CLINICAL REVIEW

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Division / Office	DAIP/OAP
Reviewer Name(s)	Brittany Goldberg, M.D. Yuliya Yasinskaya, M.D.
Review Completion Date	March 8, 2012
Established Name	Micafungin Sodium
Trade Name	Mycamine
Therapeutic Class	Echinocandin Antifungal
Applicant	Astellas
Formulation	50 mg and 100 mg vials for injection
Dosing Regimen	1 mg/kg, 2 mg/kg, or 3 mg/kg Once a Day
Indications	Candidemia and Invasive Candidiasis Esophageal Candidiasis Prophylaxis of Candida Infections in HSCT
Intended Population	Pediatric Patients 4 Months and Older

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The medical officer recommends approval of the application. This is based on the demonstration that systemic exposure following administration of micafungin at 1mg/kg, 2 mg/kg, and 3 mg/kg in pediatric patients is similar or greater than that achieved at the approved doses/indications in adults allowing for the extrapolation of efficacy from adults to children 4 months and older. Also, the safety profile of micafungin at the proposed doses of 1 mg/kg, 2 mg/kg and 3 mg/kg in pediatric patients 4 months to 17 years was comparable to that seen in adults at the approved doses of 50mg, 100 mg and 150 mg.

1.2 Risk Benefit Assessment

Currently, the antifungal drug armamentarium for treatment of confirmed and presumed invasive fungal infections in pediatric population is limited to Ambisome (>1month of age), fluconazole (>6months of age), caspofungin (>3 months of age), voriconazole (>12 years of age), and posaconazole (>13 years of age).
While incidence of invasive fungal infections in children is comparable and at times even higher than in adults (candidemia), limited PK and efficacy data in pediatric patients is available for the majority of marketed antifungals. Pediatric patients continue to endure the substantial morbidity and mortality from invasive fungal infections. Micafungin at three dosing regimens was found to achieve exposures similar to or greater than that of adults at the regimens approved based on adequate well controlled studies. Disease characteristics in pediatric patients (epidemiology, pathogenesis, and clinical presentation) are similar to adults for the approved indications (treatment of documented fungal infections (invasive candidiasis and esophageal candidiasis) and prophylaxis of *Candida* infections in HSCT recipients. Results of 11 safety/efficacy/pharmacokinetic studies in pediatric patients 4 months to <17 years provided the supportive evidence of micafungin efficacy in invasive fungal infections in pediatric patients. Safety of micafungin at the proposed regimens of 1 mg/kg, 2 mg/kg, and (b) (4) in pediatric patients 4 months to <17 years was comparable to that described in adults. Therefore, these findings support approval of micafungin for pediatric patients at 3 dosing regimens: 1 mg/kg for prophylaxis of Candida infections in HSCT recipients, 2 mg/kg for candidemia, and (b) (4) for esophageal candidiasis. Micafungin approval for pediatric patients is addressing an unmet medical need – critical information on dosing, PK, efficacy, and safety of this echinocandin antifungal in pediatric patients.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

No postmarketing risk management activities are necessary.

1.4 Recommendations for Postmarket Requirements and Commitments

Under PREA and according to the Pediatric Written Request an efficacy, safety and pharmacokinetic study of micafungin in neonates and young infants <4 months of age with invasive candidiasis (neonatal candidiasis) remains outstanding. The enrollment in this study was resumed after completion of the non-clinical investigation of micafungin and its M5 metabolite toxicity in juvenile/neonatal animals. The submission of the final study report for the neonatal candidiasis study is deferred until September 30, 2017.

2 Introduction and Regulatory Background

2.1 Product Information

Micafungin sodium is a semisynthetic lipopeptide (echinocandin) synthesized by a chemical modification of a fermentation product of *Coleophoma empetri* F-11899. Micafungin inhibits the synthesis of 1,3-beta-D-glucan, an integral component of the fungal cell wall. Inhibitors of 1,3-beta-D-glucan synthesis demonstrate a broad spectrum of antifungal activity against *Candida* and *Aspergillus* species.

2.2 Tables of Currently Available Treatments for Proposed Indications

Mycamine (micafungin sodium) is approved in adults for the following indications:

- Treatment of Patients with Candidemia, Acute Disseminated Candidiasis, Candida Peritonitis and Abscesses
- Prophylaxis of Candida Infections in Patients Undergoing Hematopoietic Stem Cell Transplantation
- Treatment of Patients with Esophageal Candidiasis

The following table depicts antifungals currently approved in the US for the above indications in adults and children.

Table 1 US marketed antifungals

Drug name	Indication			Pediatric approval
	Candida Prophylaxis	Candidemia	Esophageal Candidiasis	
Fungizone (Amphotericin B deoxycholate)	Yes	Yes	Yes	
Ambisome (Amphotericin B liposomal)		Yes (refractory/intolerant to Amphotericin B)		Yes (≥1 month)
Vfend (voriconazole)	Yes	Yes	Yes	Yes (≥12 years)
Noxafil (posaconazole)	Yes			Yes (≥13 years)
Cancidas (caspofungin)		Yes	Yes	Yes (≥3 months)
Eraxis (anidulafungin)		Yes	Yes	
Diflucan (fluconazole)	Yes	Yes	Yes	Yes (≥6 months)
Nizoral (ketoconazole)		Yes	Yes	
Ancobon (flucytosine)		Yes		
Sporanox (itraconazole)				

MO comment: It is important to emphasize that no antifungal agent is approved for neonatal age group, although incidence of invasive candidiasis in neonates, particularly premature, extremely low birth weight (ELBW) neonates is 3-5 times higher than that of adults.

2.3 Availability of Proposed Active Ingredient in the United States

Mycamine, as micafungin sodium is approved and has been marketed in the US since 2005.

2.4 Important Safety Issues With Consideration to Related Drugs

Extensive data on the safety of the echinocandins is available. Although no comparative studies have been performed across the class some differences in safety profiles have been reported with micafungin and anidulafungin. Histamine-like reactions have occurred with rapid infusion of echinocandins. Anaphylaxis has been reported.
The table below provides a list of the most common adverse drug reactions and abnormal laboratory test results for each of the three agents observed during the clinical trials. Overall, the echinocandins are similar in types of adverse reactions and laboratory abnormalities and are considered to be well tolerated.

Table 2 Frequency of Common Adverse Drug Reactions and Laboratory Abnormalities Associated with the Echinocandins in Clinical Trials

Adverse Reaction	Caspofungin	Micafungin	Anidulafungin
	N=1951	N=3227	N=204
Fever	20	20	15
Abdominal pain	6	10	6
Nausea	9	22	26
Vomiting	8	23	16
Diarrhea	14	23	18
Headache	10	2	8
Rash	8	9	4
Pruritus	-	6	< 3
Neutropenia	<5	14	< 3
Thrombocytopenia	<5	16	5
Hypokalemia	11	18	20
Abnormal LFTs	13	6	3

Information is extracted from 2008 Cancidas PI, 2008 Mycamine ISS database, and clinical review of Eraxis NDA 21-948 by Elizabeth O'Shaughnessy, M.D.

MO comment: *Overall incidence of the common events in the different members of echinocandin family appears relatively similar; however, a few of them are more common with one or the other echinocandin: liver function test abnormalities are more frequent with caspofungin, while hypokalemia is observed more frequently with micafungin and anidulafungin, and thrombocytopenia most often is seen with micafungin.*

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The sponsor enrolled pediatric patients in their clinical efficacy trials for the indications of invasive candidiasis and *Candida* infection prophylaxis in hematopoietic stem cell transplant (HSCT) patients alongside with adults. Due to reliability issues with micafungin pharmacokinetic data in pediatric patients upon approval of the indications of esophageal candidiasis (EC) and *Candida* prophylaxis indications in adults in 2005, additional studies of micafungin in pediatric patients (safety, pharmacokinetics) were requested under PREA. Ongoing discussions between the sponsor and the review

division resulted in a comprehensive pediatric development program that culminated in the issuance of pediatric written request in 2006 that included 5 studies: four of them investigating PK and safety of micafungin at different doses in pediatric patients at risk and for the treatment of invasive *Candida* infections, and one evaluating efficacy of micafungin for the treatment of neonatal candidiasis, an area of unmet medical need. Table 3 below delineates milestones in the pediatric development program for micafungin.

Table 3 Presubmission Regulatory History

Submission/Date	Event
IND 55,322 Correspondence February 5,1999	Teleconference meeting minutes to discuss the Phase 3 Prophylaxis Protocol
NDA 21-506 Sequence April 29, 2002	Original submission – includes pediatric data.
NDA 21-754 Sequence April 23, 2004	Original submission – includes pediatric data.
IND 55,322 Serial 241 May 24, 2004	SPA submitted for a phase 3, efficacy and safety trial in neonates, Protocol 04-0-199.
IND 55,322 Correspondence July 9, 2004	Division's comments on the 04-0-199 SPA including: dose and duration, primary endpoint, secondary endpoint, microbiology and additional comments
NDA 21-506 Correspondence March 16, 2005	Approval letter received for NDAs 21-506 and 21-754; pediatric study deferral.
IND 55,322 Correspondence April 18, 2005	Complete response to July 9, 2004 SPA comments on Protocol 04-0-199; follow up meeting requested.
IND 55,322 Correspondence June 7, 2005	Face-to-face meeting 04-0-199 SPA.
IND 55,322 Correspondence June 16, 2005	Division's post-meeting responses regarding the SPA.
NDA 21-506 Sequence November 8, 2005	Briefing document for the December 21, 2005 type C meeting to discuss studies to support pediatric labeling and fulfill pediatric phase 4 commitments.
IND 55,322 Serial 304 November 18, 2005	Astellas submitted responses to requests from the June 7, 2005 meeting.
NDA 21-506 Correspondence December 21, 2005	FDA teleconference meeting minutes regarding pediatric phase 4 commitments.
IND 55,322 Serial 310 March 3, 2006	Request for a teleconference — draft proposed pediatric study request (PPSR). A proposal for a toxicology study in juvenile dogs was also included.

