilirubin in multiples of ULN. Y axis represents maximum total bilirubin in multiples of ULN.
Source: Reviewer-generated in Analysis Studio using ADLB

Reviewer comment: There was 1 patient (patient (b) (6) *) with initially normal bilirubin who developed a maximum bilirubin >3 x ULN. This patient had a baseline bilirubin of 1.37 mg/dL (0.171 x ULN), which increased to 6.62 mg/dL on Day 14, and to 9.24 mg/dL (10.3 x ULN, with*

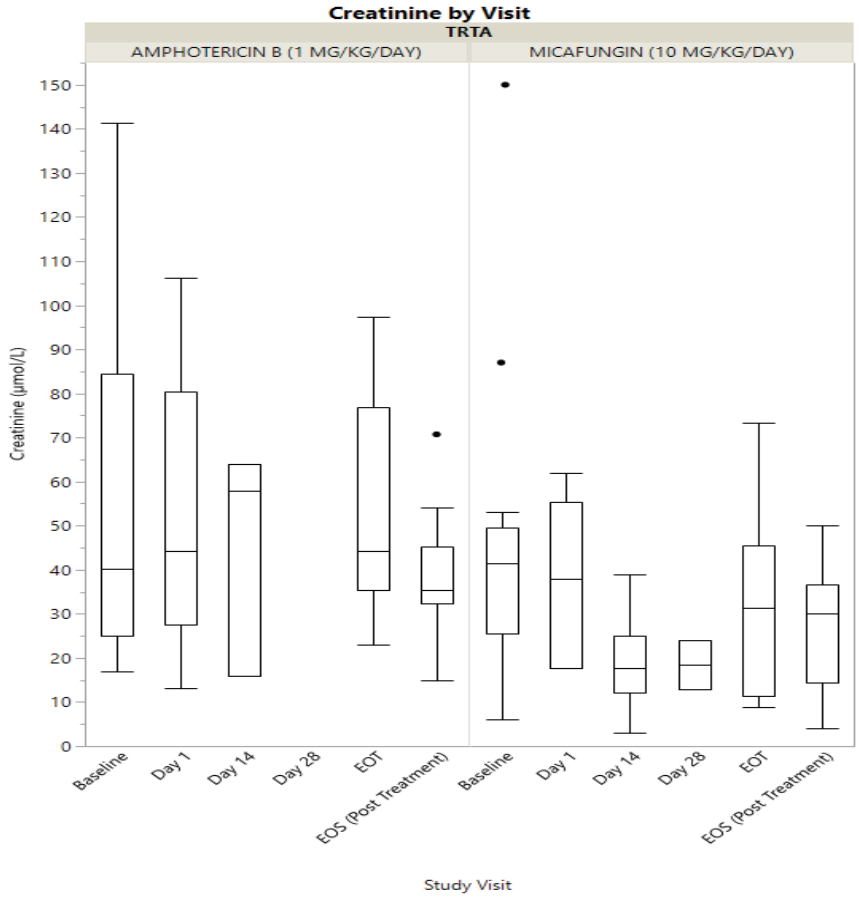
direct bilirubin of 8.1 mg/dL) on Day 19. Micafungin was stopped on Day 19. Repeat bilirubin on Day 49 was 4.2 mg/dL. Micafungin likely played a role in this patient's elevated bilirubin, but there were also underlying conditions and events as discussed.

GGT

There were no patients with a baseline GGT <ULN who developed a maximum GGT >3 x ULN (data not shown).

Creatinine

Figure 10-7: Study 9463-CL-2303: Post-Baseline Changes in Creatinine in the Two Treatment Arms



Source: Reviewer-generated in JMP using ADLB

Reviewer comment: There was no reliable trend in creatinine noted for the micafungin patients, but overall increases in creatinine seemed less pronounced with micafungin compared with amphotericin.

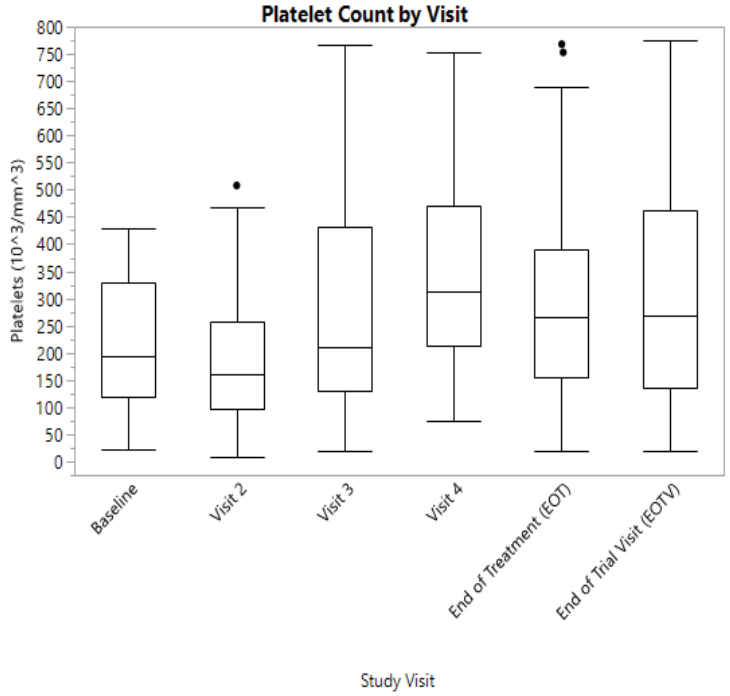
Study 9463-CL-6001

Hemoglobin

Reviewer comment: There was a mild gradual decrease in hemoglobin over the visits (data not shown), but it is likely not clinically significant and would be difficult to sort out whether this was due to micafungin or the condition of the patients. This population could have other factors contributing to anemia such as anemia of prematurity, frequent blood draws for monitoring, medications or concurrent illnesses.

Platelets

Figure 10-8: Study 9463-CL-6001 Platelet Trend over Time



Source: Reviewer-generated in JMP using ADLB

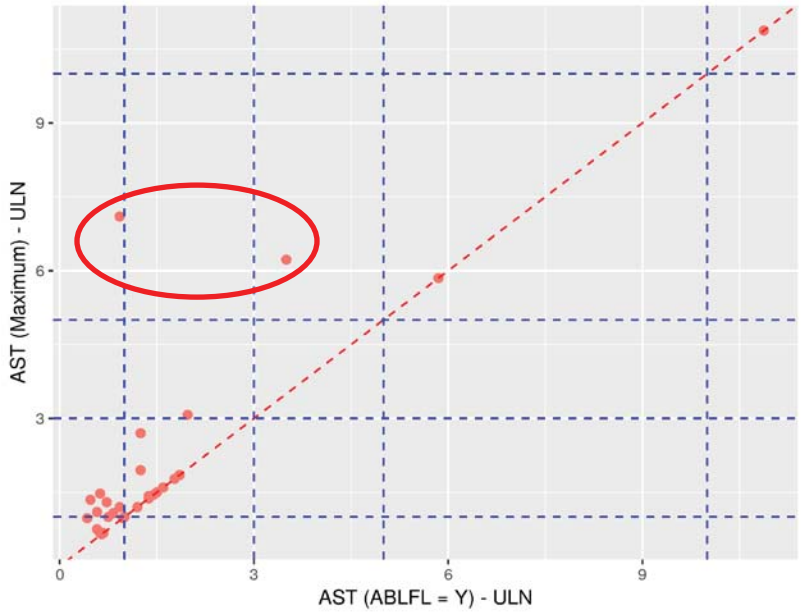
Reviewer comment: Platelets seemed to trend up gradually, and if behaving as an acute phase reactant, would be consistent with inflammation or infection in this ill population. Thrombocytopenia occurred in 3 patients according to the TEAE analysis.

White blood cell count

No reliable trend in WBC was noted (data not shown); there are several outliers with leukocytosis which could be explained by the high rate of sepsis in this population.

Liver Enzymes

Figure 10-9: Study 9463-CL-6001 Maximum Post-Baseline AST Changes (x ULN)

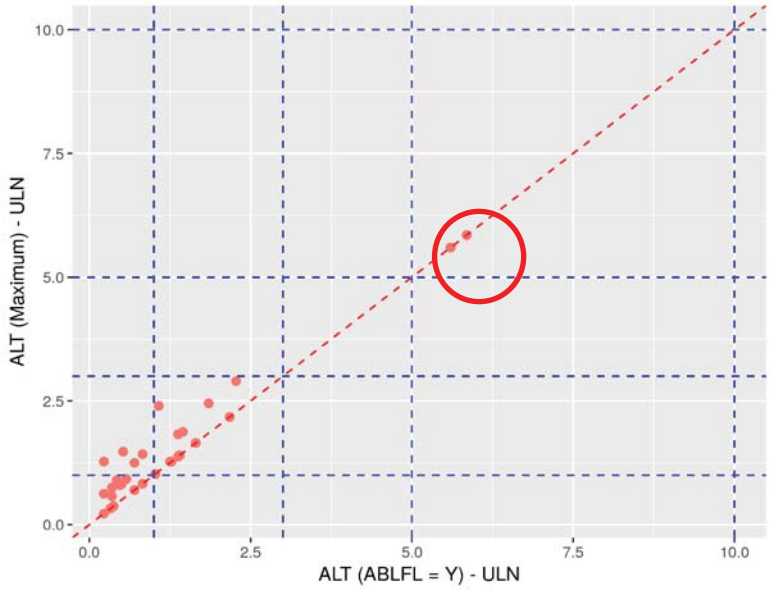


X axis represents baseline AST in multiples of ULN. Y axis represents maximum AST in multiples of ULN.
Source: Reviewer-generated in Analysis Studio using ADLB

Reviewer comment:
Patient (b) (6) *was a 0.5-month-old ex-34-week female who was treated with 4 days of micafungin at 8 mg/kg/day. The baseline AST value on Day -1 was 37 IU/L which increased to 284 IU/L (7.1 x ULN) on Day 5. The patient was transferred to another hospital so was withdrawn from the study and no repeat LFTs were available. This could have possibly been related to micafungin.*

Patient (b) (6) *was a 6.4-month-old ex-25-week female who was treated empirically with 10 days of micafungin at 8 mg/kg/day. This patient had hepatomegaly at baseline with a baseline AST value of 140 IU/L (3.5 x ULN), which increased to 249 IU/L (6.2 x ULN) on Day 9. Study drug was stopped on Day 10 because the patient's condition improved upon starting piperacillin/tazobactam due to concern for sepsis and the blood culture never grew Candida.*

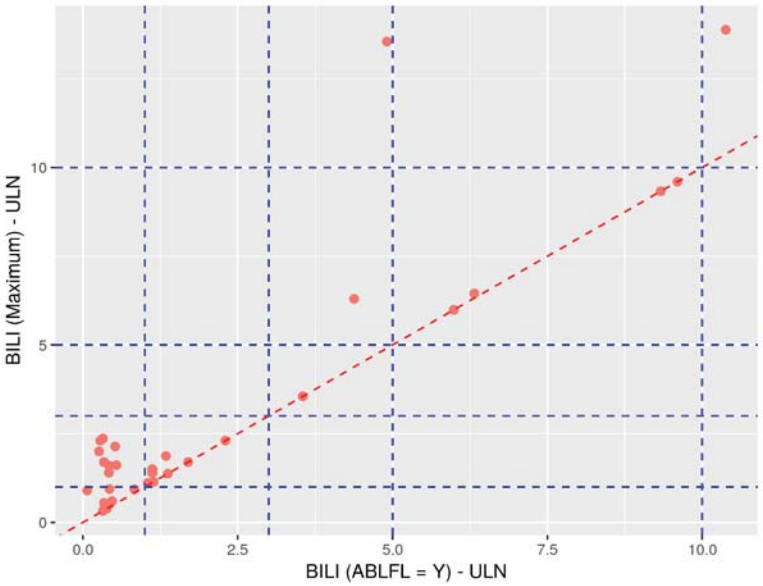
Figure 10-10: Study 9463-CL-6001 Maximum Post-Baseline ALT Changes (x ULN)



X axis represents baseline ALT in multiples of ULN. Y axis represents maximum ALT in multiples of ULN.
Source: Reviewer-generated in Analysis Studio using ADLB

Reviewer comment: The 2 circled patients in Fig. 10-10 with high ALTs (patient (b) (6) *with 5.6 x ULN and patient* (b) (6) *with 5.85 x ULN) had elevated ALT at baseline that remained elevated. There were no patients with normal baseline ALT who developed ALT >3 x ULN.*

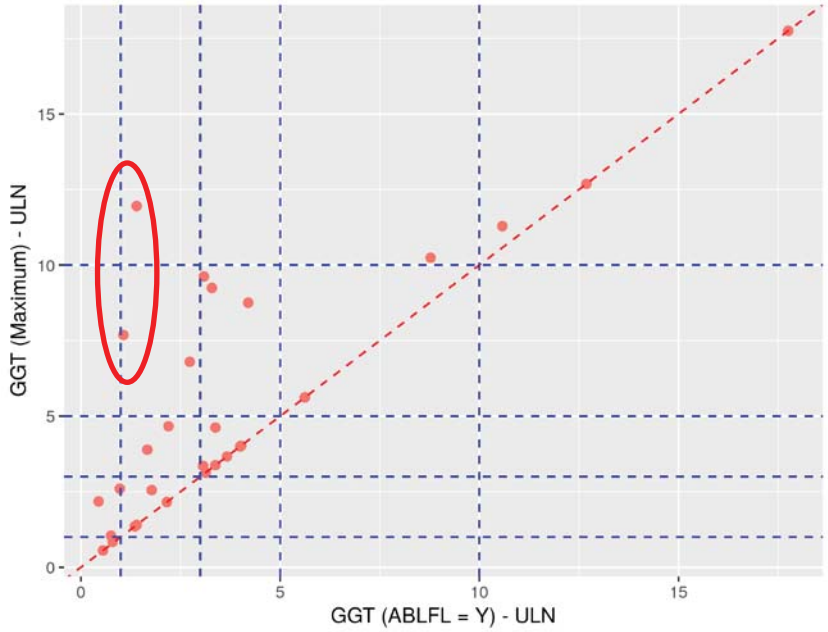
Figure 10-11: Study 9463-CL-6001 Maximum Post-Baseline Bilirubin Changes (x ULN)



X axis represents baseline total bilirubin in multiples of ULN. Y axis represents maximum total bilirubin in multiples of ULN.
Source: Reviewer-generated in Analysis Studio using ADLB

Reviewer comment: The patients with post-baseline maximum bilirubin values >3 x ULN also had abnormal baseline values (>3 x ULN).