Submission/Date	Event
IND 55,322 Serial 312 March 24, 2006	Briefing document for April 26, 2006 type B meeting.
IND 55,322 Correspondence April 26, 2006	FDA teleconference meeting minutes regarding pediatric phase 4 commitments and pediatric exclusivity.
NDA 21-506 Sequence July 25, 2006	Revised PPSR submitted based on FDA discussion.
IND 55,322 Correspondence October 3, 2006	Revised PPSR submitted based on comments from clinical investigators.
NDA 21-506 Correspondence May 25, 2007	Pediatric written request (PWR) issued on May 23, 2007
IND 55,322 Serial 335 June 7, 2007	Astellas submitted statement of intent to act on PWR.
IND 55,322 Correspondence November 08, 2007	Division provided clinical comments on pediatric protocols 9463-CL-2101, 9463-CL-2102, 9463-CL-2103 and 9463-CL-2104.
IND 55,322 Serial 350 February 22, 2008	Submission of juvenile toxicology study in dogs (MGC0700354).
IND 55,322 Serial 360 September 30, 2008	FDA notified of infusion-related pyrexia in pediatric study 9463-CL-2101 in patients in South Africa.
IND 55,322 Correspondence January 22, 2009	Fax requesting detailed information on recruitment in 12 to 16-year-old patients in the invasive candidiasis studies.
IND 55,322 Serial 371 February 9, 2009	Request for feedback on proposed dataset formats.
IND 55,322 Serial 372 February 12, 2009	Summary of investigation into infusion-related pyrexia reactions.
IND 55,322 Serial 373 March 6, 2009	Response provided to FDA January 22, 2009 fax request.
NDA 21-506 Sequence 0005 April 14, 2009	Submission of 9463-CL-2104 final study report.
IND 55,322 Serial 379 May 28, 2009	FDA notified of voluntary suspension of enrollment in the neonate study (04-0-199); also submitted to NDA 21-506 May 29, 2009 Sequence 0008.
IND 55,322 Correspondence June 8, 2009	Email request for metabolite M-5 data.
IND 55,322 Serial 380 June 11, 2009	Response to metabolite M-5 data request.

Submission/Date	Event
IND 55,322 Serial 383 December 16, 2009	Briefing document for January 20, 2010 type C meeting regarding metabolite M-5.
IND 55,322 Correspondence January 6, 2010	FDA information request regarding metabolite briefing document.
IND 55,322 Serial 385 January 8, 2010	Responses to January 6, 2010 FDA request for information related to micafungin metabolites M1, M2 and M5.
IND 55,322 Serial 411 May 6, 2010	Nonclinical metabolite toxicology study reports submitted: 9463-TX-0045, 9463-TX-0046 and 9463-TX-0047.
IND 55,322 Serial 414 July 13, 2010	Nonclinical rat toxicology data to support M-5 coverage in neonate study (9463-TX-0048) submitted.
IND 55,322 Serial 407 February 8, 2011	Nonclinical toxicology data submitted regarding M5 metabolite: evaluation of genotoxic potential of M5, DEREK, LeadScope, M5 concentration in medium, TX107003 (Ames) and TX107004 (Chromosomal Aberration).
IND 55,322 Serial 408 February 21, 2011	Nonclinical toxicology juvenile and adult rat foci comparison – 9463-TX-0043 report and expert opinion (EMA follow up measure).
NDA 21-506 Sequence 0016 March 11, 2011	Amendment 1 to 9463-CL-2104 CSR submitted.
NDA 21-506 Correspondence April 8, 2011	Revised PWR amendment 2 – study due dates consistent with PREA.
NDA 21-506 Sequence 0021 May 6, 2011	Submitted 9463-CL-2102 and 9463-CL-2103 final study reports.
NDA 21-506 Sequence 0025 July 14, 2011	Type C meeting briefing document submitted regarding 9463-CL-2101 and 9463-CL-2303 study questions.
NDA 21-506 Correspondence September 9, 2011	FDA meeting minutes from August 12, 2011 type C meeting.
NDA 21-506 Sequence 0029 November 16, 2011	Request for feedback regarding 9463-CL-2101 study patient.
NDA 21-506 Correspondence November 30, 2011	Response to Astellas November 26, 2011 request for feedback – FDA agrees with Astellas approach.
NDA 21-506 Correspondence December 5, 2011	Revised PWR amendment 3 – revision to number of patients in 9463-CL-2101 study.
IND 55,322 Serial 427 March 14, 2012	A table of micafungin nonclinical juvenile animal studies was provided to FDA in preparation for the pre-sNDA meeting on June 13, 2012.
IND 55,322 Serial 430 May 7, 2012	Submitted the pre-sNDA meeting briefing document.

Submission/Date	Event
IND 55,322 Correspondence June 8, 2012	FDA preliminary responses to pre-sNDA meeting questions.
IND 55,322 Correspondence June 12, 2012	Phone contact initiated by FDA to follow up on the Astellas request regarding nonclinical data question for the pre-sNDA meeting.
IND 55,322 Correspondence July 10, 2012	FDA pre-sNDA teleconference meeting minutes.

SPA: Special Protocol Assessment; PPSR: Proposed Pediatric Study Request; IND: Investigational New Drug; NDA: New Drug Application; PK: pharmacokinetic; CSF: cerebrospinal fluid; PREA: Pediatric Research Equity Act; PWR: Pediatric Written Request
Adapted from the sponsor's regulatory correspondence section

MO comment: During the current review, the PWR was amended on January 23, 2013 to extend the deadline for the final report submission for study 5 (neonatal candidiasis) until September 30, 2017. Deferral extension for the PREA PMR #5 with respect to the final study report submission was issued as well.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Quality and integrity of the data in the submission were evaluated. DSI inspections of the bioanalytical and three clinical sites (2260, 1888, and 1221) were requested. In September 2008, site 2160 in South Africa had reported a cluster of febrile episodes (n=8) associated with micafungin infusion. Astellas went to investigate. Comorbid conditions in the patients were deemed a likely culprit, although drug preparation techniques were cited as a possible factor. South African site 1221 was investigated, as well. Febrile reactions in three patients were reported, but they were not clustered. In addition, upon analyses of the samples from 2 South African sites (1221 and 1888) the sponsor reported micafungin concentrations were significantly lower than the reported concentrations for the age groups from other sites and studies. The following subjects were excluded from the PK analyses due to outlier concentrations: site 1221: 12211105, 12211109, 12211111, 12211116; site 1888: 18881101, 18881103, 18881104, 18881117, 18881118.
. OBI and DSI audits of the South African clinical sites 1221 and 1888, California clinical site 249, as well as bioanalytical site at (b) (4) have identified protocol violations and 483 forms were issued. The violations identified pertaining to informed consent communication/documentation, dose calculations, sample storage, and drug disposal were thought by the investigators to have minimal effect on the study data reliability.

3.2 Compliance with Good Clinical Practices

The studies submitted in the NDA under review are stated to be compliant with Good Clinical Practices.

3.3 Financial Disclosures

The applicant did not submit financial disclosures for the pediatric PK studies in this submission; the applicant considered the studies to be pharmacokinetic studies that "do not require financial certification and disclosure" per 21 CFR 54.2(e). The applicant resubmitted financial disclosure forms for the previously-reviewed phase 3 studies that included pediatric patients. No significant financial interests were reported for these trials.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Not applicable. No new CMC information was provided in the submission under review.

4.2 Clinical Microbiology

Not applicable. No new Clinical Microbiology information was provided in the submission under review. A labeling supplement, submitted on December 23, 2011, proposed revisions to the microbiology section (12.4) of the package insert. The review from Dr. Shukal Bala is being conducted concurrently with the review of this pediatric efficacy supplement. The proposed revisions to the microbiology section will be made concurrently with the pediatric use labeling changes.

4.3 Preclinical Pharmacology/Toxicology

Although no new pharmacology/toxicology information was provided in the submission under review, the sponsor previously submitted to the IND 52,322 the complete nonclinical study reports for juvenile and neonatal long term toxicity studies in rats, requested by EMA. In his review, Dr. Owen McMaster, finds that newborn /juvenile animals appear to be at no greater risk of developing foci of altered hepatocytes (FAH) at the end of 13 week of micafungin exposure at 32 mg/kg daily dose (x8 maximum human therapeutic exposure) as compared to adult animals. The nonclinical finding of FAH is adequately reflected in the product labeling, Section 13. The clinical significance of this finding remains unknown at this time.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Not applicable. No new MOA information was provided in the submission under review.

4.4.2 Pharmacodynamics

Not applicable. No new information on micafungin pharmacodynamics was provided in the submission under review.

4.4.3 Pharmacokinetics

Clinical pharmacology and pharmacometric data submitted by the sponsor in support of proposed micafungin dosing in pediatric patients ages 4 months to <17 years were evaluated by Drs. Dakshina Chilukuri, Seong Jang and Yang He.
After analysis of available pharmacokinetic data in pediatric patients 4 months to <17 years and the results of modeling the clinical pharmacology review team came to the conclusion that applicant's proposed (b) (4) dose for esophageal candidiasis will result in micafungin exposures approximately 30% higher than 90th percentile of exposures achieved with a 150-mg dose in adults in 46% of pediatric patients weighing 30-50 kg and in 21% of pediatric patients weighing >50kg.

Table 4 Steady state AUC_{tau} of Micafungin by Weight Group

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

	% Patients with AUC_{tau}		
	<112.5	0	10.7
	112.5-208.5	78.6	78.6
	>208.5	21.4	10.7

[a] The maximum dose for the patients with >50 kg of body weight
Adapted from the clinical pharmacology review p. 21

Therefore, the dosing counter-proposal presented in Table 5 was made.

Table 5 Side by Side Comparison of Applicant's and FDA proposed dosing regimens for Pediatric and Adult Patients for the Approved Indications

Indication	**Applicant's** Recommended Reconstituted Dose Once Daily (b) (4)	**FDA ClinPharm** Recommended Reconstituted Dose Once Daily		
		Pediatric Patients **≤ 30 kg**	Pediatric Patients **> 30 kg**	Adults
Prophylaxis of *Candida* Infections in HSCT Recipients		1 mg/kg up to 50 mg		50 mg
Treatment of Candidemia, Acute Disseminated Candidiasis, *Candida*, Peritonitis and Abscesses		2 mg/kg up to 100 mg		100 mg
Treatment of Esophageal Candidiasis		**3 mg/kg**	**2.5 mg/kg up to 150 mg**	150 mg

The review team was concerned about the adequacy of the available safety data at the applicant's proposed (b) (4) dose for pediatric patients with esophageal candidiasis. This concern was related to potential exposures to micafungin in these pediatric patients that are higher than the 90th percentile for exposures achieved with the 150 mg dose in adults. On the other hand, the more precise matching of pediatric micafungin exposure to adult one achieved at 150 mg dose made the dosing recommendations for the pediatric patients with esophageal candidiasis more complex.

This clinical review includes additional safety analyses pertaining to micafungin overexposure in pediatric patients. See section 7.5.4 for the additional safety analyses.

MO comment: *Extrapolation of efficacy from adult to pediatric patients, based on matching micafungin PK exposure, is the main goal of this submission as the pediatric subgroup efficacy analyses from adequate and well controlled studies in candidemia and Candida infection prophylaxis, as well as successful clinical outcome reported for isolated cases of pediatric EC from the open label or dose ranging studies cannot stand on their own as a sufficient evidence of efficacy micafungin in pediatric population. These data, however, are supportive and supplement the quality of evidence for*

exposure matching extrapolation of the indications from adults to pediatric patients. With extrapolation of efficacy, one should ensure that the dose selected will result in the majority of pediatric patient achieving exposures similar to those achieved in adults and the number of patients with exposures lower than the 10th percentile of adults is small. No matter how precise the matching of the exposures between adults and pediatric patients at the proposed doses, the safety cannot be extrapolated and therefore safety studies in pediatric patients need to be conducted. The micafungin pediatric development program includes one of the largest pediatric safety databases among the antifungals that are currently approved, second only to fluconazole. Micafungin was administered to pediatric patients at doses ranging from 1 to >4.5 mg/kg, with 109 pediatric patients receiving micafungin at ≥3 mg/kg for ≥7 days. A total of 56 pediatric patients for whom micafungin PK data were available achieved exposures higher than 90th percentile of adult exposures seen at the 150 mg dose.

5 Sources of Clinical Data

The cumulative safety population, including adults, comprises 5265 subjects who were enrolled and received at least one dose of study drug in 46 clinical studies. Of these, 3747 subjects ("all micafungin subjects"), including 3227 patients ("all micafungin-treated patients") and 520 volunteers, received at least one dose of micafungin. There were 479 pediatric patients that received at least one dose of micafungin in the cumulative safety population.

5.1 Tables of Studies/Clinical Trials

Table 6 Clinical Trials Submitted/Resubmitted in the Application Under Review

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects‡	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
PK	FG-463-21-08-R-PK-02§¶	PK of FK463 in neutropenic and non-neutropenic pediatric patients	Randomized, double-blind / active control	1-hr iv infusion of FK463 100 mg qd (2 mg/kg qd for patients weighing ≤ 40 kg) or AmBisome 3 mg/kg qd)	Enrolled = 109 FK463-treated= 52 PK Evaluable= 12	Pediatric patients (3 weeks to 15 years) with confirmed IC or candidemia	14 days to a maximum of 4 weeks (except for patients with chronic disseminated [hepatosplenic] candidiasis, Candida osteomyelitis or Candida endocarditis, who were allowed up to 8 weeks of study drug)	PK report included in sNDA 21-506 submission on 21Dec06 (IC Supplement 008)
PK	9463-CL-2101	PK and safety of iv FK463 after repeated dosing at 2 dose levels	Open-label / no control	Repeat daily dosing of iv FK463 at 3 mg/kg (wt ≥ 25 kg) or 4.5 mg/kg (wt < 25 kg) over 1 hr	78 (24 PKAS) 3 mg/kg 2-5 yrs = 1 6-11 yrs = 13 12-16 yrs = 12 4.5 mg/kg 2-5 yrs = 31 6-11 yrs = 20 12-16 yrs = 1	Children (2-5 and 6-11 years) and adolescents (12-16 years) with proven or probable esophageal candidiasis, proven or probable IC or suspected Candida infection	Minimum of 10 consecutive days to a maximum of 14 consecutive days	Complete; PK and safety report

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects‡	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
PK	9463-CL-2102	PK and safety of iv FK463 after repeated daily dosing in infants and toddlers	Open-label / no control	Repeat daily dosing of 4.5 mg/kg iv FK463 at 0.5 to 4.0 mg/mL over 1 hr	Enrolled = 9 PKAS = 8 SAF = 9 Completed = 5	Infants and toddlers (≥ 4 months to < 24 months of age) with proven or probable esophageal candidiasis or other invasive candidiasis or suspected Candida infection	Minimum of 10 consecutive days to a maximum of 14 consecutive days	PK and safety report submitted to NDA 21-506 on 06May11 (sequence
PK	9463-CL-2103	PK and safety of iv FK463 after repeated daily dosing at 2 doses as prophylaxis	Open-label / no control	Repeat daily dosing, iv infusion of FK463 at either of 2 doses: 1 mg/kg for children weighing ≥ 25 kg or 1.5 mg/kg for children weighing < 25 kg	Enrolled = 42 PKAS = 40 SAF = 40 Completed = 39	Prophylaxis in children (4 months to < 24 months, 2 to 5 years, and 6 to 11 years) and adolescents (12 to 16 years) undergoing autologous, syngeneic, or allogeneic HSCT	FK463 was initiated within 48 hrs of the start of the patient's transplant-related conditioning regimen and dosed daily for a minimum of 10 to a maximum of 14 consecutive days	Complete; PK and safety report submitted to NDA 21-506 on 06May11 (sequence 0021)
PK	9463-CL-2104	PK and safety of FK463 in neonates	Open-label / no control	Repeat daily dosing, iv infusion of FK463 Neonates < 1000 grams were assigned to receive 10 mg/kg/day	Enrolled =13 PKAS = 12 SAF = 13 Completed = 13	Neonates (greater than 48 hrs of age and up to 120 days of life) with suspected candidemia or invasive candidiasis	Daily dosing for 4 or 5 consecutive days	PK and safety report submitted to NDA 21-506 on 14Apr09 (sequence
Efficacy/ safety	98-0-050	Efficacy, safety of FK463 compared to fluconazole	Double-blind randomized / active control	1-hr iv infusion 1x daily FK463: 50 mg/day (1 mg/kg/day < 50 kg); fluconazole: 400 mg/day (8 mg/kg/day < 50 kg)	FK463: Enrolled = 426 Completed = 402 Fluconazole: Enrolled = 463 Completed = 428	Adult and pediatric patients (0.6 to 73 years) undergoing an autologous/syngeneic or allogeneic hematopoietic stem cell transplant	Treatment started at time transplant-conditioning regimen was initiated or within 48 hrs post-initiation; treated until neutrophil recovery + 0 to 5 days to max of 42 days posttransplant	Efficacy/safety report submitted on 29Apr02 NDA 21-506 (prophylaxis)

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects‡	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Efficacy/ safety	FG-463-21-08-R-CR-02§¶	Efficacy and safety of FK463 versus AmBisome in neutropenic and non-neutropenic pediatric patients	Randomized, double-blind / active control	1-hr iv infusion of FK463, 100 mg qd (2 mg/kg/day for patients weighing ≤ 40 kg) or AmBisome 3 mg/kg qd	FK463: Enrolled =54 Completed = 38 Ambisome: Enrolled = 55 Completed†† = 36	Pediatric patients (0 weeks to 15 years) with confirmed invasive candidiasis or candidemia	14 days to a maximum of 4 weeks (except for patients with chronic disseminated candidaisis, Candida osteomyelitis or candida endocarditis, for whom study drug was allowed for up to 8 weeks)	Efficacy/safety report included in the sNDA 21-506 submission on 21Dec06 (IC supplement 008)

FK463: micafungin; HSCT: hematopoietic stem cell transplant; IC: invasive candidiasis; PK: pharmacokinetics; PKAS: pharmacokinetics analysis set; PPS: per protocol set; SAF: safety analysis set;
‡ PK Studies = number included in pharmacokinetic analyses; Efficacy/safety studies = number enrolled and completed, unless specified otherwise [Note: the same patient population was used for PK and efficacy/safety studies]
§ Study FG-463-21-08 has a supplemental susceptibility report included in this submission (Report CRE050112). Study FG-463-21-08 was previously submitted with the IC Submission, NDA 21-506, Supplement 008.
¶ These studies have both a pharmacokinetic study report and an efficacy/safety report and are listed twice in the table.
†† Includes patients who have completed treatment and study as well as those patients who have just completed treatment.
Adapted from the sponsor's ISS, Module 5.2 eCTD pp. 1-3