Figure 10-12: Study 9463-CL-6001 Maximum Post-Baseline GGT Changes (x ULN)



X axis represents baseline GGT in multiples of ULN. Y axis represents maximum GGT in multiples of ULN.
Source: Reviewer-generated in Analysis Studio using ADLB

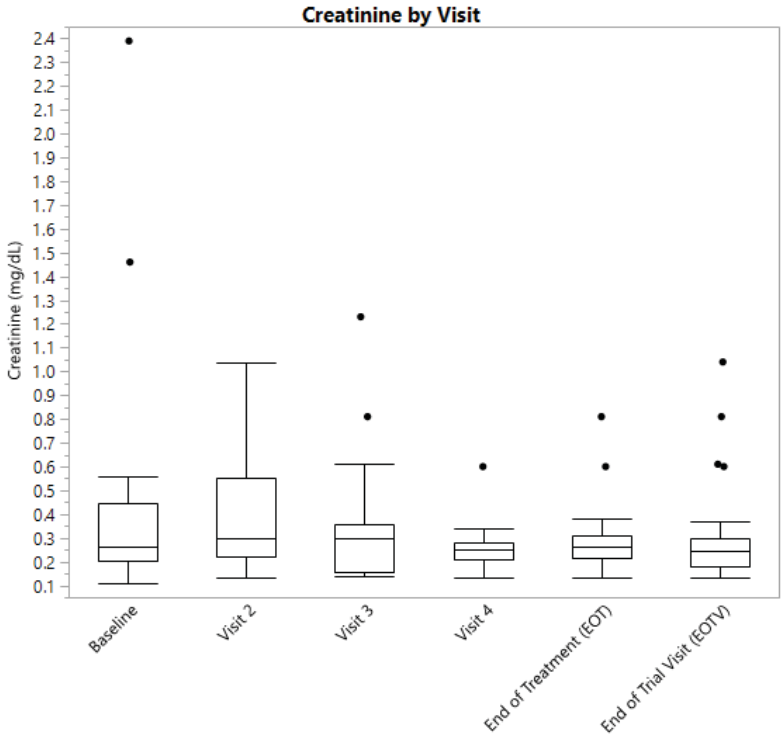
Reviewer comment: Many patients had an elevated maximum GGT, which is consistent with findings in the TEAE analysis. Several patients who had a low to normal baseline GGT and a significantly elevated maximum GGT will be discussed here. Of note, there were no reported discontinuations due to elevated GGT values.

Patient (b) (6) *was a 1.3-month-old ex-36-week female who got 16 days of micafungin at 8 mg/kg/day. The baseline GGT was 1.667 x ULN and the maximum GGT was 7.689 x ULN. This patient passed away several weeks after stopping study drug due to DIC and Klebsiella sepsis and reportedly had resolving cholestasis at that time. It is unclear whether micafungin caused the elevated GGT, but it may have been a factor.*

Patient (b) (6) *was a 0.6-month old ex-23-week female who was treated with 7 days of micafungin at 8 mg/kg/day. The baseline GGT was 1.4 x ULN and the maximum GGT was 11.9 x ULN. The drug was discontinued due to lack of efficacy; the patient died due to many complications including persistent Candida parapsilosis sepsis, respiratory failure, intestinal perforation, and multiorgan failure. Due to the multiple comorbidities and organ system involvement in this patient, it is difficult to assess the role of micafungin in the elevated GGT in this patient.*

Creatinine

Figure 10-13: Study 9463-CL-6001 Serum Creatinine Trends Over Time



Source: Reviewer-generated in JMP using the ADLB dataset

Reviewer comment: Median creatinine values remained relatively stable throughout the study, but there were several outliers. Those who had persistently elevated Cr at more than one time-point will be discussed here. Other outliers are not discussed because their elevated Cr resolved after one measurement.

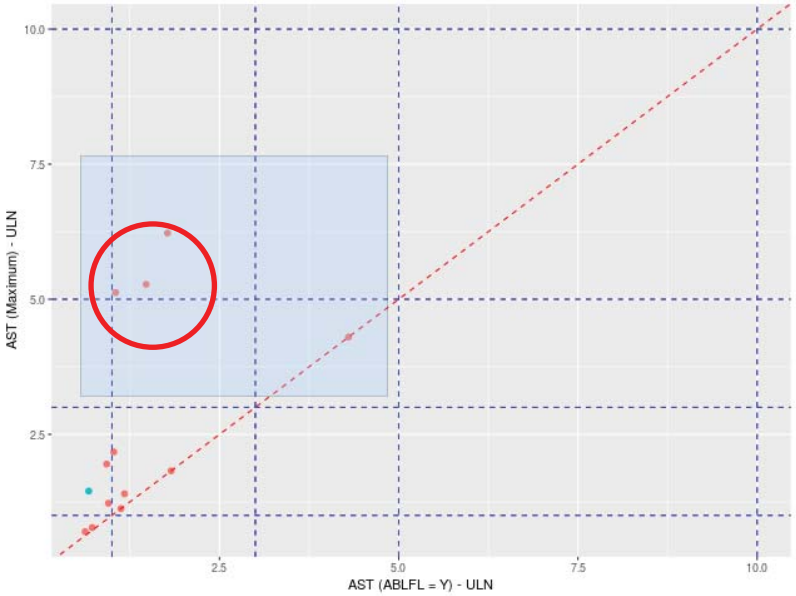
Patient (b) (6) *was a 2.2-month old ex-24-week female with sepsis who was treated with micafungin 8 mg/kg/day for 15 days, and with vancomycin. Creatinine on Day 4 was 0.47 mg/dL, which increased to 0.81 mg/dL on Day 11. No repeat values are available. It is unclear whether the elevated creatinine was due to micafungin, especially in the setting of sepsis and administration of other nephrotoxic agents such as vancomycin.*

Patient (b) (6) *was a 0.6-month old ex-28-week female who was treated with micafungin 8 mg/kg/day for 14 days. This patient was reported to be oliguric on Day -1. Baseline Cr on Day 1 was 0.55 mg/dL, and maximum Cr was 1.23 mg/dL on Day 11. Treatment for acute renal failure included sodium bicarbonate and albumin. Cr on Day 14 decreased to 0.6 mg/dL. Elevated creatinine may have been related to micafungin administration, but causality is difficult to judge given her background of underlying renal disease and coadministration of several nephrotoxic medications including vancomycin, piperacillin-tazobactam and furosemide.*
Study 9463-CL-6002

There was no CBC data available for this study according to the Applicant.

Liver Enzymes

Figure 10-14: Study 9463-CL-6002 Maximum Post-Baseline AST Changes (x ULN)



X axis represents baseline AST in multiples of ULN. Y axis represents maximum AST in multiples of ULN.
Source: Reviewer-generated in Analysis Studio using ADLB

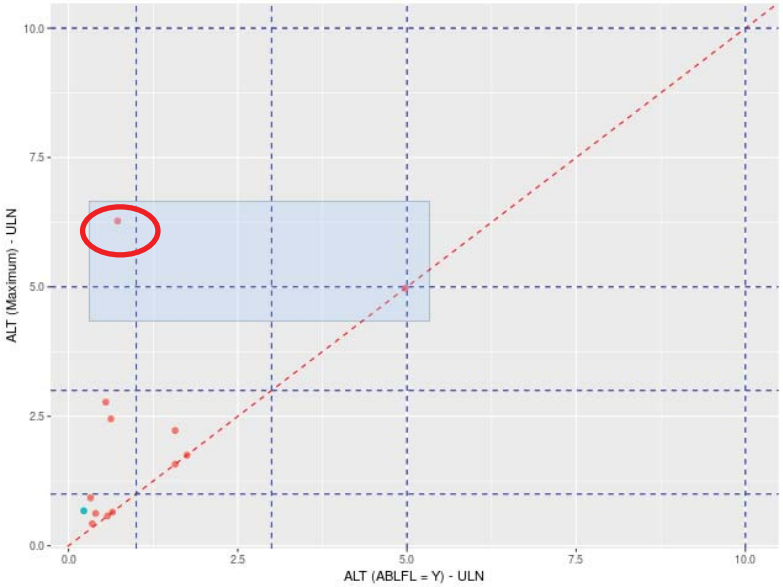
Reviewer comment: Three patients had baseline AST <3 x ULN with maximum AST values > 5 x ULN. Patient (b) (6) *was a 180-day-old ex-35-week female who was treated with 22 days of micafungin at 10 mg/kg/day. The baseline level on Day -3 was 71 IU/L (1.8 x ULN) and the value on Day 20 was 249 IU/L (6.2 x ULN). There are no values available from the post-treatment period, so AST trends are unknown. Micafungin may have contributed to the AST elevation, but it is difficult to say in the context of comorbidities of prematurity, seizures and respiratory failure and multiple medications.*

Patient (b) (6) *was a 95-day-old ex-29-week female who was treated with 15 days of micafungin (Days 1-3 were at 10 mg/kg and Days 4-15 were at 8 mg/kg). Baseline AST at Day -11 was 59 IU/L (1.5 x ULN) and on Day 9, AST rose to 211 IU/L (5.3 x ULN). No further measurements are available until Day 38 when AST was 36 IU/L. The patient was on concomitant fluconazole. The elevated AST may have been due to micafungin, but factors such as concomitant medications (i.e. fluconazole) sepsis or TPN use could have contributed.*

Patient (b) (6) *was a 4-day old ex-38-week male who was treated with 21 days of micafungin at 8 mg/kg/day. The baseline AST on Day -1 was 42 IU/L (1.1 x ULN) and the maximum AST was 205 IU/L (5.1 x ULN) on Day 23, after micafungin treatment was already complete. No repeat values are available. Micafungin may have contributed to the AST*

elevation.

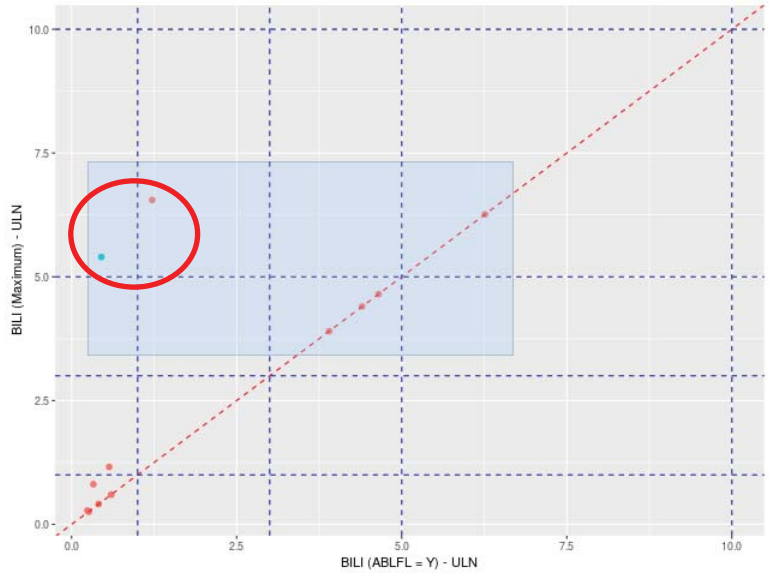
Figure 10-15: Study 9463-CL-6002 Maximum Post-Baseline ALT Changes (x ULN)



X axis represents baseline ALT in multiples of ULN. Y axis represents maximum ALT in multiples of ULN.
Source: Reviewer-generated in Analysis Studio using ADLB

Reviewer comment: Patient (b) (6) *(discussed above under the AST section) had a baseline ALT of 29 IU/L on Day -11 and a maximum ALT of 251 IU/L on Day 9. A repeat ALT level on Day 38 was 28. This patient was also on fluconazole and TPN, so causality is difficult to ascertain.*

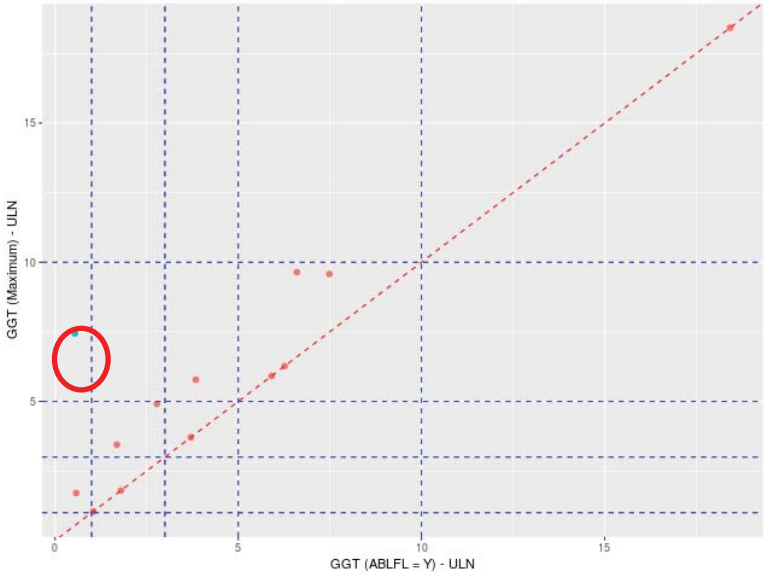
Figure 10-16: Study 9463-CL-6002: Maximum Post-Baseline Changes in Bilirubin (x ULN)



X axis represents baseline total bilirubin in multiples of ULN. Y axis represents maximum total bilirubin in multiples of ULN.

Reviewer comment: Two patients with normal total bilirubin at baseline developed post-baseline hyperbilirubinemia. Patient (b) (6) *also had elevated AST and ALT and is discussed above.*

Figure 10-17: Study 9463-CL-6002: Maximum Post-Baseline GGT Changes (x ULN)



X axis represents baseline GGT in multiples of ULN. Y axis represents maximum GGT in multiples of ULN.
Source: Reviewer-generated in Analysis Studio using ADLB

Reviewer comment: One patient with normal baseline GGT developed a post-baseline GGT value >5 x ULN. Patient (b) (6) *(discussed above in the bilirubin section) had a GGT level on Day -1 of 26 IU/L, which increased to 156 IU/L (7.4 x ULN) on Day 12, then 335 IU/L on Day 23, the day micafungin was stopped. GGT remained elevated at 313 IU/L through Day 54, and no further values were provided. This GGT elevation may have been related to micafungin, but it would be unusual for the GGT to remain elevated for such a long time.*

The laboratory data for patients in study 6002 with abnormal post-baseline LFTs are summarized in Table 10-12. There was no comment in the patient profiles about presence of liver abscess.