***MO comment**: the focus of this review will be 4 new pediatric PK/safety studies: 2101, 2102, 2103, and 2104. Subgroup analyses of efficacy of micafungin in pediatric population enrolled in clinical trials previously reviewed for adult indications of prophylaxis and candidemia will be referenced in this review, as no new efficacy data in pediatric patients were submitted. Integrated safety analyses will include the whole safety database of micafungin exposed adult and pediatric patients in clinical trials. Comparison of safety profiles between adults and children exposed to micafungin will be made.*

Table 7 Studies Previously Submitted and Reviewed for the Approved Indications in Adults

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects†	Healthy Subjects or Diagnosis of Patients	Duration of Treatment with FK463	Previous Submission
PK	98-0-043‡	PK of FK463 in febrile pediatric age groups 2-12 years and 13-17 years	Open-label, sequential dose escalation / no control	1-hr iv infusion FK463, 1x daily at 0.5, 1.0, 1.5, 2.0, 3.0, or 4.0 mg/kg/day	73	Febrile, neutropenic pediatric patients (2 to 17 years) with 1 of the following: leukemia or lymphoma (except patients on maintenance chemo therapy); bone marrow or peripheral stem cell transplant; chemotherapy inducing >10 days of neutropenia; aplastic anemia; or myelodysplastic syndrome	At least 3 days to max of 4 weeks or until neutrophil recovery	CL and PK reports in NDA 21-506; complete PK report and CL synopsis in NDA 21-754
PK	99-0-063	PK and tolerance in premature infants of 3 doses of FK463	Open-label /no control	30 min iv single dose FK463 0.75 mg/kg, 1.5 mg/kg and 3.0 mg/kg	Enrolled = 23 and clearance calculated for 21	Premature infants ≤40 weeks postconception age and body weight ≥ 500g	1 day iv infusion over a 30 min time period	NDA 21-754
PK	FJ-463-FP01§	To analyze PK of FK463 using data on plasma concentration of FK463 and its metabolites obtained in the phase 3 study of pediatric patients with deep mycosis	Open-label /no control	1-3 hr iv infusion of FK463, 1 mg/kg up to a max. 6 mg/kg per day (without exceeding 300 mg/day); dose escalation allowed after 7 days of continuous treatment with a consistent dose	Enrolled = 20 Treated = 20 PK Evaluable = 19	Japanese pediatric patients 8 months to 15 years with deep mycosis caused by Aspergillus or Candida species	Up to 56 days	Complete; NDA 21-506 S-008

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects†	Healthy Subjects or Diagnosis of Patients	Duration of Treatment with FK463	Previous Submissio n
Efficacy/ safety	98-0-043‡	Maximum tolerated dose and safety of FK463 in age groups 2-12 years and 13-17 years	Open-label, sequential dose escalation / no control	1-hr iv infusion FK463 1x daily, 0.5 mg/kg/day; escalation to 1.0, 1.5, 2.0, 3.0, and 4.0 mg/kg/day; because of slow enrollment highest dose for 13-17 year olds was 1.5 mg/kg/day	Enrolled = 78 Completed = 76	Febrile, neutropenic pediatric patients (2 to 17 years) with 1 of the following: leukemia or lymphoma (except patients on maintenance chemotherapy); bone marrow or peripheral stem cell transplant; chemotherapy inducing >10 days of neutropenia; aplastic anemia; or myelodysplastic syndrome	Treatment at onset of fever while neutropenic for min of 3 days to max of 4 weeks or until neutrophil recovery	Both CL and PK reports in NDA 21-506; complete PK report and CL synopsis in NDA 21-754
Efficacy/ Safety	98-0-046¶/ FG-463-21-01	Efficacy and safety of FK463 in adult and pediatric patients	Open-label /historical control	1-hr iv infusion FK463 1x daily (min of 3 days/week); beginning dose of 75 mg/day (1.5 mg/kg/day <40 kg), increases in 75 mg increments (1.5 mg/kg/day increments <40 kg) after 7 days to 225 mg/day (4.5 mg/kg/day < 40 kg) or higher with approval	Enrolled = 331 Completed = 128	Adult and pediatric patients (0.2 to 84 years) with a proven or probable (pulmonary only) invasive infection due to *Aspergillus* species.	7-90 days, or more with approval	NDA 21-754
Efficacy/ Safety	98-0-047†† / FG-463-21-02	Efficacy and safety of iv FK463 in adult and pediatric patients	Open label /historical control	1-hr iv infusion FK463 1x daily (or min 3 days/week); beginning dose 50 mg/day (1 mg/kg/day <40 kg) or 100 mg/day (2 mg/kg/day < 40 kg) if germ tube negative *Candida* infection or non-*C. albicans* infection; increases in 50 mg increments (1 mg/kg increments <40 kg) after 5 days up to a maximum of 200 mg/day	Enrolled = 357 Completed = 221	Adult and Pediatric patients (0.0 to 92 years) with candidemia or invasive candidiasis	Min of 5 days to max of 6 weeks	Complete; NDA 21-506 S-008 and NDA 21-754

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects†	Healthy Subjects or Diagnosis of Patients	Duration of Treatment with FK463	Previous Submissio n
Efficacy/ safety	FJ-463-FP01§	To estimate the appropriate dosage and administration of FK463 in pediatric patients on the basis of safety and PK data across studies in Japanese and non-Japanese adults and non- Japanese pediatric patients	Open-label /no control	1-hr iv infusion FK463, 1 mg/kg up to a max. 6 mg/kg per day (without exceeding 300 mg/day); dose escalation allowed after 7 days of continuous treatment with a consistent dose	Enrolled =20 Completed = 10	Japanese pediatric patients with deep mycosis caused by *Aspergillus* or Candida species	Up to 56 days	Complete; NDA 21-506 S-008

CL: clinical; FK463: micafungin; PK: pharmacokinetic;

† PK studies = number included in pharmacokinetic analyses; Efficacy/safety studies = number enrolled and number completed [Note: the same patient population was used for PK and efficacy/safety studies]

‡Pharmacokinetic data from this study was re-analyzed and an updated PK report was provided in NDA 21-754. Both PK as well as Efficacy/Safety reports are listed twice in the table.

§ Study FJ-463-FP01 clinical and associated population PK reports

¶A final clinical study report was provided in NDA 21-754 (including the Independent Reviewer's Report and a Literature Synthesis); interim reports of the results of several data cuts while the study was ongoing were submitted to regulatory authorities including an interim report provided to Japanese regulatory authorities, followed by a second interim report in NDA 21-506, and a third interim report submitted to the EMEA.

††A final clinical study report was provided in (b) (4) NDA 21-506 (QOD sNDA 060224) and NDA 21-754 (including the Independent Reviewer's Report and a Literature Synthesis); interim reports of the results of several data cuts while the study was ongoing were submitted to regulatory authorities including an interim report provided to Japanese regulatory authorities, followed by a second interim report in NDA 21-506, and a third interim report submitted to the EMEA.

Adapted from the sponsor's ISS, Module 5.2 eCTD pp. 4-6

5.2 Review Strategy

The NDA 21-506, S-037 was reviewed by a multidisciplinary team. The clinical pharmacology review of 4 PK studies 2101, 2102, 2103, and 2104, as well as the PK data collected in 2 safety/efficacy studies 043 and 044 was conducted by Dakshina Chilukuri, Ph.D., Seong Jang, Ph.D., and Yang He, Ph. D.. Clinical review of safety and efficacy was performed by Yuliya Yasinskaya, MD, while individual PK/Safety studies 2101-2104 were reviewed by Brittany Goldberg, M.D. Statistical review of the previously submitted efficacy data was done by Dr. Cheryl Dixon.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 Study 2101

Study 2101: A Phase 1, Open-Label Study of the Safety and Pharmacokinetics of Repeated-Dose Micafungin (FK463) in Children (2 - 5 Years and 6 - 11 Years) and Adolescents (12 - 16 Years) with Esophageal Candidiasis or Other Invasive Candidiasis

5.3.1.1 Methods

INVESTIGATORS: 15 investigators, 10 of whom enrolled subjects

STUDY CENTERS: 15 centers, 11/15 centers recruited subjects (8 U.S, 3 South Africa)

STUDY PERIOD: 14-October 2007 to 08-September 2011

OBJECTIVES: To evaluate the pharmacokinetics and safety of intravenous micafungin after repeated daily dosing at two dose levels determined by patient's weight (3.0 mg/kg or 4.5 mg/kg) in children and adolescents. Three age groups (2-5 years, 6-11 years and 12-16 years) with proven or probable esophageal candidiasis, proven or probable candidiasis or suspected *Candida* infection were evaluated.

METHODOLOGY: Prospective open-label, multicenter, repeat-dose study

NUMBER OF SUBJECTS: Total enrollment was 84 patients, 78 received at least one dose of study medication.

STUDY DRUG: IV micafungin in 0.9% sodium chloride was administered at a dose of 3.0 mg/kg to patients with a weight greater than or equal to 25 kg, or 4.5 mg/kg to patients with a weight less than 25 kg. Patients received test drug as Mycamine in 50 mg/vial from lot numbers 0500 and 021160. Each vial contained 50 mg of lyophilized micafungin and 200 mg of lactose with citric acid and/or sodium hydroxide. Maximum daily dose administered to any patient was 150 mg.