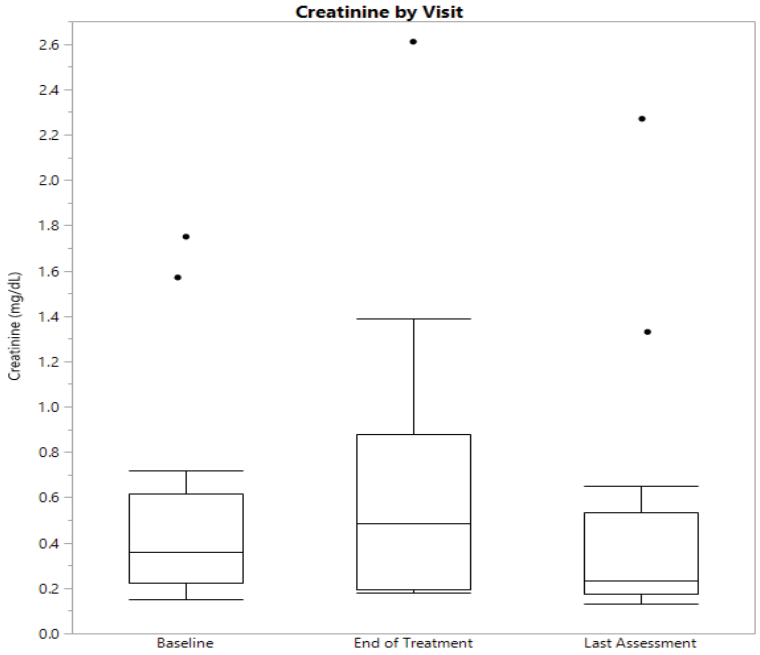
Table 10-12: Summary of Patients with Abnormal LFTs in Study 9463-CL-6002

USUBJID	Maximum AST (IU/L)	Maximum ALT (IU/L)	Maximum bilirubin (mg/dL)	Maximum GGT (IU/L)
(b) (6)	58 (Day 12)	27 (Day 12)	5.4 (Day -12)	335 (Day 23)
	211 (Day 9)	251 (Day 9)	6.55 (Day 38)	431 (Day 9)*
	205 (Day 23)	98 (Day 23)	4.65 (Day -1)	77 (Day 23)
	249 (Day 20)	199 (Day -3)	0.41 (Same on Day -3 and Day 20)	266 (Day -3)

*Baseline GGT was already elevated at 337 IU/L

Creatinine

Figure 10-18: Study 9463-CL-6002: Changes in Creatinine Over Time



Source: Reviewer-generated in Analysis Studio using ADLB

Reviewer comment: Median creatinine values increased slightly from baseline to the end of treatment visit, but then decreased below baseline at the last assessment. There were several outliers at each timepoint. Patient (b) (6) *and patient* (b) (6) *both had elevated creatinine at the last assessment, but both had a diagnosis of kidney failure due to unknown etiology at admission. The limited sample size makes this trend difficult to interpret.*

Vital Signs

Vital sign changes in study 9463-CL-6001 and 9463-CL-2303 were small and not felt to be clinically relevant by the Applicant. Underlying sepsis and other comorbidities in most patients likely contributed to the vital sign changes observed. The study report for study 9463-CL-6002 does not mention any measurement of vital signs.

Reviewer comment: Vital sign measurements in this small study of 12 patients, would be unlikely to alter our assessment of safety, especially because the other studies included in this sNDA did not find any clinically relevant trends in vital signs. Additionally, most neonates in these studies were ill with sepsis, candidemia or bacteremia, and other comorbidities – thus hypotension and changes in heart rate, if seen, were most likely related to underlying conditions.

Electrocardiograms (ECGs)

ECGs were not collected for studies 9463-CL-2303 or 9463-CL-6002. The study design for study 9463-CL-6001 stated that a 12-lead ECG should be performed before the beginning and after

the end of the first infusion of micafungin and should be repeated at subsequent visits. Six patients had baseline and post-baseline ECG assessments and their ECGs remained unchanged.

QT

There were no reports of QT prolongation in this submission.

According to the original 2005 MYCAMINE review, there was no increase in QT interval in preclinical or clinical studies. A consult by the Interdisciplinary Review team for QT studies from 7/23/07 stated that Astellas had evaluated cardiovascular safety in normal volunteers. However, the QT/IRT team had concerns that the studies had many limitations and recommended that FDA request a thorough QT study from the Applicant. A record of a QT study for micafungin could not be located. A literature search did not reveal any signal of QT prolongation with micafungin.

Immunogenicity

There is no known immunogenicity with micafungin and no specific immunogenicity studies were done in this efficacy supplement.

10.5. Analysis of Submission-Specific Safety Issues

10.5.1. Hepatotoxicity

TEAEs of hepatic enzyme abnormal/increased, liver function test increased/abnormal, alanine aminotransferase increased, aspartate aminotransferase increased, hepatic function abnormal, liver function test increased, and hepatic failure occurred in 18 (10.7%) infants across a micafungin dose range of 1-14 mg/kg in the 9 studies. Hyperbilirubinemia occurred in 26 (15.5%) patients across the same dose range, while increased GGT indicative of cholestasis occurred in 19 (11.3%) at doses of 3-14 mg/kg/day. The frequency of these laboratory abnormalities was slightly higher in the 5 neonates who received 15 mg/kg of micafungin, but the very limited sample size precludes definite conclusions regarding liver toxicity at this dose. Increases in AST, ALT, GGT and total bilirubin in laboratory data are discussed in Section 10.4 The neonatal population may have a higher frequency of hepatic injury due to prematurity, underlying comorbidities, and multiple medications, including micafungin. There were 2 SAEs and 2 discontinuations due to hepatotoxicity, but no deaths. Given the medical complexity of patients with neonatal candidiasis, establishing causality to micafungin was very challenging.

10.5.2. Bone Marrow Toxicity

Anemia was a prominent signal in the TEAE analysis, and hemoglobin values appear to decrease over time in the laboratory data analysis for studies 9463-CL-2303 and 9463-CL-6001. This could be due to many factors such as anemia of prematurity, blood draws, sepsis, and concurrent medications, including micafungin. There was one SAE of neutropenia, but no SAEs, deaths or discontinuations due to leukopenia. There were no SAEs, deaths or discontinuations due to

thrombocytopenia. Bone marrow toxicity could not be assessed for study 6002 due to the lack of CBC data.

10.5.3. Hypersensitivity

There were no PTs of anaphylaxis, anaphylactoid reaction or hypersensitivity among the 9 studies submitted to the sNDA. Seventeen patients (10.1%) who received micafungin doses of 0.75-10 mg/kg had treatment-emergent skin disorder, dermatitis diaper, dermatitis, skin discoloration, decubitus ulcer, rash, rash neonatal, rash papular, erythema, and petechiae in the Skin and Subcutaneous Tissue Disorders SOC.

10.5.4. Infusion Related Reactions

In the safety database of nine studies, a total of nine of 168 patients (5.4%) had infusion-related reactions consisting of infusion site extravasation in 7 (4.2%), infusion site phlebitis in 1 (0.6%), infusion site rash in 1 (0.6%), and infusion related reaction in 2 (1.2%).

10.5.5. Renal Insufficiency

Nineteen (19/168, 11.3%) patients across the 9 studies had AEs of renal failure, azotemia, acute kidney injury, renal impairment and renal tubular necrosis. However, only 10 (6%) of those patients appeared to have TEAEs; associated average daily doses of micafungin ranged between 1 and 14.2 mg/kg and most received at least 7 days of treatment. Seven (4.2%) patients who received 1-14.2 mg/kg micafungin had treatment-emergent oliguria, anuria, hematuria and pyelocaliectasis.

Reviewer comment: The analyses of treatment-emergent AESIs, in common with analyses of other TEAEs, were incomplete as only neonates with available dosing information were included (168/244 [68.9%]). Every attempt was made to ensure that similar PTs were combined for robust evaluation of potential safety signals, but all percentages must be interpreted with caution due to data limitations.

10.6. Specific Safety Studies/Clinical Trials

As outlined in Section 10.1, data from 9 studies were submitted in support of this sNDA. The safety review primarily focused on 3 of them as described above, but also included additional analyses of patients from all studies to bolster patient numbers and conduct an analysis of possible dose-response for safety. These studies are all described in Section 10.1.

10.7. Additional Safety Explorations

Safety Analyses by Demographic Subgroups

No specific subgroup analyses were done due to the limited sample size; pooling was difficult due to varying study designs, inclusion/exclusion criteria and endpoints.

Analysis of Possible Dose-Response Relationship for Safety

In this sNDA, based on data from the rabbit model described previously (Section 9), the Applicant proposed a 10 mg/kg dose of micafungin daily for treatment of neonatal candidiasis given the high risk of meningoencephalitis in these patients. Despite the limitations of the safety database in terms of variability of studies and small numbers, the clinical team attempted to evaluate the safety of higher doses of micafungin compared to the highest currently approved pediatric dose, which is 3 mg/kg/day. A dose-response table was constructed using the ISSNEO flag in the ADSL dataset (n=282). This population included mostly patients ≤120 days of age, but 7 older infants (129-247 days of age) were also included. Patients who got less than 7 days of micafungin (n=67) were excluded because patients with candidemia or IC would likely not receive duration of treatment shorter than 7 days. Patients with known average daily doses of micafungin who received 7 or more days of therapy (n=185) were divided into dose group categories: ≤2 mg/kg/day, >2-<6 mg/kg/day, ≥6-<8 mg/kg/day, ≥8-<10 mg/kg/day, ≥10-<11 mg/kg/day, and >11 mg/kg/day. TEAEs of special interest were identified, and included categories such as liver function and cholestasis, rash or other infusion reaction, renal function, and blood dyscrasias. Preferred terms were combined into relevant umbrella terms, such as “anemia,” which combined “anemia,” “anaemia neonatal,” and “haematocrit decreased,” and frequencies were tabulated by dose group. The table below demonstrates this analysis and includes amphotericin for comparison. Those with unknown micafungin doses (n=54) or unknown amphotericin doses were excluded.

Table 10-13: Selected TEAEs by Dose Group in ISSNEO Population

	Micafungin Dose Groups in mg/kg/day						
	≤2 n=25 (N%)	>2-<6 n=20 (N%)	≥6-<8 n=21 (N%)	≥8-<10 n=29 (N%)	≥10-<11 n=27 (N%)	>11 n=8 (N%)	Amphotericin B n=9 (N%)
Hypokalemia[1]	3 (12)	6 (30)	1 (4.8)	1 (3.4)	0	1 (12.5)	0
Cholestasis[2]	3 (12)	6 (30)	8 (38.1)	11 (37.9)	3 (11.1)	6 (75)	1 (11.1)
Thrombocytopenia[3]	3 (12)	5 (25)	5 (23.8)	5 (17.2)	7 (25.9)	6 (75)	3 (33.3)
Hyperbilirubinemia[4]	6 (24)	4 (20)	9 (42.9)	5 (17.2)	7 (25.9)	4 (50)	1 (11.1)
Vomiting	2 (8)	4 (20)	1 (4.8)	0	1 (3.7)	0	0
Anemia[5]	8 (32)	4 (20)	2 (9.5)	2 (6.9)	12 (44.4)	4 (50)	4 (44.4)
Acidosis[6]	4 (16)	3 (15)	0	0	1 (3.7)	3 (37.5)	0
Leukocytosis	0	3 (15)	1 (4.8)	0	0	0	1 (11.1)
Oxygen saturation decreased	0	3 (15)	1 (4.8)	0	0	0	0
Abdominal distension	0	2 (10)	1 (4.8)	0	0	0	0
Bradycardia neonatal	1 (4)	2 (10)	0	0	0	0	0

	Micafungin Dose Groups in mg/kg/day						
	≤2 n=25 (N%)	>2-<6 n=20 (N%)	≥6-<8 n=21 (N%)	≥8-<10 n=29 (N%)	≥10-<11 n=27 (N%)	>11 n=8 (N%)	Amphotericin B n=9 (N%)
Cardiac murmur	0	2 (10)	0	0	1 (3.7)	0	0
Fluid overload	1 (4)	2 (10)	0	0	0	0	0
Hyperkalemia	3 (12)	2 (10)	1 (4.8)	0	0	0	0
Hypocalcemia	1 (4)	2 (10)	0	0	0	0	0
Hypoglycemia	1 (4)	2 (10)	1 (4.8)	0	0	0	0
Infusion site extravasation	0	2 (10)	0	0	1 (3.7)	0	1 (11.1)
Neonatal hypotension	2 (8)	2 (10)	0	0	0	0	0
Pyrexia	0	2 (10)	0	1 (3.6)	1 (3.7)	0	2 (22.2)
Rash[7]	2 (8)	2 (10)	0	0	1 (3.7)	0	1 (11.1)
Elevated Transaminases[8]	6 (24)	2 (10)	5 (23.8)	3 (10.3)	7 (25.9)	1 (12.8)	2 (22.2)
Renal failure[9]	3 (12)	2 (10)	7 (33.3)	2 (6.9)	3 (11.1)	6 (75)	0

[1]Hypokalemia, Blood Potassium Decreased
[2]GGT increased, blood alkaline phosphatase increased, cholestasis
[3]Thrombocytopenia, platelet count decreased, thrombocytopenia neonatal
[4]Blood bilirubin increased, bilirubin conjugated increased, blood bilirubin abnormal, hyperbilirubinemia, hyperbilirubinemia neonatal
[5]Anemia, Anaemia neonatal, haematocrit decreased
[6]Acidosis, Metabolic Acidosis
[7]Rash, Infusion Related Reaction, Infusion Site Rash, Rash Neonatal, Rash Papular
[8]Hepatic Function Abnormal, Hypertransaminasaemia, Alanine Aminotransferase Increased, Aspartate Aminotransferase Increased, Hepatic Enzyme Abnormal, Hepatic Enzyme Increased, Liver Function Test Abnormal, Liver Function Test Increased
[9]Acute Kidney injury, Blood urea increased, Blood creatinine increased, Anuria, Renal failure, Renal failure neonatal, Renal tubular necrosis
Source: Reviewer-generated with JMP and Analysis Studio using ADAE dataset

Reviewer comment: Our analysis does not demonstrate a specific dose-response for safety up to 11 mg/kg/day. Patients who got >11 mg/kg/day of micafungin, did show increased rates of certain AEs such as cholestasis (65%), hyperbilirubinemia (50%), thrombocytopenia (75%), anemia (50%), acidosis (37.5%) and renal failure (75%), although the very small sample size of 8 (including 5 who received 15 mg/kg/day) limits interpretation. However, the listed toxicities are easily monitorable in a NICU population, and the benefits of using a higher dose with increased potential efficacy for treatment of meningoencephalitis outweigh the risks of these TEAEs if morbidity including long-term neurological sequelae, or even mortality, can be prevented.

Neonates with Central Nervous System Infection

Across the 9 studies with neonatal data considered in this submission, only 6 patients had *Candida* meningoencephalitis proven by imaging or culture/PCR of CSF. Only 4 patients had CSF PK data collected. For discussion of the limited CSF PK data, please refer to the Clinical Pharmacology section of this review.

Study 9463-CL-2303 included two patients with CNS disease based on imaging findings, but no CSF cultures were performed. Patient (b) (6), a 4-week-old ex-22-week GA female, discontinued treatment after 16 days of micafungin 10 mg/kg/day due to persistently positive blood culture with *C. parapsilosis*, and later died of NEC. Patient (b) (6), a 2-week-old ex-27-week GA male, only got one dose of micafungin before switching to fluconazole. One CSF sample was collected for micafungin PK analysis, but it could not be analyzed due to hemolysis.