DURATION OF TREATMENT: Injections were given over one hour at the same time every morning for a minimum of 10 consecutive days to a maximum of 14 consecutive days. Infusions that were not completed as inpatients were given on an outpatient basis by the investigator/staff.

TREATMENT COMPLIANCE: Compliance and completion of all study procedures were recorded in the source documents and electronic case reports form.

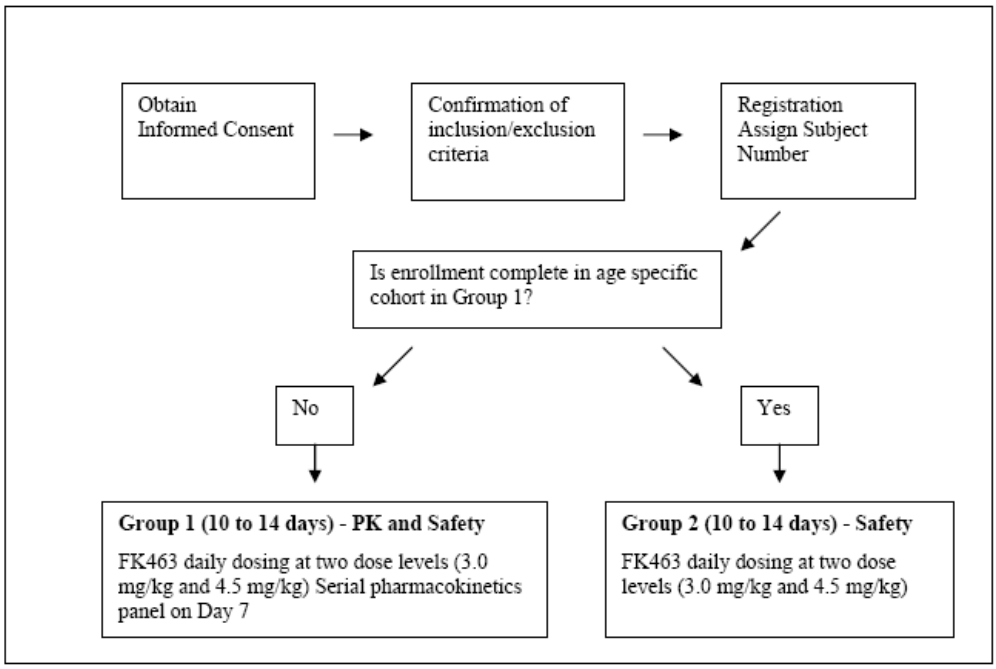
STUDY DESIGN: This was a prospective, multicenter, open-label, repeat-dose study to evaluate the pharmacokinetics and safety of micafungin. Patients were enrolled in two groups. Group 1 collected serial blood samples for assessment of pharmacokinetics and safety information. Group 2 collected trough blood samples and safety information. Patients could only be enrolled in one group of the study.

Group 1: Patients received a minimum of 10 consecutive days of micafungin, of which 8 must have been administered as an inpatient. The remaining doses were administered as outpatients to a maximum of 14 days. Serial blood samples were drawn for the day 7 dose at predose ("0 hr") and 1, 2, 4 and 10 hours postdose. Single blood samples for trough micafungin concentration were drawn predose on days 4, 6 and 8.

Group 2: Patients received at least 10 consecutive days of micafungin. If discharged before day 10, patients received daily infusions as outpatients. Single blood samples were drawn within 10 minutes prior to infusion start time (predose) on days 4, 6 and 8. A final blood sample was obtained 24 hours post dose of the last micafungin infusion on day 11, 12, 13, 14 or 15 as applicable.

MO comment: *This study was conducted in response to the pediatric written request (PWR) issued in May 2007, and most recently amended in August, 2012. The PWR stipulations were generally fulfilled by the study. The type of study, objectives, age groups, and study endpoints were followed, as specified by the PWR. The study did fail to recruit the minimum number of patients (8) for the evaluation of pharmacokinetics in the 6-11 year age group.*

Figure 1 Study 2101 Flow Diagram



Adopted from Astellas study 2101 page 18

SAMPLE SIZE: Children ages 2-5 years and 6-11 years and adolescents aged 12-16 years with proven or probable esophageal candidiasis, other invasive candidiasis or suspected *Candida* infection were enrolled. Approximately 60 male and female pediatric patients were to be enrolled into the study. At least 24 patients were to be enrolled in Group 1 (pharmacokinetics and safety), with at least 8 in each age cohort. At least 36 patients were to be enrolled in Group 2 (safety), with at least 12 in each age cohort. Patients who withdrew early from Group 1 could be replaced at the discretion of Astellas to ensure adequate micafungin, M1, M2 and M5 concentration data for pharmacokinetic analyses.

INCLUSION CRITERIA:

General

- Age 2 to 16 years
- Negative pregnancy test within 72 hours of first dose, and agreed to use birth control if sexually active
- Informed consent provided by patient, parent or legal guardian
- Patient or guardian agreed to comply with study requirements
- Patient had sufficient venous access for administration of study drug and collection of blood samples

1. Proven or probable candidiasis or suspected *Candida* infection:
    a. Proven or probable candidiasis documented within 5 days of first dose of study drug as follows:
        i. Diagnosis of esophageal candidiasis by endoscopy with histological/cytological and culture confirmation of infection AND/OR typical clinical symptoms AND
        ii. Clear signs/symptoms of esophagitis AND
        iii. At least one clinical symptom of esophageal candidiasis with a grade > 0 at baseline.
2. Proven candidemia or other invasive candidiasis
    a. A positive culture and/or histology from a sample obtained no more than 96 hours prior to first dose of study medication (or positive culture within the last 4 weeks for chronic invasive candidiasis AND
    b. At least one typical clinical sign or symptom
    c. For candidemia, preliminary evidence of yeast could be used for enrollment. Confirmation of *Candida* species must have been obtained within one week after first dose.
    d. For invasive candidiasis, culture results could be pending if histology/cytology revealed yeast.
3. Probable candidiasis
    a. A positive scan consistent with chronic, disseminated candidiasis AND
    b. Clinical signs or symptoms noted by the investigator consistent with candidiasis
4. Suspected *Candida* infection documented as follows:
    a. Patients who required board spectrum antibiotics and were at risk for invasive *Candida* infection AND
    b. Persistent fever of 100.4 F for which there was no known etiology OR
    c. A recurrent fever of >100.4 on 2 measurements of temperature at least 3 hours apart or single measurements of 101.3 F.

MO Comment: *The sponsor conducted a number of efficacy studies that are of relevance to the study under review: study 005 (pivotal adult study of esophageal candidiasis), study 2109 (supportive phase 2 adult study of esophageal candidiasis), study 003 (phase 2 adult dose finding study in EC) and study 047. Micafungin doses selected for evaluation in the study under review were thought to closely approximate exposures achieved at the approved 150 mg dose for EC in adults that was evaluated for efficacy and safety in studies 2109 and 005. Due to significant differences in design between the study under review and the pivotal efficacy studies for EC in adults, the comparison of efficacy outcomes between the two studies is difficult.*

Study 98-0-047 was a phase 2 open-label non-comparative multinational study evaluating the efficacy of micafungin in the treatment of adult and pediatric patients diagnosed with candidemia or other invasive candidiasis, including esophageal disease. Patients were started on a dose of 50 mg (1 mg/kg for patients <40 kg) or 100 mg (2 mg/kg for patients <40 kg) for non-albicans Candida infection. The dose could be

increased in 50 mg increments to a maximum of 200 mg (4 mg/kg for patients <40 kg) in the event of continued symptoms after five days of medication administration.

Inclusion criteria for study 98-0-047 included positive blood culture within 96 hours, biopsy with invasive fungal elements, characteristic lesions visualized endoscopically and confirmed by biopsy. Chronic disseminated candidiasis was defined by characteristic signs and symptoms as well as positive blood culture or biopsy. Patients with persistent or intermittent fever and abdominal imaging consistent with disseminated disease were also considered to have possible infection.

These inclusion criteria are more stringent than those observed by 9463-CL-2101 and do not rely solely on clinical symptomatology. Study 98-0-047 does include patients with "typical clinical signs and symptoms" of candidemia or invasive candidiasis, but requires culture confirmation. 97 of 209 patients (46.4%) in 98-0-047 had esophageal candidiasis. The doses used in 2101 are most appropriate for the treatment of esophageal candidiasis, and an analysis of efficacy will be more applicable for this patient population.

EXCLUSION CRITERIA:

1. Patient had evidence of significant liver disease, as defined by aspartate aminotransferase (AST), alanine aminotransferase (ALT), bilirubin or alkaline phosphatase > 5 times the upper limit of normal (ULN).
2. Patient had concomitant medical condition that in the opinion of the investigator and/or medical monitor precluded enrollment into the study.
3. Patient had history of anaphylaxis, hypersensitivity or any serious reaction to the echinocandin class of antifungals.
4. Patient had received treatment with an echinocandin within one week prior to first dosing.
5. Patient status was unstable and patient was unlikely to complete all study required procedures.
6. Female patient was pregnant or nursing.
7. Patient had participated in another clinical trial involving an investigational drug within 30 days (or 5 half-lives of the drug) prior to day 1 of the study except for those trials involving primary cancer therapy.
8. Patient was previously enrolled in this study.
9. Patient had yeast or mold-like infection other than invasive candidiasis or candidemia.
10. Patient whose diagnosis of invasive candidiasis was based on evidence of infection limited to a positive culture for *Candida* sputum, or broncho-alveolar lavage, vascular catheter tip or urinary catheter drainage. A patient with a positive urine culture obtained via in/out catheterization or suprapubic aspiration who had signs and symptoms of upper urinary tract disease could be enrolled.