Reviewer comment: Patient (b) (6) *discontinued treatment due to lack of efficacy in clearing blood cultures, presumably due to the same organism as his radiologically confirmed Candida meningoencephalitis. Long-term outcome related to ME could not be assessed as the patient died of NEC. It is impossible to assess the efficacy of a single dose of micafungin given to patient* (b) (6)*.*

Study 9463-CL-6001 included one patient (patient (b) (6), a 1.6-month-old ex-28-week GA female) with possible CNS infection based on a positive *Candida* PCR in the CSF; CSF PK data was also collected. This patient had a reservoir placed for hydrocephalus on Day 6 in the setting of intraventricular hemorrhage. Amphotericin B was administered prior to and during micafungin treatment (Day -12 to Day 12). Prior to Day 1, the first day of micafungin given as part of this study, the patient had also been on micafungin from Day -29 to Day -1. Treatment with micafungin 8 mg/kg/day was stopped on Day11; it was unclear why micafungin was stopped. Amphotericin B was restarted on Day 13 and was ongoing. CSF PCR was not repeated.

Reviewer comment: It is not possible to assess the efficacy of micafungin in this patient due to the concomitant treatment with amphotericin B.

Study 9463-CL-6002 included one patient (patient (b) (6), a 161-day-old ex-29-week female) with culture proven *Candida* meningitis due to *C. albicans*; she was treated with micafungin 10 mg/kg/day for 74 days, and CSF culture was negative twice subsequently. CSF PK data was collected on this patient.

Reviewer comment: This patient's treatment with micafungin was successful based on clearance of CSF cultures.

Study 9463-CL-7001 included one patient (patient (b) (6), an 18-day-old ex-23-week GA female) with positive CSF culture for *Candida* on Day -4 . This patient initially received amphotericin B from Day -2 to Day 1, then received 5 days of micafungin (Day 1 to Day 5), but dosing information was unavailable. Repeat CSF culture on day 5 of micafungin was negative.

Reviewer comment: This patient does not have available dosing information and she only got 5 days of micafungin, so it is not possible to assess efficacy of micafungin. Although CSF culture was negative on Day 5, this patient would not have had a sufficient treatment duration for ME and there was no comment on whether an alternative antifungal was started on day 5.

Study FG-21-08 included one patient with *C. albicans* CNS disease diagnosed by CSF culture. Patient (b) (6) was a 32-day-old female (GA unknown) who was treated with 36 days of micafungin at <2 mg/kg/day (average daily dose 1.89 mg/kg/day). There was a relapse of fungal meningitis on Day 53 which resolved on Day 85 after treatment with amphotericin B.

Reviewer comment: This patient's relapse could have been related to micafungin under-dosing. A full narrative was not available for this patient so many clinical details are missing.

Table 10-14: Outcomes of patients with CNS disease

Unique Subject Identifier	Consolidated Infection Site	Treatment Duration (Days)	Survival at End of Study Flag	Other Anti-Fungal Taken During Treatment (Number of Treatment Days)	Mycological Response at EOT Flag	Recurrent Fungal Infection (Description)
9463-CL-2303-(b) (6)	BLOOD	1	Y	N	N	N
9463-CL-2303-	BLOOD	16	N	N	N	N
9463-CL-6002-	BLOOD AND CSF DAY OF SAMPLE	74	N	N	Y	
FG-21-08-(b) (6)	BLOOD, CNS/BRAIN	36	Y	N	Y	Y (DISSEMINATED, CNS/BRAIN)
9463-CL-6001-(b) (6)	N/A	11	Y	Y	N	N
9463-CL-7001-	N/A	5	Y	N	Y	N

Reviewer comment: Due to the difficulties in recruiting patients and accurately diagnosing this entity, the submitted data in this sNDA does not provide sufficient information to support a specific dose of micafungin for treatment of neonatal disseminated candidiasis with possible or proven meningoencephalitis.

Human Carcinogenicity or Tumor Development

No specific studies on human carcinogenicity were performed. This drug is not meant to be used long-term. No new nonclinical carcinogenicity studies were submitted.

Human Reproduction and Pregnancy

This supplement includes studies of neonatal patients and therefore does not include investigations of micafungin's effects on reproduction and pregnancy.

Pediatrics and Assessment of Effects on Growth

This drug is not meant to be used long-term, so its effects on growth were not studied.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Micafungin is an antifungal drug that is administered by healthcare professionals in a controlled hospital setting. There is no known drug abuse potential or propensity for withdrawal or rebound effects.

10.8. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

A literature review was done on PubMed using the search term "micafungin adverse event" and "micafungin safety" with an age filter for birth to 23 months. Studies including pediatric patients were reviewed for safety concerns.

A 2019 study[14] of 110 pediatric patients receiving micafungin for prophylaxis or treatment describes multiple AEs in the patient population of oncology, NICU, and PICU patients. Median duration among the treatment groups ranged from 11-29 days. The mean daily dose for oncology patients ≤40kg was 1.3 mg/kg/day compared to 7.6 mg/kg/day for neonates; they did not provide dose ranges, so the maximum dose was not available. The authors felt that several AEs were possibly attributable to micafungin including pancytopenia, elevated transaminases >3 x ULN, and liver nodules.

A 2014 observational study[15] of 108 pediatric and adult patients (36 of whom were pediatric) treated with micafungin reported AEs of rash, anemia, worsening tremor, increased bilirubin, and increased transaminases. Median daily dose for pediatric patients was 2.2 mg/kg. Maximum dose was not provided. Median duration of treatment was 13 days. No pediatric patient discontinued micafungin due to an AE.

A 2011 review[16] of micafungin safety in pediatric clinical trials (296 patients <16 years of age) found that the most frequent AEs were vomiting, pyrexia, diarrhea, nausea and hypokalemia. Other AEs included increased transaminases, hypokalemia, hyperbilirubinemia, and hypertension. There were 18 patients <4 weeks old and 48 patients >4 weeks-1 year of age. Daily dose range of micafungin was 0.4-8.6 mg/kg and median duration was 15 days. Although there were small sample sizes which limits interpretation of clinical significance, the AEs occurring at rates of >5% in the two youngest age groups were increased ALT, increased alkaline phosphatase, abnormal LFT, and thrombocytopenia.

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[14] Levarger G, Timsit, J, Milpied N et al. Use of micafungin for the prevention and treatment of invasive fungal infections in everyday pediatric care in France: Results of the MYRIADE study. *Pediatric Infectious Disease Journal.* 2019;38(7):716-721.
[15] Viscoli C, Bassetti M, Castagnola E, et al. Micafungin for the treatment of proven and suspected invasive candidiasis in children and adults: Findings from a multicenter prospective observational study. *BMC Infectious Diseases.* 2014;14.
[16] Arrieta A, Maddison P, and Andreas H. Safety of micafungin in pediatric clinical trials. *Pediatric Infectious Disease Journal***.** 2011;30(6):e97-e102.

A randomized study from 2018[17] comparing micafungin and fluconazole in 36 neonates noted similar rates of anemia and thrombocytopenia in the two arms. No AEs were thought to be related to study drug and there were no discontinuations. Micafungin 15 mg/kg was given as a loading dose and continued at 10mg/kg/day. Treatment duration ranged from 1-35 days.

A 2018 retrospective review[18] of 19 extremely low birth weight infants treated with micafungin (7.5 ± 2.0 mg/kg for a mean of 16.5 days) reported increased LFTs and increased direct bilirubin, especially in those who underwent any abdominal surgical interventions. GGT, hemoglobin and platelets remained stable.

Reviewer comment: Overall, the safety profile of micafungin in the current review appears to be consistent with literature reports and current labeling. A review of FDA Adverse Event Reporting System (FAERS) reports was not conducted during this review.

Expectations on Safety in the Postmarket Setting

We expect that the safety profile of micafungin will be consistent with the events described in the literature and in this review.

10.9. Integrated Assessment of Safety

The review of safety for micafungin [redacted] (b) (4) dose of 10 mg/kg/day for treatment of invasive candidiasis including candidemia and *Candida* ME in infants younger than 4 months was challenging for several reasons. In general, although there is need for alternative safe and effective drugs in this patient population, they are a difficult population to study as common infections disseminate easily, involving sheltered sites, e.g. CNS, making extrapolation of efficacy from adults and older children difficult; their inherent vulnerability both physical and as perceived by parents, physicians and institutional review boards limit feasibility of large adequate and well-controlled clinical trials. Because the Phase 3 trial (9463-CL-2303) was terminated early due to limited enrollment, the Applicant attempted to support their proposed dose and indication with additional data from a variety of sources. In addition to data from study 9463-CL-2303, the safety database included data from studies 9463-CL-6001 and 9463-CL-6002 that utilized higher micafungin doses of 8-10 mg/kg/day, buttressed by additional data at these doses from studies 9463-CL-2104 and 9463-CL-7001. Data from 4 other studies using micafungin at various doses in the range of 0.75-15 mg/kg/day were also provided.

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[17] Leroux S, Jacqz-Aigrain E, Elie V et al. Pharmacokinetics and safety of fluconazole and micafungin in neonates with systemic candidiasis; a randomized, open-label clinical trial. *British Journal of Clinical Pharmacology*. 2018;84(9).
[18] Schuller S, Bauer C, Unterasinger, L, and Berger, A. Safety and efficacy of micafungin in extremely low birth weight infants. *Pediatric Infectious Disease Journal*. 2018;37(6):e169-e172.

The safety database thus consisted of 9 studies that included 244 patients <120 days exposed to micafungin, but only 68.9% (168 patients) were included in safety analyses as the rest lacked dosing information. Further, the studies varied in design, scheduled assessments, dosing regimens, duration of treatment, and endpoints. There were missing data, such as doses, sites of infection, and outcomes in several of the studies. Importantly, there were only 6 patients with proven CNS involvement; of these, 4 received 8-10 mg/kg of micafungin, one was treated with micafungin for a single day, one received concomitant amphotericin and one was older than 120 days. Thus, while the data were insufficient to establish efficacy for the (b) (4) indication and dose of micafungin, review of micafungin safety across a range of doses from 0.75 to 15 mg/kg/day in 9 submitted studies allowed for an exploratory assessment of a dose response for safety. No discernible dose response for safety was detected in patients who received micafungin for a minimum duration of 7 days.

In the 3 main studies, there were several deaths, but review of the brief narratives provided by the Applicant along with other available data did not clearly establish micafungin-related causality due to multiple confounding factors including but not limited to prematurity and its complications, disease under study, concomitant procedures and medications. In general, the most common TEAEs encountered in infants younger than 4 months treated with micafungin were comparable to a TEAE profile of micafungin in patients older than 4 months. The most common SAE in study 9463-CL-2303 was anemia in 4/20 (20%) of patients. The most common TEAEs in the micafungin arm of study 9463-CL-2303 were anemia in 10/20 (50%), neutropenia in 3/20 (15%), thrombocytopenia in 2/20 (10%), abnormal LFTs in 6/20 (30%) and septic shock in 6/20 (30%). The most common SAEs in study 9463-CL-6001 were sepsis (septic shock in 10.7%, *Klebsiella* sepsis in 7.1%, bacterial sepsis in 7.1%), bradycardia (7.1%) and respiratory failure (7.1%). The most common TEAEs in study 9463-CL-6001 were elevated GGT (28.6%) and edema (17.9%). Thrombocytopenia, cholestasis, and hyponatremia each occurred in 10.7% of patients. Study 9463-CL-6002 had no SAEs, and only 2 TEAEs (a patient with elevated AST, ALT and GGT, and another patient with elevated GGT).

Data from the remaining 6 studies were evaluated in aggregate in an effort to identify TEAEs of concern. The pattern of TEAEs across these studies did not differ appreciably from those identified in the 3 main studies in the sNDA. The most frequent adverse reactions (≥15%) in pediatric patients younger than 4 months old receiving a MYCAMINE dose of approximately 4 mg/kg/day included hypokalemia (25%), thrombocytopenia (25%), acidosis (20%), sepsis (20%), anemia (15%), oxygen saturation decreased (15%), and vomiting (15%). Patients in the highest dose group of >11 mg/kg/day (n=8) did have higher rates of acidosis (37.5%), anemia (50%), hyperbilirubinemia (50%), cholestasis (75%), thrombocytopenia (75%), and renal failure (75%), but the limited number of patients did not allow conclusions about dose-dependency to be made.

Common labeled AEs for micafungin in pediatric patients >4 months of age include vomiting, diarrhea, nausea, and abdominal pain; these were not observed at high frequencies in the

population of pediatric patient younger than 4 months of age, at least in part because neonates may not express some of these symptoms. Older pediatric patients experienced rash and pruritus at rates >10%, but they had lower rates of thrombocytopenia and hepatic toxicity compared with the neonatal population.

The occurrence of adverse events of special interest (AESIs), with emphasis on hypersensitivity, anaphylaxis, infusion-related events, renal insufficiency, and hepatotoxicity was evaluated. There were no cases of anaphylaxis; rash and infusion-related TEAEs were uncommon. Renal insufficiency TEAEs occurred in about 10% of the population, but again, causality to micafungin was difficult to ascribe given the general severity of underlying illness, occurrence of sepsis, other comorbidities, prematurity and use of concomitant medications. Hepatic events are similarly difficult to attribute to a specific drug in an ill population; thus, our analysis focused on patients who had significant elevations of liver enzymes from a normal baseline. While micafungin likely did contribute to some of the significant elevations seen in patients from all 3 main studies (discussed in Section 10.4 and 10.5), these changes are easily monitored and appeared to improve in most patients upon discontinuation of micafungin. There were no deaths attributable to hepatotoxicity, but 2 patients had SAEs or drug discontinuations due to hepatic enzyme elevation.

A review of recent literature focused on micafungin use in pediatric patients did not yield unexpected post-market adverse event information.

Although there were insufficient data to support the 10 mg/kg micafungin dose for treatment of invasive candidiasis including candidemia and ME in patients younger than 4 months, doses of at least 10 mg/kg/day may be necessary to treat ME as discussed in Section 8.4. An extrapolated dose of 4 mg/kg for treatment of candidemia *without* ME, based on randomized controlled trials in adults and older pediatric patients and PK in patients younger than 4 months, was established by the review team as the appropriate dose. As discussed, safety of micafungin at this dose was consistent with the safety profile in older pediatric patients and adults. In addition, the clinical team found that the overall safety of micafungin in infants younger than 4 months at doses up to 15 mg/kg is comparable to older pediatric patients and adults, but clinicians should be aware that hematologic and hepatic side effects may be more common in neonates and young infants receiving micafungin. Appropriate laboratory parameters should be monitored regularly in infants receiving micafungin; if done, the potential benefits of higher doses of micafungin for treatment of pediatric patients younger than 4 months with candidemia and suspected ME may outweigh the risks of TEAEs.

10.10. Conclusions and Recommendations

Based on evidence from adequate and well-controlled studies in adults and pediatric patients 4 months of age and older with the additional pharmacokinetic and safety data in pediatric patients younger than 4 months reviewed in this sNDA, the safety and effectiveness of 4 mg/kg of micafungin for treatment of candidemia, acute disseminated candidiasis, *Candida* peritonitis and abscesses *without* ME have been established. There are insufficient clinical data in this submission to support the efficacy of micafungin at a dose of 10 mg/kg/day for neonatal candidiasis with ME. However, despite the limitations of the database, safety of micafungin at doses up to 15 mg/kg/day appears to be generally comparable to the safety profile of micafungin in adults and older pediatric patients; the most common TEAEs of cholestasis, hyperbilirubinemia, thrombocytopenia, anemia, acidosis and renal insufficiency are often related to the presenting illness or underlying conditions and can be monitored and appear to resolve with discontinuation of micafungin.

Given the difficulty of conclusively ruling out Candida meningoencephalitis in premature and often unstable patients <4 months of age with candidemia and the potential adverse consequences of under-treatment with dose of 4 mg/kg/day, it was considered important to include relevant information on fungal burden reduction obtained from the rabbit model of HCME as well as a brief summary of existing neonatal safety data for micafungin doses from 5-15 mg/kg/day in labeling. A limitation of use is included in labeling to clarify that micafungin is not approved for the treatment of meningoencephalitis and/or ocular disease.

11 Advisory Committee Meeting and Other Consultations

An Advisory Committee meeting was not held for this sNDA. Input was requested from the following regarding inclusion of dosing information > 4mg/kg and description of nonclinical findings in labeling:

- Medical Policy and Program Review Council (MPPRC). The sNDA was discussed at the MPPRC on December 4, 2019. The main points from the discussion are listed below:
    - The limitations of clinical data submitted to the sNDA were acknowledged, along with the need to inform clinicians in labeling that doses higher than 4 mg/kg/day would likely be needed for the treatment of neonatal candidiasis with ME in infants younger than 4 months of age.
    - Limitations of Use should allow clinicians to make a clinical determination of the likelihood of ME or ocular involvement and the consequent need for higher micafungin doses especially in situations where diagnostic options are limited or uninformative.
    - Data from the rabbit model showing fungal burden reduction in various CNS compartments, along with available clinical data at varying micafungin doses, should be included in Section 8.4 of labeling.
    - Adequacy of the existing clinical information to support an indication in labeling was discussed. It was noted that the available clinical information including the data for a selection of an appropriate dose regimen for the treatment of candidemia/disseminated candidiasis with meningoencephalitis in pediatric patients younger than 4 month of age was not adequate to support an indication, and efficacy could not be extrapolated as the disease characteristics were different in this patient population compared older children and adults.

- Office of Pediatric Therapeutics (OPT): A consult was provided by Dr. Gerri Baer, the Neonatology Team Lead in OPT. She reviewed the neonatology literature and the Applicant's clinical overview, summary of clinical efficacy and summary of clinical safety to address whether including a dosing recommendation for micafungin in neonates with candidemia without CNS involvement based on extrapolation from adults will be informative in the micafungin product labeling and discussed additional clinical and nonclinical information from the development program important for labeling to inform clinicians of the limitations of micafungin use in this patient population specifically as it relates to *Candida* ME and a potential need for higher than approved micafungin dose in suspected/confirmed ME.

    - Dr. Baer was of the opinion that the submitted data represented a tremendous effort from the Applicant and the scientific community but had

concerns about the limitations of the data informing an effective dose for *Candida* meningoencephalitis similar to those of the review team. Based on the rabbit model and PK modeling along with clinical studies, she estimated that 10 mg/kg/day would be expected to treat CNS infection in 96% of patients. Dr. Baer did not identify any unexpected safety signals in the submitted studies. She noted that the main safety concern is the risk of neurodevelopmental morbidity if micafungin is given at a suboptimal dose to treat ME. She was concerned that providing the 4 mg/kg/day dose in the labeling without including and clarifying the limitations of clinical data and available nonclinical data suggesting micafungin antifungal activity in the CNS at doses higher than 4 mg/kg/day may be misleading to clinicians, especially because CNS involvement is difficult to definitively rule out, so she recommended including information about relevant clinical studies and the rabbit model in the labeling.

12 Pediatrics

The sNDA was discussed at the FDA Pediatric Review Committee – its members concluded that there is serious concern for potential under-dosing leading to morbidity and mortality if the 4 mg/kg extrapolated micafungin dose for candidemia *without* ME in infants younger than 4 months was used to treat infants with candidemia *with* undiagnosed ME. The Committee made the following recommendations:

a) Details of the CNS fungal burden reduction observed with increasing micafungin doses in the rabbit model of HCME, and the reasonable safety profile of micafungin at doses up to 15 mg/kg should be provided in relevant sections of the label.
b) The apparent need for at least 10-15 mg/kg micafungin for treatment of *Candida* ME should be included in the label

13 Labeling Recommendations

13.1. Prescription Drug Labeling

The Applicant's proposed labeling was revised extensively during the review (b) (4) Because diagnosis of ME in premature and often unstable infants younger than 4 months of age is challenging, there is need for additional treatment options, and the consequences of under-dosing with micafungin are potentially dire, the indication was limited to the treatment of candidemia, acute disseminated candidiasis, *Candida* peritonitis and abscesses ***without*** meningoencephalitis and ocular dissemination. Further, a limitation of use statement was included in the Indications and Usage as well as Dosage and Administration sections conveying that the approved dose regimen of 4 mg/kg/day is inadequate to treat ME and higher dosages may be needed although the optimal dosage has not been established. Changes to the Applicant's proposed labeling that pertain to the pediatric population younger than 4 months of age are described here along with rationale for the changes.

FULL PRESCRIBING INFORMATION

- Section 1 Indications and Usage
  - The recommended dose regimen is 4 mg/kg/day for treatment of candidemia, acute disseminated candidiasis, *Candida* peritonitis/abscesses **without** meningoencephalitis and ocular dissemination
  - Limitations of use statement: to acknowledge that 4 mg/kg/day may not be high enough to treat ME/ocular dissemination, but that the optimal dosage is unknown; directs reader to section 8.4 for discussion of the rationale for this statement

Reviewer comment: The team did not want to state that 4 mg/kg/day should only be used if ME can be ruled out because of the difficulty in definitively diagnosing this condition, but did not want to imply that 4 mg/kg/day would be sufficient if ME and/or ocular involvement are suspected

- Section 2 Dosage and Administration, Subsection 2.3 Dosage for Pediatric Patients Younger than 4 Months of Age
  - (b) (4)
  - The following text was included to be consistent with section 1: *The recommended dosage for pediatric patients younger than 4 months of age for the treatment of Candidemia, Acute Disseminated Candidiasis, Candida Peritonitis and Abscesses <u>without</u> Meningoencephalitis and Ocular Dissemination is 4 mg/kg once daily. If meningoencephalitis cannot be excluded,*

doses higher than 4 mg/kg may be needed but the appropriate dosage has not been established [see Use in Specific Populations (8.4), Clinical Pharmacology (12.3) and Microbiology (12.4)].

- Section 6 Adverse Reactions, subsection 6.1 Clinical Trials Experience
  - Because 76 of the 244 neonates from the 9 studies (b) (4) did not have dosing information, description and analysis of AEs was limited to 168 neonates with known doses of micafungin of whom 59 received≤4mg/kg/day and 109 received >4 mg/kg/day (5-15 mg/kg/day)
  - Because the extrapolated dose for treatment of candidemia, disseminated candidiasis, *Candida* peritonitis and abscesses *without* ME was 4 mg/kg, AEs observed in the group that received a micafungin dosing regimen of "approximately 4 mg/kg/day" (b) (4)
  - The most frequent adverse reactions (≥15%) in pediatric patients younger than 4 months old receiving a MYCAMINE dose of approximately 4 mg/kg/day included hypokalemia (25%), thrombocytopenia (25%), acidosis (20%), sepsis (20%), anemia (15%), oxygen saturation decreased (15%), and vomiting (15%). Similar PTs were combined to obtain percentages of occurrence.
  - Clinically significant adverse reactions at rates of <15% of pediatric patients younger than 4 months were listed, excluding certain underlying conditions such as retinopathy of prematurity and bronchopulmonary dysplasia

Reviewer comment: Section 6.1 was organized around the population of neonates younger than 4 months who received the amended dosage regimen in Sections 1 and 2.

- Section 7 Drug Interactions
  - Reorganization of section was recommended, in particular, reclassification of certain drugs in terms of their inhibitor/substrate categories

- Section 8 Use in Specific Populations, subsection 8.4 Pediatric Use
  The following statements were added:
  - *The safety and effectiveness of MYCAMINE for the treatment of candidemia, acute disseminated candidiasis, Candida peritonitis and abscesses <u>without</u> meningoencephalitis and ocular dissemination at a dosage of 4 mg/kg once daily have been established in pediatric patients younger than 4 months of age. This use and dosage of MYCAMINE are supported by evidence from adequate and well-controlled studies in adult and pediatric patients 4 months of age and older with additional pharmacokinetic and safety data in pediatric patients younger than 4 months of age.*
  - *The safety and effectiveness of MYCAMINE have <u>not</u> been established for the treatment of candidemia <u>with</u> meningoencephalitis and ocular dissemination in pediatric patients younger than 4 months of age.*

- Evidence of a linear micafungin dose-response for fungal burden decrease in CNS compartments relative to untreated controls in the rabbit model was described as the basis for the potential need for higher than approved doses in infants younger than 4 months with suspected ME along with a disclaimer that the clinical significance of a lower CNS fungal burden is unknown. A dosage range of 10-25 mg/kg in pediatric patients younger than 4 months was suggested by the rabbit data.
- Existing clinical data from Study 9463-CL-2303, including fungal-free survival and all-cause mortality, as well as data from other clinical studies were described, though no efficacy conclusions could be made due to the small sample sizes and variations in study design.
- Data on the 6 patients in the sNDA with proven meningoencephalitis including their dosage regimens of 2 mg/kg, 8 mg/kg, and 10 mg/kg were included, along with the following statement: *No conclusions regarding the efficacy of a particular dosage of MYCAMINE in these patients can be drawn due to multiple confounding factors, variable study designs, and limited numbers of patients.*
- Results of the team's review of micafungin safety in patients treated with 10-15 mg/kg/day that did not reveal additional safety signals was also included to communicate that doses up to 15 mg/kg/day had an acceptable safety profile.
- Finally, the statement that safety and effectiveness of MYCAMINE for treatment of esophageal candidiasis or prophylaxis of *Candida* infections in patients younger than 4 months of age undergoing hematopoietic stem cell transplantation has not been established was included.

Reviewer comment: The clinical team considered Section 8.4 as critical in discussing the nonclinical and limited clinical data that supported the Limitation of Use statement that doses greater than 4 mg/kg were needed for treatment of candidemia with ME in infants younger than 4 months. Indeed, independent analysis of individual animal data from the rabbit HCME model studies by the Clinical Pharmacology team during the review indicated that significant reduction in CNS fungal burden was seen over a range of 16-32 mg/kg corresponding to a micafungin dosage range of 10-25 mg/kg in neonates and infants younger than 4 months. Thus, despite the limitations of the rabbit data, there was evidence that the optimal dose for treatment of ME in these young infants may actually be greater than 10 mg/kg. Because the highest dose studied in the 9 clinical studies in this sNDA and in the literature reviewed by the team was 15 mg/kg/day, a description of safety up to this dose was also included. The decision to include a discussion of higher than approved doses for candidemia with ME and/or ocular involvement in pediatric patients younger than 4 months of age in Section 8.4 was discussed at length with the OND Labeling Team, the Office of Pediatric Therapeutics, the Pediatric Review Committee and the Medical Policy and Program Review Council. The consensus opinion was that the provision of all existing information on micafungin dosing for treatment of patients younger than 4 months with candidemia with ME and/or ocular involvement was extremely important to guide treating clinicians as these the safety of these vulnerable patients could be compromised by exposing them to potentially ineffective micafungin dosage regimens.

- Section 12 Clinical Pharmacology, subsection 12.2 Pharmacodynamics
  - The pharmacodynamics of micafungin related to hematogenous *Candida* ME were described in other sections of the prescribing information: Use in Specific Populations (8.4) and Microbiology (12.4).

- Section 12 Clinical Pharmacology, subsection 12.3 Pharmacokinetics
  - Derivation of the 4 mg/kg/day dosing regimen was based on higher body weight-normalized micafungin clearance in pediatric patients younger than 4 months and comparable steady state AUC with the AUC seen with approved doses in older pediatric patients and adults
  - (b) (4)

- Section 12 Clinical Pharmacology, subsection 12.4 Microbiology
  - The dose-dependent manner in which micafungin reduced fungal burden of a single strain of *Candida* in the rabbit HCME model was described in greater detail than Section 8.4.
  - Other nonclinical data supporting micafungin effect on survival and fungal burden in various tissues, including brain, in the murine and neutropenic rabbit models was provided.

- (b) (4)

14 Risk Evaluation and Mitigation Strategies (REMS)

No REMS were considered necessary.

15 Postmarketing Requirements and Commitments

None

16 Division Director (Clinical) Comments

I agree with the review team's assessment and recommendations.

17 Appendices

17.1. Financial Disclosure

Covered Clinical Study (Name and/or Number): 9463-CL-2303

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 72		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator: 1 Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Limited details were provided for the 1 investigator who had disclosable financial interests. Dr. (b) (6) disclosed that he has a significant equity interest in Astellas. He screened (b) (6) patients and enrolled (b) (6) at his study site ((b) (6)).

Covered Clinical Study (Name and/or Number): 9463-CL-6001

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 2		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator: Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): 9463-CL-6002

Astellas assumed sponsorship after the study completion, so they state that no financial disclosure forms were collected.

Was a list of clinical investigators provided:	Yes ☐	No ☒ (Request list from Applicant)
Total number of investigators identified: 1		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): _____		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

17.2. OCP Appendices (Technical documents supporting OCP recommendations)

17.2.1. Summary of Bioanalytical Method Validation and Performance

Multiple validated liquid chromatography (LC) and mass spectrometry (MS) assays with or without ultraviolet (UV) detection were used for the quantification of micafungin in plasma and cerebrospinal fluid (CSF) collected in the submitted pediatric PK studies as shown in Table 17-1 and Table 17-2. Study 9463-CL-2303 used a bioanalytical assay that was previously validated and reviewed during a previous micafungin sNDA submission. Additionally, the bioanalytical site for Study 9463-CL-2303 was inspected and the concentration data reported in this study were found to be reliable.

For Studies 9463-CL-6001 and 9463-CL-6002, only an abbreviated validation report was submitted. The abbreviated validation report does not provide details on the assay or serial chromatograms for analysis and as such does not meet current standards for bioanalytical assays outlined in the Agency's Bioanalytical Method Validation guidance. Because the study was conducted in (b) (4), inspection of the bioanalytical site was infeasible given the 6-month timeframe for review after sNDA submission.