MO Comment: *Study 98-0-047 excluded patients with abnormal transaminases >10x*

ULN and patients who required other systemic antifungal agents. They did not explicitly exclude patients with a diagnosis based on urinary, BAL or sputum results, or yeast/mold infections.

STUDY PROCEDURES: Micafungin was given at 3.0 mg/kg in patients weighing greater than or equal to 25 kg or 4.5 mg/kg to patients weighing less than 25 kg with a maximum dose of 150 mg. Micafungin was reconstituted and diluted with 0.9 % sodium chloride for injection infused over one hour (+/- 3 min) at a final concentration of 0.5 to 4.0 mg/mL. Maximum volume infused was not to exceed 100 mL. Dose concentrations >1.5 mg/mL were recommended to be infused through a central catheter to minimize the potential for infusion-related toxicity. Infusions were administered at approximately the same time every morning for a minimum of 10 consecutive days to a maximum 14 consecutive days.

Table 8 Schedule of Assessments

Assessments	Baseline Procedures	Procedures by Study Days				
		1	2 - 10	11 - 14	EOT[a]	EOS[b]
Informed consent (prior to any study procedures)	X					
Demographics and medical History	X					
Record clinical symptoms of EC, OC or IC[c]	X[D]				X	
Assessment of fungal infection[e]	X[d]				X	
Physical examination	X[f]	X			X	
Weight	X[f]	X	X[g]		X	
Electrocardiogram[h]	X[f]		X		X	
Pregnancy test[i]	X[f]				X	
Vital signs (BP, heart rate, body temperature), height[j]	X[F]	X	X	X	X	X
Clinical laboratory tests[k]	X[f]	X	X	X	X	X
Microbiology/histopathology[l]	X					
Evaluation of inclusion/ exclusion	X	X				
Antifungal and concomitant medication	X	X	X	X	X	X
Adverse event recording		X	X	X	X	X
Micafungin dosing[n] (infusion over 1 hr)		X	X[o]	X		
Pharmacokinetic Blood Sampling						
Group 1						
Predose (0 hr; ≤ 10 min before infusion start)[p]			X			
1, 2, 4 and 10 hrs relative to infusion start time[g]; 1 mL			X			
Group 2						
Predose (0 hr; ≤10 min before infusion start)[p]			X			

24 hr (relative to infusion start time)[q]; 1 mL				X		

Adapted from Astellas study 2101 report p. 25

Note: In Group 1, the first serial pharmacokinetic blood sample (within 3 minutes after the end of the infusion) must not have been collected from the same location as used for study drug infusion. Other pharmacokinetic samples in Group 1 and all samples in Group 2 could be collected from the same approximate location as micafungin infusion only when appropriate predose and postdose flushing techniques had been performed.

BP: blood pressure; EOT: end of therapy; EOS: end of study; EC: esophageal candidiasis; OC: oropharyngeal candidiasis; IC: invasive candidiasis

A EOT visit occurred within 72 hours after the final micafungin dose was administered.

B EOS visit occurred 14 days (+/- 2 days) after the final micafungin dose was administered.

C Grading scales for assessment of clinical symptoms and mucosal grades for EC are provided. Patient with esophageal candidiasis must have had at least one clinical symptom of oropharyngeal candidiasis with a grade > 0 at baseline for enrollment.

D Completed within 5 days prior to first dosing

E Documentation of infection using institution standard of care; assessment of fungal infection performed at baseline and at EOT.

F Completed within 72 hours prior to first dosing

G Day 7 only

H 12-lead ECG with 10 second rhythm strip was obtained within 72 hours prior to first dosing, once between day 4 and day 8 (within +/-15 minutes of the end of micafungin infusion) and at the EOT visit.

I Pregnancy test was performed on adolescent females of child-bearing potential within 72 hours prior to study drug administration on day 1 and at EOT.

J Height (length) was recorded once within 72 hours prior to first dosing. Vital signs were taken at baseline and twice (prior to the start of the infusion and within one hour postinfusion) daily during therapy with study drug and at EOT and EOS. On days when pharmacokinetic sampling was scheduled (days 4, 6, 7 and 8 [Group 1] and days 4, 6 and 8 [Group 2]) predose vital signs were taken before pharmacokinetic blood draws.

K Clinical lab samples were collected within 72 hours prior to first dosing, once between day 2 and day 7, once between day 8 and day 14 (each weekly draw separated by at least 3 days), at the EOT visit (within 72 hours after the final intravenous micafungin infusion) and at EOS (14 +/- 2 days after the last micafungin infusion). If clinical lab samples were obtained per local standard of care these samples could be used as the clinical labs for this study. Hematology: hematocrit, hemoglobin, red blood cell count, white blood cell count with differential, platelet count, absolute neutrophil count. Serum chemistry: creatinine, blood urea nitrogen, AST, ALT, alkaline phosphatase, GGT, total bilirubin, sodium, potassium, chloride, calcium, magnesium, total protein, albumin, LDH.

L Tissue or fluid sample from infected sites for fungal culture stains and histopathologic examination if location of infection was readily accessible for sampling and clinically indicated.

M Treatment associated with patient's underlying condition (including immunosuppressives, chemotherapy and anti-infectives) and any antifungals (oral, non-absorbable and systemic) received in the 14 days prior to first dose of study drug were recorded. Use of all concomitant medications, both prescribed and over-the counter, from baseline to EOS was recorded. Patients could not receive any echinocandin therapy for one week prior to first dosing or during the study. Patients could not be failing prior therapy.

N Micafungin was administered for 10 to 14 days per investigator clinical judgment (as per protocol).

O Patients could be discharged from the hospital after the day 8 administration of intravenous micafungin, but were required to return for remaining daily micafungin infusions.

P Group 1: days 4, 6, 7 and 8 only; Group 2: days 4, 6 and 8 only

Q A 24-hour post dose pharmacokinetic sample (relative to the infusion start time of the last dose) was collected after the final dose of micafungin on day 11, 12, 13, 14 or 15.

PHARMACOKNIETICS: Pharmacokinetic parameters were established from the patients in Group 1. Analyte concentration data were collected on micafungin,

metabolite 1 [M1], metabolite 2 [M2], and metabolite 5 [M5]. Parameters included: area under the plasma micafungin concentration-time curve from t = 0 hr (time of dosing) to 24 hours postinfusion (AUCtau) and micafungin Cmax at steady-state, t1/2, tmax, clearance and volume of distribution during the elimination phase [Vz]. In general, M2 was close to or below the lower limit of quantification, and no pharmacokinetic parameters were estimated.

REASONS FOR WITHDRAWAL:

1. Patient did not fulfill the inclusion or did fulfill exclusion criteria
2. AE
3. Withdrawal of consent
4. Patient lost to follow-up
5. Protocol violation
6. Investigator felt it was in the patient's best interest
7. Astellas elected to terminate the study
8. Patient required the use of a prohibited treatment or medication

MO Comment: *Study 98-0-047 withdrew patients who required therapy with another systemic anti-fungal agent, while patients lost to follow-up were not considered withdrawals.*

ADVERSE EVENTS: AE were assessed regularly during the study from first dosing on day 1 through the EOS visit. Any signs or symptoms present on day 1 before the first dose of study drug were recorded as baseline conditions in the medical history. All AE and SAE were captured on the source documents and eCRFs up to the EOS. Spontaneously reported SAE that occurred after EOS up to 30 days after the last dose of study drug were captured on the SAE worksheet and not on the eCRF.

STATISTICS: Two populations were identified for analysis as follows:

- Safety analysis set (SAF) consisted of those enrolled patients who received at least one dose of micafungin. The SAF combined patients from Groups 1 and 2 for reporting. The SAF was used for summaries of demographic and baseline characteristics and all safety and tolerability related variables.
- Pharmacokinetic analysis set (PKAS) consisted of all Group 1 patients in the SAF for whom sufficient plasma micafungin concentration data were available to facilitate the derivation of at least one pharmacokinetic parameter.

Descriptive statistics for continuous variables included the number of patients, mean, geometric mean, SD, SE, median, minimum, maximum and coefficient of variation (CV). Frequencies and percentages were used to describe categorical data.

EVALUATION OF SAFETY: Safety was assessed by evaluating the following variables:

- Treatment-emergent adverse events (TEAE)
- Clinical laboratory results (hematology and serum chemistry)
- Vital sign measurements (systolic and diastolic blood pressure, temperature and heart rate)
- Physical examination findings
- ECG findings

PROTOCOL CHANGES: Significant protocol changes are included below. These changes did not affect PWR compliance.

- The addition of a safely visit 14 days after final dose of study drug
- Modification of exclusion criteria to allow patients who previously enrolled in clinical trials that did not involve an investigational drug or were for primary cancer therapy.
- The addition of an ECG and GGT to safety monitoring
- Extend monitoring of AE from 3 days after last infusion to 14 days
- Modification of inclusion criteria to allow patients with suspected *Candida* infection
- Removal of requirement for completion of pharmacokinetic cohort before enrollment in safety cohort and allow for additional safety cohort beyond n = 12.