Table 17-1. Summary of Bioanalytical Assay Methods.

Validation Report Number	Laboratory Site	Analyte(s)	Detection Method	Study(ies)
MS-2009-009	Astellas Research Institute of America, Skokie, Illinois	FK463 and its metabolite, M5 (plasma)	LC-MS	9463-CL-2303
MS-2009-003	Astellas Research Institute of America, Skokie, Illinois	FK463 (CSF)	LC-MS	9463-CL-2303
(b) (4)	(b) (4)	Amphotericin B (plasma)	LC-MS/MS	9463-CL-2303
		Amphotericin B (CSF)	LC-MS/MS	9463-CL-2303
NA	(b) (4)	FK463 (plasma and CSF)	HPLC UV	9463-CL-6001, 9463-CL-6002

FK463: micafungin; M5: metabolites of micafungin; HPLC: high performance liquid chromatography; UV: ultraviolet LC: liquid chromatography; MS: mass spectrometry; NA: Not Available

Table 17-2. Bioanalytical Assay Validation Precision and Accuracy.

Study	9463-CL-2303			9463-CL-6001 and -6002	
Analyte	MCF	MCF M5	MCF	MCF	MCF
Vehicle	Plasma	Plasma	CSF	Plasma	CSF
Intrabatch Precision (CV%)	2.3% – 10.2%	2.5% - 14.7%	2.1% - 6.5%	<7.6%	<11.1%
Intrabatch Accuracy (RE%)	-6.1% – 9.3%	-11.2% - 8.1%	-10.9% - 17.4%	±15%	±15%
Interbatch Precision (CV%)	4.5% – 8.2%	6.3% - 12.7%	3.1% - 7.4%	<8.3%	<6.2%
Interbatch Accuracy (RE%)	0.1% – 6.9%	-3.7% - 5.2%	-7.6% - 9.9%	±15%	±15%

MCF: Micafungin, MCF M5: Metabolite of Micafungin, CSF: Cerebrospinal fluid, CV: Coefficient of variation, RE: Relative Error

Reviewer Comments:
The bioanalytical assay validation and performance for Study 9463-CL-2303 is deemed to be acceptable.

Micafungin concentrations collected from rabbits (see Section 17.2.3 for further details) were not supported by assay validation. Micafungin concentration data from assays without validation or with limited validation (as in Studies 9463-CL-6001 and -6002) should be interpreted with caution and only in the context of other validated micafungin concentration data.

17.2.2. Individual Study Reviews

Study 9463-CL-2303: A Phase 3, Randomized, Double-Blind, Multi-Center Study to Compare the Efficacy and Safety of Micafungin Versus Amphotericin B Deoxycholate for the Treatment of Neonatal Candidiasis

Pediatric patients less than or equal to 120 days of age with candidiasis were randomized to receive 10 mg/kg/day micafungin (n=20) or 1 mg/kg/day amphotericin B deoxycholate (CAB, n=10) for 21 to 42 days. Two of the enrolled patients had infections with CNS involvement. Up to three plasma PK samples were drawn no earlier than the fourth day of therapy. The pharmacokinetic (PK) data for micafungin and the M5 metabolite are summarized in Table 17-3.

Table 17-3. Mean (CV%) Plasma Concentrations of Micafungin and M5 Metabolite in 12 Pediatric Patients 120 Days of Age or Less Following IV Administration of 10 mg/kg/day of Micafungin (Study 2303)

Sample Time	**Analyte Concentration (µg/mL)**	
	Micafungin	**M5**
0-15 min postdose	25.1 (56%)	4.6 (77%)
4-8 hr postdose	23.8 (40%)	5.11 (66%)
15-24 hr postdose	14.1 (88%)	5.04 (69%)

One sample from cerebrospinal fluid (CSF) was drawn but was not analyzable due to hemolysis.

Study 9463-CL-6001: Determination of Plasmatic and CSF Levels of High Doses of Micafungin in Neonates Suffering from Systemic Candidiasis and/or Candida Meningitis

Thirty-five infants with systemic candidiasis were enrolled in the study. Of the 35 total infants, 28 were <4 months of age (80%). One patient had a Candida infection with CNS involvement. Patients received 8 mg/kg/day IV micafungin infused over 1 hour for a minimum of 14 days. Up to 4 plasma PK samples were drawn between the third and tenth treatment day.

Capillary plasma samples of micafungin drawn from the heel were collected in 34 patients and are summarized in Table 17-4.. There appears to be a trend towards higher micafungin concentrations in pediatric patients ≥4 months relative to pediatric patients <4 months. This finding may be indicative of higher weight-normalized clearance in younger patients.

Table 17-4. Mean (CV%) Capillary Plasma Concentrations of Micafungin Following IV Administration of 8 mg/kg/day in 34 Pediatric Patients 0 to 8 Months of Age (Study 6001)

Sample Time	Micafungin Concentration (µg/mL)	
	Age <4 months	Age ≥4 months
Predose	5.31 (42%)	7.2 (53%)
1 hr postdose	16.4 (38%)	20.4 (31%)
3 hr postdose	14.1 (30%)	21.4 (39%)
8 hr postdose	9.52 (29%)	13.2 (31%)

In eight patients, both capillary and venous samples of micafungin were drawn; the capillary and venous plasma concentrations of micafungin are summarized in Table 17-5.

Table 17-5. Mean (CV%) Capillary and Venous Plasma Concentrations of Micafungin Following IV Administration of 8 mg/kg/day in 8 Pediatric Patients (Study 6001)

Sample Time	Micafungin Concentration (µg/mL) at Sample Site	
	Capillary	Venous
Predose	6.2 (46%)	6.4 (44%)
1 hr postdose	19.2 (29%)	22.4 (22%)
3 hr postdose	16.9 (24%)	19 (21%)
8 hr postdose	11.8 (21%)	13 (21%)

On average, micafungin venous concentrations were 10.7% higher than micafungin concentrations in heel capillaries. The difference between capillary and venous concentrations of micafungin is not considered clinically significant.

Additionally, 4 CSF PK samples of micafungin were collected in one patient and the CSF concentrations of micafungin ranged from 1.9-2.1 µg/mL over the course of 8 hr.

Study 9463-CL-6002: Determination of Plasmatic and CSF Levels of High Doses of Micafungin for Preterm Neonates and Infants with Invasive Candidiasis

Neonates and infants with ages up to six months treated with micafungin intravenously between 2012 and 2015 with sepsis or meningitis due to Candida were analyzed in this retrospective study. Eighteen patients were enrolled: 2 received doses 5-7.8 mg/kg/day while the remaining 16 received doses 8-10.7 mg/kg/day IV micafungin. One patient had a Candida infection with CNS involvement. Up to 5 plasma PK samples were drawn between the third and tenth treatment day. A summary of plasma micafungin concentrations is shown in Table 17-6.

Table 17-6. Mean (CV%) Plasma Concentrations of Micafungin Following IV Administration of <8 mg/kg/day and >8 mg/kg/day in 18 Pediatric Patients (Study 6002)

Sample Time	Micafungin Concentration (µg/mL)	
	Dose <8 mg/kg/day	Dose ≥8 mg/kg/day
Predose	4.4 (53%)	7.3 (58%)
0.5 hr postdose	18.7 (23%)	26.6 (40%)
1 hr postdose	28 (NA)	21.2 (40%)
2 hr postdose	21.8 (57%)	18.6 (40%)
8 hr postdose	9.7 (37%)	12.5 (44%)

CSF samples were drawn in 3 patients. A comparison of plasma and CSF micafungin concentrations in those patients is shown in Table 17-7.

Table 17-7. Comparison of Plasma and CSF Micafungin Concentrations (µg/mL) in Study 6002 (n=3).

Sample Time	Patient 1					
	Study Day 3		Study Day 16		Study Day 17	
	Plasma	CSF	Plasma	CSF	Plasma	CSF
Predose	5.8	0.8	6.7	ND	ND	0.27
0.5 hr postdose	21.9	0.9	17.4	ND	ND	ND
1 hr postdose	ND	ND	ND	ND	ND	ND
2 hr postdose	17.9	1.1	13.2	ND	ND	0.5
8 hr postdose	12.2	0.8	8.9	ND	ND	0.3
	Patient 2					
	Study Day 3		Study Day 6		Study Day 24	
	Plasma	CSF	Plasma	CSF	Plasma	CSF
Predose	3.2	ND	2.9	1.23	ND	0.15

0.5 hr postdose	21.7	ND	15.6	ND	ND	0.15
1 hr postdose	ND	ND	ND	ND	ND	ND
2 hr postdose	17.3	ND	12.2	ND	ND	0.15
8 hr postdose	6.58	ND	8.9	ND	ND	0.15

	Patient 3	
	Study Day 8	
	Plasma	**CSF**
Predose	9.12	2
0.5 hr postdose	ND	ND
1 hr postdose	27	1.8
2 hr postdose	24.56	1.7
8 hr postdose	16.84	1.3

CSF: cerebrospinal fluid; ND: not determined

The CSF PK profile of micafungin did not follow the plasma PK profile. For instance, in Patients 1 and 2, plasma but no CSF concentrations were detected on the second day of sampling while the reverse was shown on the third day of sampling. It is not possible to make definitive conclusions regarding CSF exposure due to the limited sample size and lack of accompanying bioanalytical information.

17.2.3. Pharmacometrics Review

Population Pharmacokinetic (POP PK) Modeling Review

The Applicant previously submitted POP PK Model 9463-PK-1001 to support the approval of micafungin in pediatric patients greater than or equal to four months of age in the treatment and prophylaxis of *Candida*-related infections. In the current submission, the Applicant updated Model 9463-PK-1001 with data in pediatric patients less than 4 months of age to create Model 9463-PK-1002. Table 17-8. shows the studies that supplied data in patients less than 4 months of age. Of note, only data from Studies 6001 and 6002 were new additions to Model 1002 as the other studies had been included in Model 1001.

Table 17-8. Clinical Studies Used in Model 9463-PK-1002 Including Data in Pediatric Patients Less than 4 Months of Age

Study	PK Samples	Patients
9463-CL-2104: A Phase 1 Open-Label Study of the Safety and Pharmacokinetics of Repeated-Dose Micafungin in Neonates Protocol for Phase 1 Study of Micafungin	65	13
9463-CL-2303: A Phase 3, Randomized, Double-Blind, Multi-Center Study to Compare the Efficacy and Safety of Micafungin Versus CAB for the Treatment of Neonatal Candidiasis	38	12
FG-463-21-08: A Multicenter, Double Blind, Comparative, Randomized Study to Evaluate the Efficacy and Safety of Micafungin (FK463) versus Liposomal Amphotericin B (AmBisome®) in the Treatment of Invasive Candidiasis and Candidemia	73	17
9463-CL-6001: Determination of Plasmatic and CSF Levels of High Doses of Micafungin in Neonates Suffering from Systemic Candidiasis and/or Candida Meningitis	108	27
9463-CL-6002: Determination of Plasmatic and CSF Levels of High Doses of Micafungin for Preterm Neonates and Infants with Invasive Candidiasis	56	12
99-0-063: Pharmacokinetic, Safety, And Tolerance Study of Three Dose Levels of Micafungin (FK463) In Premature Infants	111	22

*Numbers of PK samples and patients reflect the number included in PPK Model 1002.

The final PK parameter estimates in Models 1001 and 1002 are shown in Table 17-9.. While Model 1002 includes data from more patients, the PK parameters do not appear to be significantly different.

Table 17-9. Parameter Estimates from Population PK Models 1001 and 1002.

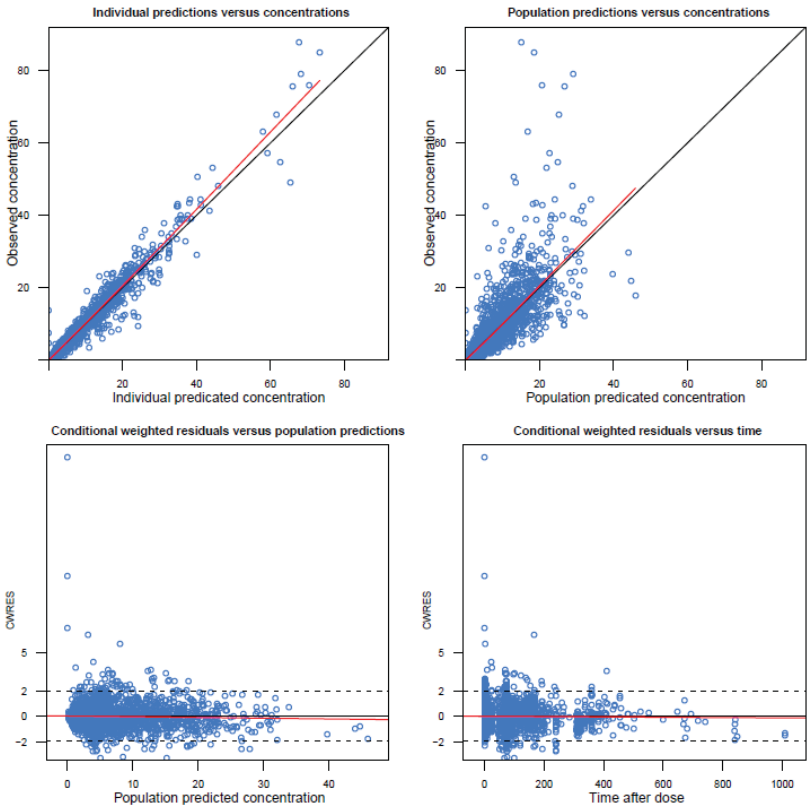
Parameter	Model 9463-PK-1001		Model 9463-PK-1002	
	Estimate	RSE%	Estimate	RSE%
Fixed Effects				
CL (L/h)	0.356	2.5	0.302	1.80
V1 (L)	1.21	10.7	1.61	10.9
Q (L/h)	5.54	12.7	5.78	16.3
V2 (L)	4.62	3.2	3.3	4.60
Effect of WT on CL and Q	0.787	3.7	0.752	2.00
Effect of WT on V1 and V2			0.78	2.50
Effect of ALT on CL	-0.0601	46.6	-0.0449	40.5
Effect of TBL on CL	-0.0492	47.0	-0.0611	27.7
Intersubject Variability				
η_{CL2}	0.0763	12.0	0.0926	11.1
$cov_{\eta V1,\eta CL}$			0.0622	34.4
η_{V12}	0.953	18.6	0.655	12.2
$cov_{\eta Q,\eta CL}$			0.0973	36.4
$cov_{\eta Q,\eta V1}$			0.494	20.1
η_{Q2}	1.52	13.1	0.986	20.9
η_{V22}	0.0277	40.1	0.0383	35.0
Residual Error				
Proportional	0.0313	8.20	0.164	5.60
Proportional SA	0.13	21.8	0.256	27.6
Additive	0.00461	54.9	0.676	26.5

RSE: Residual Standard Error, CL: clearance, V1: central volume of distribution, Q: intercompartmental clearance, V2: peripheral volume of distribution, WT: weight, ALT: Alanine Aminotransferase, TBL: total bilirubin, cov: covariance, SA: Data obtained from Study 2101

Goodness of Fit (GOF)

GOF plots for the final model are shown in Figure 17-1. The figure shows reasonable agreement between the observations and predictions. The conditional weighted residuals appear to center at 0 and are relatively homoscedastically dispersed with exceptions at the very end of the time interval.

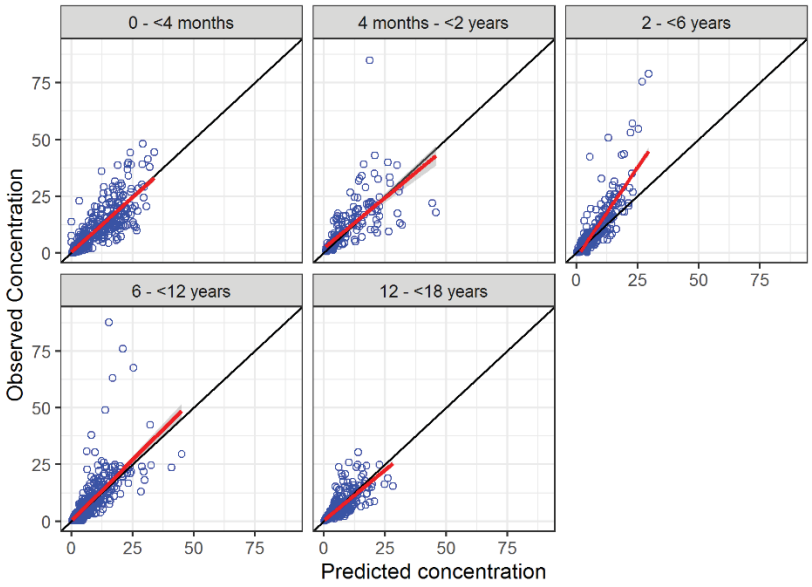
Figure 17-1. Micafungin PPK Model GOF Plots.



CWRES: Conditional Weighted Residuals. The red line represents the trend of the data relative to the line of unity (black line).

A comparison of the population predictions and the observed concentrations stratified by age cohort is shown in Figure 17-2. The trend line comparing the predictions and observations in each age cohort appears to match the line of unity, with the exception of the 2-<6 yr age cohort, which shows underprediction of the observed concentrations.

Figure 17-2. Micafungin Observations Compared to Predications Stratified by Age Cohort.



The red line represents the trend of the data relative to the line of unity (black line). ALT, total bilirubin, and weight are the only covariates used in defining CL in the model. These covariates appear to be sufficient to describe the trends in CL across age without including a specific covariate for age. A comparison of CL-relevant parameters (weight-normalized clearance, residual inter-individual variability (ETA) on clearance, bilirubin, and ALT) are shown in Figure 17-3. Weight-normalized clearance appeared to be highest in the youngest patients, which could be indicative of a clearance parameter described by allometric scaling. There were no apparent trends in the residual CL ETA with age with the exception of a slight increase around age=0.333 yr. ALT is comparable among the age range of patients included in the model while there is a trend towards increases in total bilirubin and total bilirubin variability in the youngest patients.

Figure 17-3. Trends in Clearance-Relevant Parameters by Age in Model 1002.

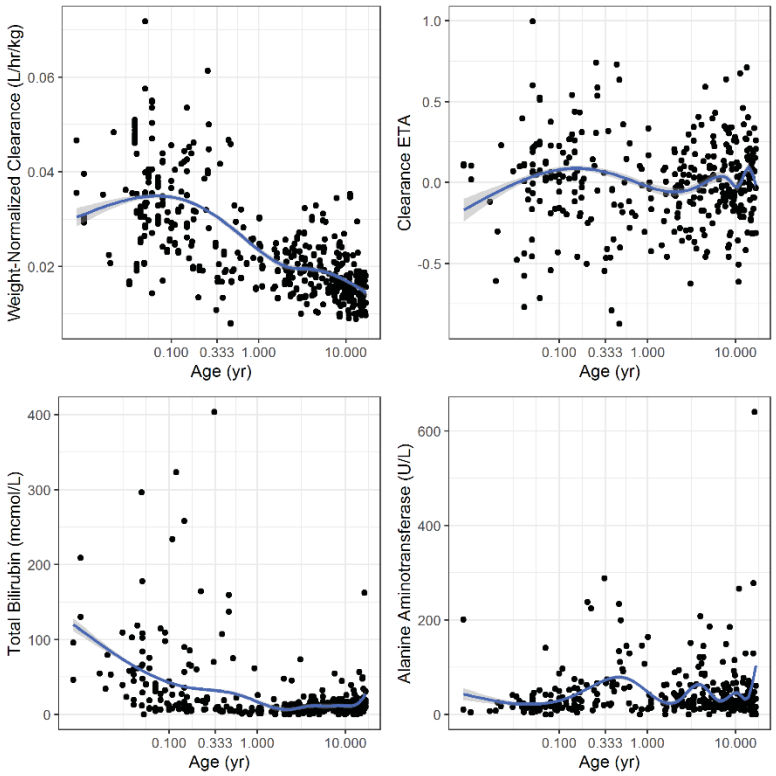
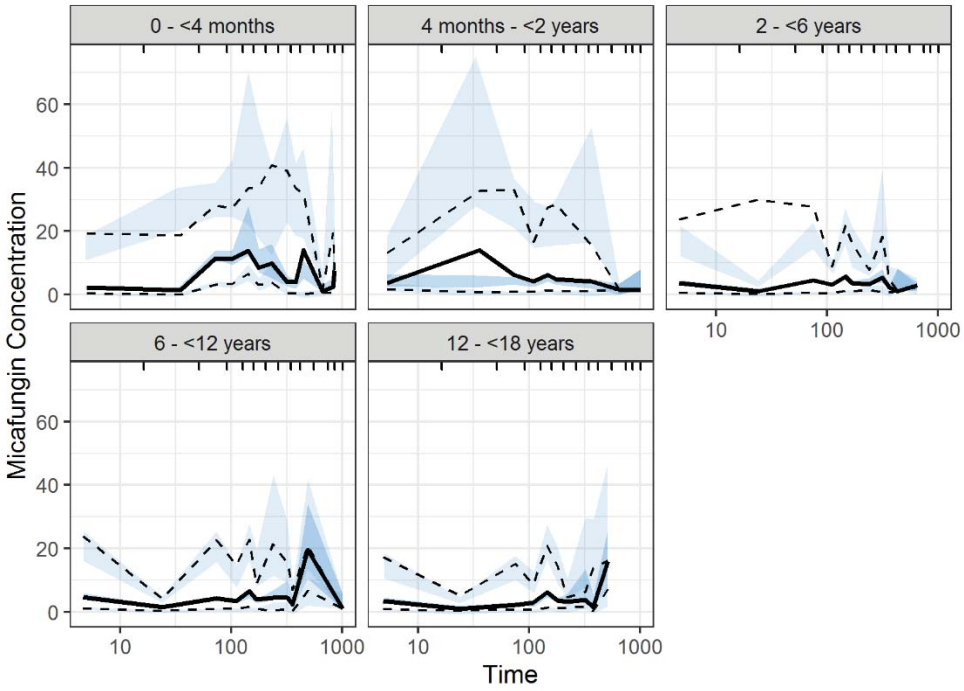


Figure 17-4 shows a visual predictive check (VPC) of Model 1002 stratified by age cohort. Overall, the predictions of the PPK model appear to be reasonably similar to the observed concentrations, especially in the <4 months age group, which is the main focus of the model and the current submission. There is trend of underprediction of observed concentrations in the 4 months - <2 years and 2 - <6 years age groups.

Figure 17-4. VPC for MCF Model 1002 Stratified by Age Cohort



The black lines represent the median (solid) and 5th and 95th percentiles (dashed) of observed concentration. Median concentration. The shaded areas represent the 90% prediction interval of the median (blue) and 5th and 95th percentiles (light blue). Time: Time after first dose in hours. Micafungin concentration in mcg/mL.

In summary, the PPK model appears to reasonably describe micafungin PK in pediatric patients <4 months. This PPK model is acceptable to be used to describe the individual micafungin PK in pediatric patients <4 months.

Dose-Response Relationship in Pediatric Patients <4 Months

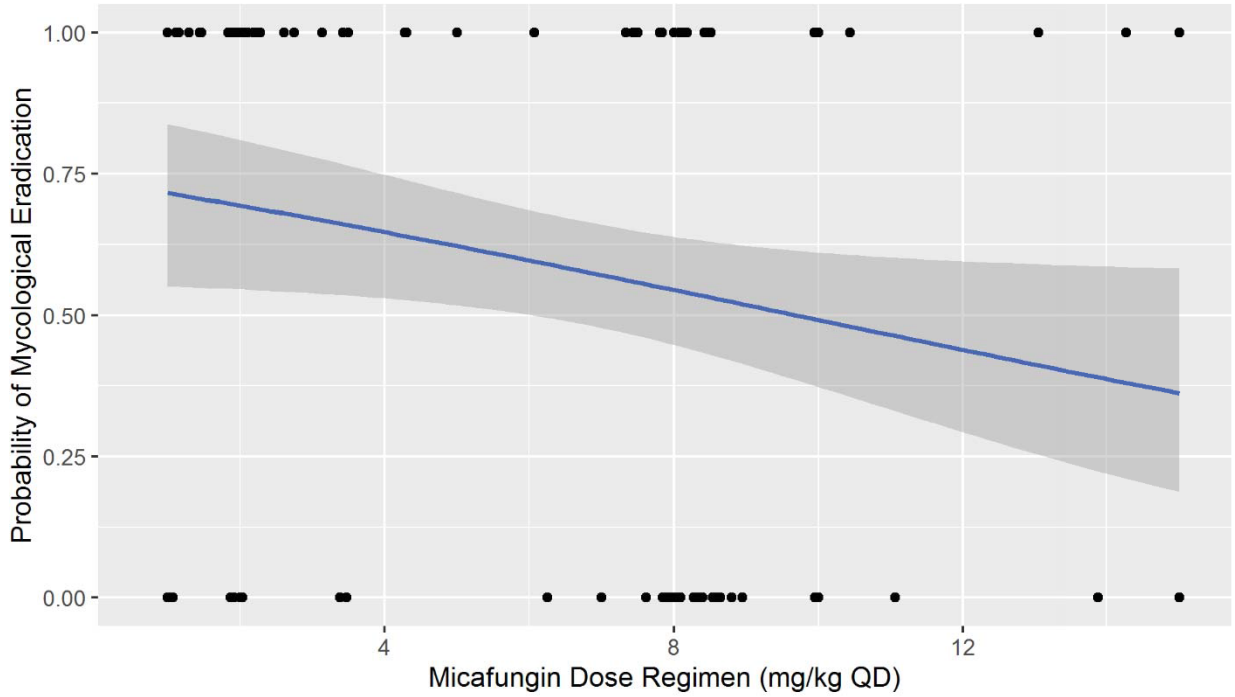
A dose-response relationship for mycological eradication in pediatric patients <4 months was evaluated. A dose-response relationship was analyzed instead of an exposure-response relationship due to lack of PK data in otherwise evaluable patients. The dose-response relationship was created based on data collected from 119 pediatric patients less than or equal to 4 months of age. Table 17-10. shows the breakdown of patients by study. The response endpoint was mycological eradication at end of treatment, defined as 2 negative cultures for blood or 1 negative for all other sites of infection (e.g., CSF, urine). The relationship between dose and mycological eradication was evaluated using logistic regression.

Table 17-10. Patient Data Used to Assess Micafungin Dose-Response Relationship.

Study	Patients
9463-CL-2303	20
9463-CL-6001	28
9463-CL-6002	12
9463-CL-7001	19
98-0-047	20
FG-463-21-08	20

Figure 17-5 shows the dose-response relationship of micafungin in pediatric patients <4 months. Paradoxically, lower weight-normalized micafungin doses were associated with increased probability of mycological eradication at a statistical significance level of 0.05.

Figure 17-5. Dose-Response Relationship of Micafungin in Pediatric Patients <= 120 Days.

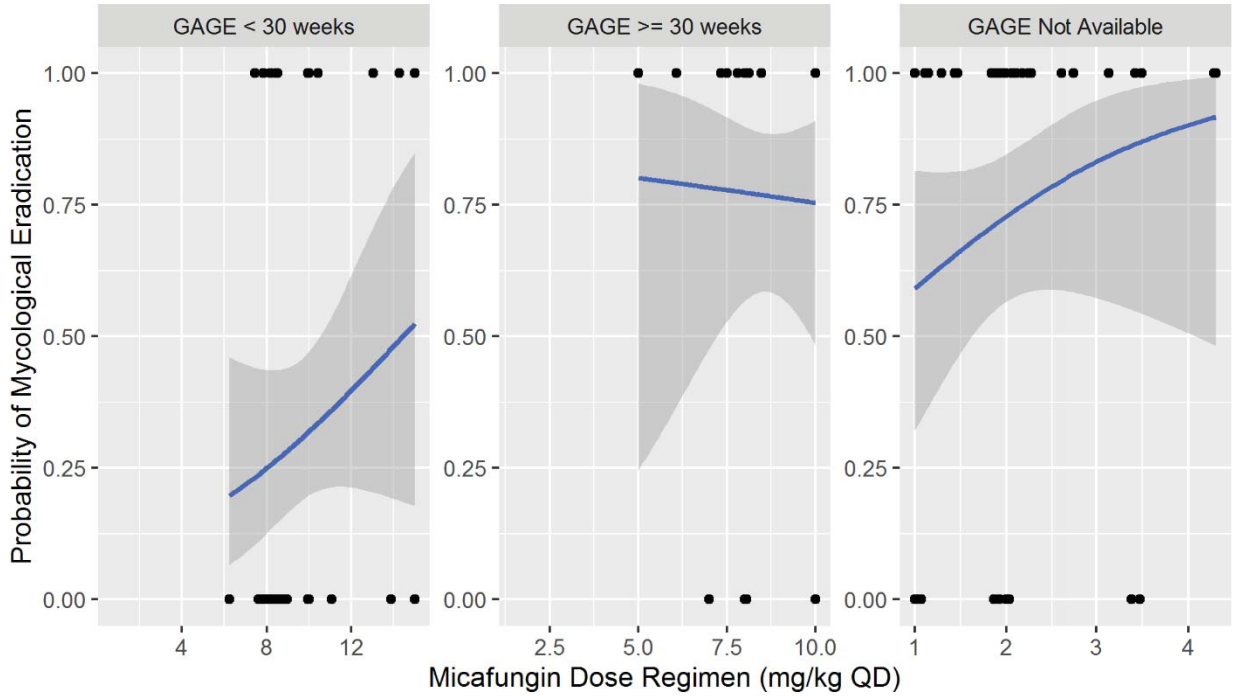


The points represent mycological success (1) or failure (0) for each individual patient. The blue line reflects the logistic regression analysis. The gray shaded area represents the 95% confidence interval of the relationship between the probability of mycological eradication and micafungin dose.