RESULTS:

Table 9 Data Analysis Sets

Analysis Set	Number of Patients by Treatment Group						Total
	3 mg/kg			4.5 mg/kg			
	2 - 5 Years	6 - 11 Years	12 - 16 Years	2 - 5 Years	6 – 11 Years	12 - 16 Years	
Overall†	**(n = 1)**	**(n = 13)**	**(n = 12)**	**(n = 31)**	**(n = 20)**	**(n = 1)**	**(n = 78)**
Safety Analysis Set‡	1 (100%)	13 (100%)	12 (100%)	31 (100%)	20 (100%)	1 (100%)	78 (100%)
Pharmacokinetic	0	4 (30.8%)	8 (66.7%)	8 (25.8%)	3 (15.0%)	1 (100%)	24 (30.8%)
Group 1¶	**(n = 0)**	**(n = 4)**	**(n = 11)**	**(n = 11)**	**(n = 10)**	**(n = 1)**	**(n = 37)**
Safety Analysis Set‡	0	4 (100%)	11 (100%)	11 (100%)	10 (100%)	1 (100%)	37 (100%)
Pharmacokinetic Analysis Set§	0	4 (100%)	8 (72.7%)	8 (72.7%)	3 (30.0%)	1 (100%)	24 (64.9%)
Group 2††	**(n = 1)**	**(n = 9)**	**(n = 1)**	**(n = 20)**	**(n = 10)**	**(n = 0)**	**(n = 41)**
Safety Analysis Set‡	1 (100%)	9 (100%)	1 (100%)	20 (100%)	10 (100%)	0	41 (100%)

Adapted from Astellas study 2101 report p. 39
†Six patients who registered but never received study drug are not counted in the summary
‡All enrolled patients who received at least one dose of micafungin
§All patients in the Safety Analysis Set for whom sufficient plasma micafungin concentration data were available to facilitate the derivation of AUC_{tau}, excluding patients with outlier data (Pharmacokinetic Analysis Set)
¶Patients with serial pharmacokinetic panel on day 7
††Patients with trough pharmacokinetic data only

MO Comment: *Per protocol, the study had anticipated enrolling 60 patients, 24 in Group 1 and 36 in Group 2. While they met those goals, the patient distribution is uneven. The study had anticipated 8 patients per age cohort in Group 1 and 12 patients per age cohort in Group 2. The 6-11 year cohort in group 1 only has 7 PKAS patients enrolled.*

Although eighty-four patients were enrolled in this study, only 78 of these patients received at least one dose of study drug. Other patients excluded:

- *9 patients with full pharmacokinetic profiles that were identified as outliers and were replaced from the PKAS*
- *1 patient with 2 abnormally high micafungin concentrations was excluded from the PKAS.*
- *3 patients who did not obtain full pharmacokinetic profiles were excluded from the PKAS.*
- *4 patients in Group 2 identified as low exposure outliers in preliminary pharmacokinetic analysis and were excluded from descriptive statistics in the safety analysis.*

Table 10 Demographics and Other Baseline Characteristics

Characteristic	Micafungin Treatment Group						Total (n = 78)
	3 mg/kg			4.5 mg/kg			
	2 - 5 Years (n = 1)	6 - 11 Years (n = 13)	12 - 16 Years (n = 12)	2 - 5 Years (n = 31)	6 - 11 Years (n = 20)	12 - 16 Years (n = 1)	
Sex, n (%)							
Male	1 (100%)	6 (46.2%)	6 (50%)	14 (45.2%)	9 (45%)	1 (100%)	37 (47.4%)
Female	0	7 (53.8%)	6 (50%)	17 (54.8%)	11 (55%)	0	41 (52.6%)
Race, n (%)							
White	1 (100%)	6 (46.2%)	9 (75%)	12 (38.7%)	3 (15%)	1 (100%)	32 (41%)
Black or African-American	0	7 (53.8%)	3 (25%)	17 (54.8%)	17 (85%)	0	44 (56.4%)
Asian	0	0	0	1 (3.2%)	0	0	1 (1.3%)
Other	0	0	0	1 (3.2%)	0	0	1 (1.3%)
Ethnicity, n (%)							
Non-Hispanic or Latino	0	12 (92.3%)	8 (66.7%)	23 (74.2%)	19 (95%)	1 (100%)	63 (80.8%)
Hispanic or Latino	1 (100%)	1 (7.7%)	4 (33.3%)	8 (25.8%)	1 (5%)	0	15 (19.2%)
Age, yrs							
Mean (SD)	4.3	9.0 (1.36)	14.7 (1.67)	3.4 (1.19)	8.4 (1.50)	16.0	7.5 (4.26)
Median	4.3	8.6	14.9	3.3	8.0	16.0	7.43
Range	4.3, 4.3	7.4, 11.3	12.2, 16.9	2.0, 5.9	6.5, 11.3	16.0, 16.0	2.0, 16.9
Weight, kg							
Mean (SD)	27.7	32.2 (5.92)	54.1 (15.48)	13.7 (2.48)	18.9 (3.77)	23.0	24.6
Median	27.7	29.7	54.2	13.2	19.7	23.0	(15.74)
Range	27.7, 27.7	25.0, 44.0	26.0, 73.7	8.7, 19.0	12.0, 24.0	23.0, 23.0	18.7

Adapted from Astellas study 2101 report p. 42

All patients enrolled in the study who received at least one dose of micafungin (Safety Analysis Set)

MO Comment: *Study 98-0-047 did not provide demographic information for pediatric patients. Of all enrolled patients, 54.8% were male and 60.0% were Caucasian, 20.4% were Mestizo and 15.2% Black.*

Table 11 Final Diagnosis of Enrolling Fungal Infection

Fungal Infection	Type	Treatment Group		Total (n = 78)
		3 mg/kg (n = 26)	4.5 mg/kg (n = 52)	
Proven	Esophageal	1 (3.8%)	9 (17.3%)	10 (12.8%)
	Fungemia	9 (34.6%)	14 (26.9%)	23 (29.5%)
	Invasive fungal infection	1 (3.8%)	1 (1.9%)	2 (2.6%)
Probable	Esophageal	5 (19.2%)	23 (44.2%)	28 (35.9%)
	Invasive fungal infection	1 (3.8%)	0	1 (1.3%)
Suspected	Unknown	9 (34.6%)	5 (9.6%)	14 (17.9%)

Adapted from Astellas study 2101page 42.

All patients enrolled in the study who received at least one dose of micafungin (Safety Analysis Set)

MO Comment: *In Study 98-0-047, 46.4% of all infections were esophageal and 35.9% were blood infections. All infections in 98-0-047 were culture confirmed, however, in study 2101, probable or suspected were permitted due to problems with low patient enrollment.* (b) (4) *only patients who received 3 mg/kg for the treatment of esophageal candidiasis will be examined as part of the efficacy assessment.*

Pharmacokinetic Results:

Table 12 Summary of Study Drug Exposure, PKAS

3 mg/kg Treatment Group	2 - 5 Years (n = 0)	6 - 11 Years (n = 4)	12 - 16 Years (n = 8)	Total (n = 12)
Duration, days < 10 ≥ 10 Mean(SD) Median Min, Max	N/A	1 (25%) 3 (75%) 12.0 (3.6) 13.0 7, 15	1 (12.5%) 7 (87.5%) 13.3 (4.2) 13.5 8, 22	2 (16.7%) 10 (83.3%) 12.8 (3.9) 13.5 7, 22
Total Cumulative Dose, mg Mean (SD)	N/A	1257.5 (433.8)	1853.4 (659.2)	1654.8 (643.4)
Total Cumulative Dose, mg/kg Mean (SD)	N/A	35.5 (10.4)	34.2 (15.2)	34.6 (13.3)
Mean Daily Dose, mg Mean (SD)	N/A	103.2 (13.3)	140 (16.4)	127.7 (23.4)
Mean Daily Dose, mg/kg Mean (SD)	N/A	3 (0.1)	2.6 (0.4)	2.8 (0.4)
4.5 mg/kg Treatment Group	**2 - 5 Years (n = 8)**	**6 - 11 Years (n = 3)**	**12 - 16 Years (n = 1)**	**Total (n = 12)**
Duration, days < 10 ≥ 10 Mean (SD) Median Min, Max	2 (25%) 6 (75%) 11.0 (2.7) 10 9, 17	0 3 (100%) 10 (0) 10 10, 10	0 1 (100%) 10 10 10, 10	2 (16.7%) 10 (83.3%) 10.7 (2.2) 10 9, 17
Total Cumulative Dose, mg Mean (SD)	581 (133.3)	900 (206.2)	1040	699 (225.3)
Total Cumulative Dose, mg/kg Mean (SD)	48.3 (13.1)	45 (0)	45.2	47.2 (10.6)
Mean Daily Dose, mg Mean (SD)	53.9 (12.8)	90 (20.6)	104	67.1 (24)
Mean Daily Dose, mg/kg Mean (SD)	4.4 (0.2)	4.5 (0)	4.5	4.4 (0.2)

Adapted from Astellas study 2101 report, p. 46

All patients in the Safety Analysis Set for whom sufficient plasma micafungin concentration data were available to facilitate the derivation of AUC_{tau}, excluding patients with outlier data (Pharmacokinetic Analysis Set)

Max: maximum; Min: minimum; N/A: not applicable; PKAS: Pharmacokinetic Analysis Set