The relationship between dose and mycological eradication is confounded by gestational age. Gestational age (GAGE) is a statistically significant predictor of mycological eradication ($p < 0.05$) with higher gestational ages increasing the probability of eradication. Once gestational age is adjusted in the logistic regression, micafungin dose is no longer a statistically significant predictor of mycological eradication. The relationship between micafungin dose, gestational

age (greater than or less than 30 weeks or not available), and mycological eradication is shown in Figure 17-6.

Figure 17-6. Dose-Response Relationship of Micafungin Stratifed by Gestational Age.



The points represent mycological success (1) or failure (0) for each individual patient. The blue line reflects the logistic regression analysis. The gray shaded area represents the 95% confidence interval of the relationship between the probability of mycological eradication and micafungin dose. GAGE: Gestational age (weeks).

No consistent trend was observed across different groups of gestational age. In patients with gestational age <30 weeks or unknown gestational age, there appears to be a positive dose-response relationship. On the other hand, in patients with gestational age ≥30 weeks, there appears to be a negative dose-response relationship. This could point to a difference in disease status in patients depending on gestational age. However, the presence of 40 patients without a gestational age measurement confounds the analysis further.

Overall, the available data were not robust enough to support a conclusive dose-response analysis in patients younger than 4 months of age.

Assessment of Pharmacodynamics of Micafungin in Non-Neutropenic Rabbits in a Hematogenous Candida Meningoencephalitis (HCME) Model

An exposure-response relationship for changes in fungal burden was assessed based on the HCME model in non-neutropenic rabbits as described in Section 9.3.2 and in two

publications.[19,20] Briefly, rabbits were inoculated with 10^6 organisms/mL Candida albicans (MIC 0.125 mcg/mL). Treatment was initiated 48 h after inoculation with micafungin 0.25-32 mg/kg QD or amphotericin B 1 mg/kg QD along with a negative control arm. The Applicant submitted data from both articles of non-neutropenic studies rabbits in Section 9.3.2, which was further analyzed by the clinical pharmacology review team.

First, the concentration-time data after the sixth dose of micafungin was reassessed as shown in Table 17-11. Of note, the review team (Agency) calculated an AUC_{0-24} while the study authors calculated an AUC_{0-inf}, because an AUC_{0-24} is more directly applicable for comparing AUC exposure between rabbits and pediatric patients younger than 4 months of age. The review team calculation of the micafungin AUC_{0-24} was performed using a noncompartmental analysis approach in R using the PKPDMisc package.

Table 17-11. Pharmacokinetics of Micafungin Administered to Non-Neutropenic Rabbits in HCME Model.

Micafungin Dose in Rabbits (mg/kg QD)	Petraitiene Mean (SD) AUC_{0-inf} (mcg*hr/mL)	Agency Mean (SD) AUC_{0-24} (mcg*hr/mL)	Relative Difference from Petraitiene Paper
0.25		5.09 (0.65)	
0.5	10.75 (0.59)	9.9 (0.89)	-8%
1		19.5 (1.74)	
2	49.55 (7.88)	52.5 (13.6)	6%
4	77.83 (20.24)	86.7 (25.7)	11%
8	137.22 (30.05)	152 (33.4)	10%
16	305.71 (24.96)	353 (56.4)	15%
24	767.33 (466.23)	842 (478.1)	10%
32	788.5 (230.83)	889 (257.3)	13%

Next, the review team assessed the relationship between micafungin AUC and mean residual fungal burden in cerebrum, cerebellum, and spinal cord after the 7th dose of micafungin as shown in Figure 17-7. The variability is high across the range of micafungin AUC estimates with some untreated rabbits having zero residual fungal burden. Overall, fungal burden appears to decrease with increase in micafungin AUC with no apparent plateau to signify maximal activity as in Figure 17-7.

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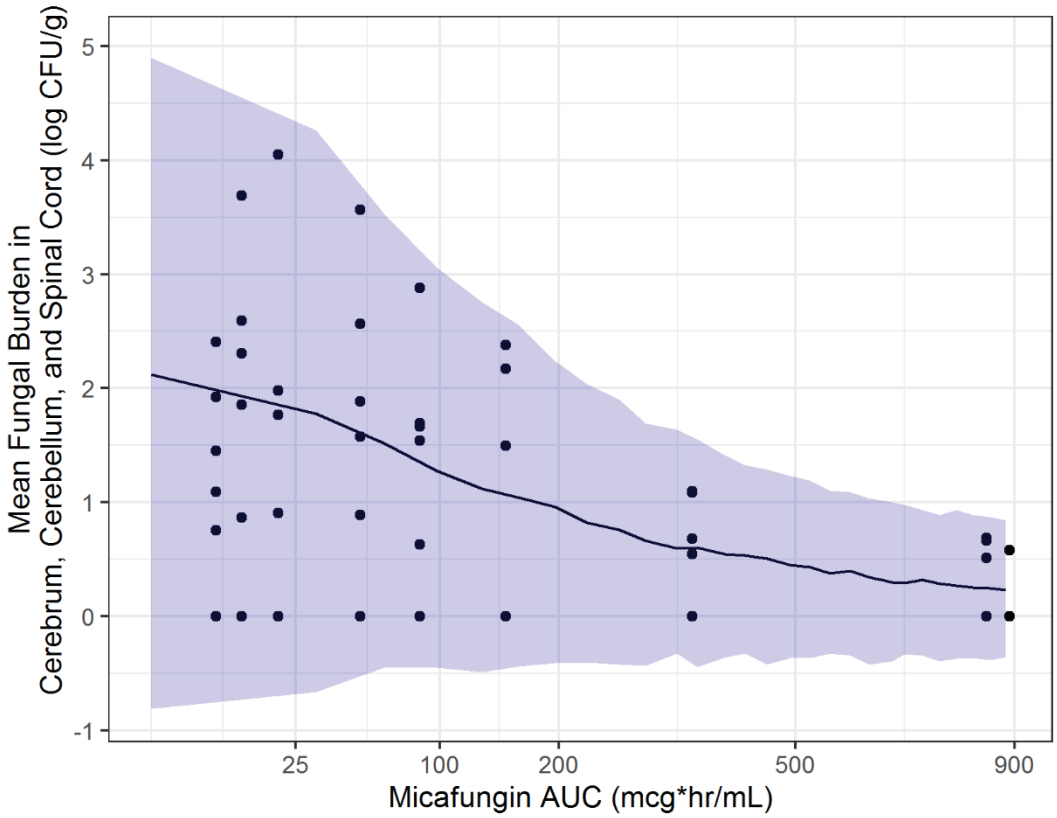
[19] Hope WW, Mickiene D, Petraitis V, et al. The pharmacokinetics and pharmacodynamics of micafungin in experimental hematogenous Candida meningoencephalitis: implications for echinocandin therapy in neonates. J Infect Dis. 2008;197(1):163-71.

[20] Petraitiene R, Petraitis V, Hope WW, et al. Cerebrospinal fluid and plasma (1-->3)-beta-D-glucan as surrogate markers for detection and monitoring of therapeutic response in experimental hematogenous Candida meningoencephalitis. Antimicrob Agents Chemother. 2008;52(11):4121-9.

Figure 17-7. Relationship Between Micafungin AUC and Mean Fungal Burden in Selected CNS Compartments.



The line represents the trend of median fungal burden across the micafungin AUC range and the blue shaded area represents the 95% prediction interval.

These data were described using an Emax function using a mixed-effect model approach in NONMEM as described by the following equation:

$$Residual\ Fungal\ Density = \ Untreated\ Fungal\ Density\ (E) - Emax * \frac{AUC}{AUC + AUC50}$$

The associated parameter estimates (residual standardized error) are untreated fungal burden = 2.06 (10.1%) log CFU/g, Emax = 2.22 (16.8%) log CFU/g, and AUC50 = 185 (50.4%) mcg*hr/mL, with additive and proportional errors equal to 0.469 and 0.0718, respectively.

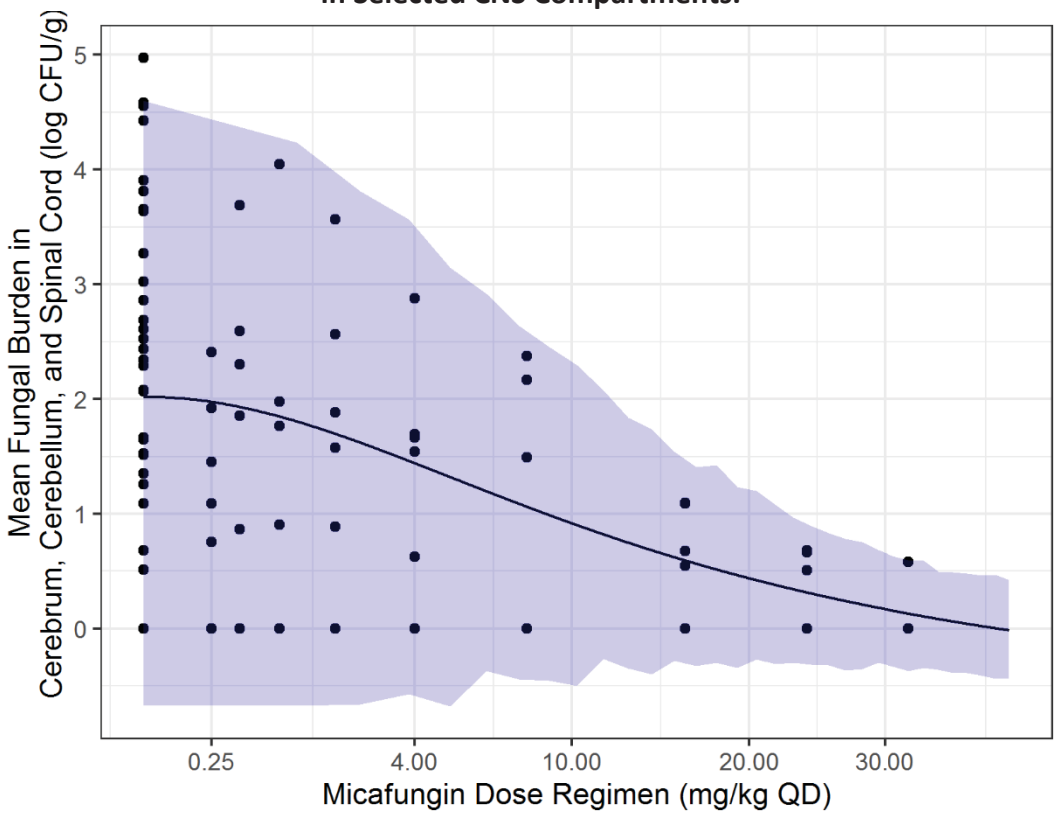
Additionally, the review team assessed the relationship between micafungin dose administered to rabbits and mean residual fungal burden in the cerebrum, cerebellum, and spinal cord after the 7th dose of micafungin as shown in **Figure 17-8**.These data were described using an Emax function using a mixed-effect model approach in NONMEM as described by the following equation:

$$\text{Residual Fungal Density} = \text{Untreated Fungal Density (E)-Emax*}\frac{\text{Dose}}{\text{Dose} + \text{Dose50}}$$

The associated parameter estimates (residual standardized error) are untreated fungal burden = 2.03 (9.8%) log CFU/g, Emax = 2.8 (31%) log CFU/g, and Dose50 = 15.4 (72.1%) mg/kg QD, with additive and proportional errors equal to 0.479 and 0.05, respectively. Dose represents the micafungin dose regimen administered to rabbits.

Of note, both the estimated AUC50 and Dose50 in the exposure- and dose-response analyses had high residual standardized errors (>50%). The high residual standardized error terms could be a result of difficulty in estimating the parameter reflecting half-maximal activity.
This analysis showed similar trends to the AUC-response relationship regarding lowering of fungal burden and high variability.

Figure 17-8. Relationship Between Rabbit Micafungin Dose Regimen and Mean Fungal Burden in Selected CNS Compartments.



The line represents the trend of median fungal burden across the micafungin dose range with the blue shaded area representing the 95% prediction interval.

These data were described using an Emax function using a mixed-effect model approach in NONMEM as described by the following equation:

$$Residual\ Fungal\ Density = \ Untreated\ Fungal\ Density\ (E) - Emax * \frac{Dose}{Dose + Dose50}$$

The associated parameter estimates (residual standardized error) are untreated fungal burden = 2.03 (9.8%) log CFU/g, Emax = 2.8 (31%) log CFU/g, and Dose50 = 15.4 (72.1%) mg/kg QD, with additive and proportional errors equal to 0.479 and 0.05, respectively. Dose represents the micafungin dose regimen administered to rabbits.

Of note, both the estimated AUC50 and Dose50 in the exposure- and dose-response analyses had high residual standardized errors (>50%). The high residual standardized error terms could be a result of difficulty in estimating the parameter reflecting half-maximal activity.

The pairwise comparisons of each tested dose of micafungin was compared to the untreated controls and assessed for statistical significance using a t-test while correcting for multiple comparisons using the Bonferroni method ($p<0.05$ after correction). The results of this statistical test are shown in Table 17-12. Of note, the micafungin doses 16-32 mg/kg QD produced a lower residual fungal burden relative to untreated controls that was found to be statistically significant.

Table 17-12. Change in Residual Mean Fungal Burden in Cerebrum, Cerebellum, and Spinal Cord at Different Doses of Micafungin Based on T-Test of Rabbit PD Data.

Rabbit Micafungin Dose Regimen (mg/kg QD)	Mean (95% Confidence Interval) Change in Mean Fungal Burden	p-value
0.25	0 (-0.7, 0.7)	0.35
0.5	-1 (-1.95, -0.06)	1
1	-0.39 (-1.77, 0.99)	1
2	-0.54 (-2.37, 1.3)	1
4	-0.53 (-1.85, 0.79)	0.88
8	-0.87 (-1.94, 0.2)	0.38
16	**-1.27 (-2.48, -0.05)**	**5.82E-06**
24	**-1.85 (-2.46, -1.23)**	**2.82E-05**
32	**-1.81 (-2.42, -1.2)**	**3.00E-08**

In all three analyses describing the relationship between change in residual mean fungal burden and micafungin dose or AUC, there is a trend of increases in micafungin exposure or dose and lowering of residual fungal burden relative to untreated controls, which suggests that micafungin has antifungal activity in the rabbit HCME study. However, the nature of the study is hypothesis generation not confirmation, and there is significant variability and uncertainty in translating these findings to clinical application. The data suggest that a micafungin dose regimen in the range of 16 to 32 mg/kg QD results in a significantly lower mean fungal burden in cerebrum, cerebellum, and spinal cord relative to untreated controls. However, insufficient data are present to establish a single, optimal dose regimen in rabbits that could then be translated to pediatric patients with meningoencephalitis.

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