Table 13 Summary of Study Drug Exposure, SAF

3 mg/kg Treatment Group	2 - 5 Years (n = 1)	6 - 11 Years (n = 13)	12 - 16 Years (n = 12)	Total (n = 26)
Duration, days				
< 10	0	5 (38.5%)	3 (25%)	8 (30.8%)
≥ 10	1 (100%)	8 (61.5%)	9 (75%)	18 (69.2%)
Mean (SD)	10	11.2 (5.8)	11.3 (4.6)	11.2 (5.1)
Median	10	10	10.5	10
Min, Max	10, 10	4, 27	4, 22	4, 27
Total Cumulative Dose, mg Mean (SD)	829.5	1049.3 (500.6)	1528.8 (733.8)	1262.1 (650)
Total Cumulative Dose, mg/kg Mean (SD)	30	33 (16.6)	29.9 (14.8)	31.4 (15.2)
Mean Daily Dose, mg Mean (SD)	82.9	95.7 (17.8)	134.3 (22.6)	113.1 (28.1)
Mean Daily Dose, mg/kg Mean (SD)	3	3	2.6 (0.4)	2.8 (0.3)
4.5 mg/kg Treatment Group	**2 - 5 Years (n = 31)**	**6 - 11 Years (n = 20)**	**12 - 16 Years (n = 1)**	**Total (n = 52)**
Duration, days				
< 10	7 (22.6%)	3 (15.0%)	0	10 (19.2%)
≥ 10	24 (77.4%)	17 (85.0%)	1 (100%)	42 (80.8%)
Mean SD)	10 (2.2)	9.8 (1.5)	10	9.9 (1.91)
Median	10	10	10	10
Min, Max	5, 17	7, 14	10, 10	5, 17
Total Cumulative Dose, mg Mean (SD)	606.8 (143.9)	831.3 (223.6)	1040	701.5 (212.4)
Total Cumulative Dose, mg/kg Mean (SD)	45 (10.2)	43.9 (6.4)	45.2	44.6 (8.8)
Mean Daily Dose, mg Mean (SD)	61.4 (11.5)	84.6 (17.3)	104	71.1 (18.4)
Mean Daily Dose, mg/kg Mean (SD)	4.5 (0.3)	4.5 (0.1)	4.5	4.5 (0.2)

Adapted from Astellas study 2101, p. 47
All patients enrolled in the study who received at least one dose of micafungin (Safety Analysis Set)
Max: maximum; Min: minimum; SAF: Safety Analysis Set

MO Comment: *16.7% of patients in the PKAS and 30.8% of patients in the SAF did not meet the minimum study goal of 10 days of study drug. In general the cumulative dose given to the SAF was lower than the PKAS population, consistent with the inclusion criteria for the SAF population. Weight adjusted daily dose between the two populations was essentially the same.*

Table 14 Plasma Micafungin Pharmacokinetic Parameters on Day 7, Group 1, 3 mg/kg

Parameter		6 - 11 Years (n = 4)	12 - 16 Years (n = 8)	Adult patients with Esophageal Candidiasis [Day 1]	Adult patients with Esophageal Candidiasis [Day 14]
AUC_{tau}, hr•mcg/mL	Mean (SD) CV Median Min, Max Geo. mean	247.5 (46.4) 18.7 249 191.8, 300.1 244.1	193.3 (30.9) 16 184.5 158.9, 240.1 191.2	151 ± 45	167 ± 40
C_{max}, mcg/mL	Mean (SD) CV Median Min, Max Geo. mean	20.8 (4.1) 19.9 20.8 16.8, 24.8 24.5	20.5 (10.3) 50.3 16.1 12.2, 44.5 18.9	11.6 ± 3.1	16.4 ± 6.5
$t_{1/2}$, hr	Mean (SD) CV Median Min, Max Geo. mean	14.3 (1.9) 13 14.2 12.3, 16.6 14.2	11.3 (2.8) 24.8 10.3 9.1, 17.3 11	14.1 ± 2.6	15.2 ± 2.2
CL_{ss}/ Wt, mL/hr/kg	Mean (SD) CV Median Min, Max Geo. mean	12.3 (2.4) 19.6 11.9 10, 15.4 12.1	13.5 (3.1) 22.9 12.6 9.5, 19 13.2	20.4±5.5	17.82±4.8

Adapted from Astellas study 2101 report, p. 53

AUC_{tau}: area under the plasma analyte concentration-time curve from t = 0 (time of dosing) to 24 hours postinfusion; C_{avg}: average plasma analyte concentration over 24 hrs postinfusion start; CL_{ss}/Wt: weight-normalized CL_{ss};

Table 15 Plasma Micafungin Pharmacokinetic Parameters on Day 7, Group 1, 4.5 mg/kg

Parameter		2 - 5 Years (n = 8)	6 - 11 Years (n = 3)	12 - 16 Years (n = 1)	Adult patients with Esophageal Candidiasis [Day 1]	Adult patients with Esophageal Candidiasis [Day 14]
AUC_{tau}, hr•mcg/mL	Mean (SD) CV Median Min, Max Geo. mean	248.9 (68.1) 27.4 247.5 110, 335.4 238.3	278.4 (41.6) 14.9 264.3 245.6, 325.2 276.4	339 N/A 339 339, 339 339.020	151 ± 45	167 ± 40
C_{max}, mcg/mL	Mean (SD) CV Median Min, Max Geo. mean	21.125 (6.1038) 28.89 21.850 8.40, 28.70 20.059	20.700 (3.0806) 14.88 20.200 17.90, 24.00 20.550	24.9 N/A 24.9 24.9, 24.9 24.9	11.6 ± 3.1	16.4 ± 6.5
$t_{1/2}$, hr	Mean (SD) CV Median Min, Max Geo. mean	12.8 (1.9) 14.8 12.7 10.2, 16.9 12.7	11.8 (1.1) 9.6 11.2 11.1, 13.1 11.8	17.4 N/A 17.4 17.4, 17.4 17.4	14.1 ± 2.6	15.2 ± 2.2
CL_{ss}/Wt, mL/hr/kg	Mean (SD) CV Median Min, Max Geo. mean	20 (8.9) 44.5 18.3 13.4, 40.9 18.8	16.4 (2.3) 14.1 17 13.8, 18.3 16.3	13.3 N/A 13.3 13.3, 13.3 13.3	20.4±5.5	17.8±4.8

Adapted from Astellas study 2101 page 55

AUC_{tau}: area under the plasma analyte concentration-time curve from t = 0 (time of dosing) to 24 hours postinfusion; C_{avg}: average plasma analyte concentration over 24 hrs postinfusion start; CL_{ss}: total body clearance at steady-state; CL_{ss}/Wt: weight-normalized CL_{ss};

MO Comment: *Tables 12 and 13 show that micafungin clearance in pediatric patients decreases with age. Thus, exposure to micafungin increases with age until adulthood. In the adult population treated for esophageal candidiasis, the clearance is similar to pediatric patients 2-5 years old, but higher than pre and adolescent children.*

Safety Results*:*

Table 16 Patient Disposition

Patient Disposition	Number (%) of Patients by Treatment Group						Total (n = 78)
	3 mg/kg			4.5 mg/kg			
	2 - 5 Years (n = 1)	6 - 11 Years (n = 13)	12 - 16 Years (n = 12)	2 - 5 Years (n = 31)	6 - 11 Years (n = 20)	12 - 16 Years (n = 1)	
End of Therapy							
Completed therapy	1 (100%)	8 (61.5%)	8 (66.7%)	24 (77.4%)	17 (85%)	1 (100%)	59 (75.6%)
Reason for discontinuation:							
Adverse event	0	0	2 (16.7%)	1 (3.2%)	1 (5%)	0	4 (5.1%)
Withdrew consent†	0	0	0	0	1 (5%)	0	1 (1.3%)
Sponsor elected to discontinue‡	0	2 (15.4%)	0	2 (6.5%)	0	0	4 (5.1%)
Other§	0	3 (23.1%)	2 (16.7%)	4 (12.9%)	1 (5%)	0	10 (12.8%)
End of Study							
Completed study¶	1 (100%)	9 (69.2%)	10 (83.3%)	26 (83.9%)	16 (80%)	1 (100%)	63 (80.8%)
Reason for discontinuation							
: Death	0	0	1 (8.3%)	0	2 (10%)	0	3 (3.8%)
Lost to follow-up	0	0	1 (8.3%)	0	0	0	1 (1.3%)
Other††	0	4 (30.8%)	0	5 (16.1%)	2 (10%)	0	11 (14.1%)

Adapted from the 2101 study report p. 40
All patients enrolled in the study who received at least one dose of micafungin (Safety Analysis Set)
†Not related to an adverse event
‡Sponsor decided to discontinue subject
§Other reasons for discontinuing therapy were: patient discharged from hospital (6 patients), death, unable to establish iv access, worsening of retroviral disease and insufficient venous access (1 patient each)
¶Includes patients who discontinued therapy but stayed until the end of study
†† Other reasons for discontinuing study were: Sponsor decided to discontinue patient (6 patients), patient discharged from hospital and switched to po, patient did not return for final visit, due to patient improvement only 9 days of study drug were administered, loss of iv access and patient withdrew consent (1 patient each)

MO Comment: *Of all patients in study 98-0-047, 62.6% completed study, 28.7% died and 5.1% were lost to follow-up. It should be noted that study 98-0-047 had a significantly longer duration of study drug. Of those that withdrew from the study, 18.8% was due to an adverse event.*

In study 2101, end of therapy discontinuation reasons included adverse events in 4 patients (generalized pruritic rash, low magnesium, febrile seizure and fever), withdrawal of consent in 1 patient (not related to AE), 4 patients in which the sponsor elected to discontinue and 10 patients listed as 'other' [death (1), discharge (6), loss of IV access (2), worsening of retroviral disease (1)]

End of study discontinuation reasons included 3 patients who died, 1 patient lost to follow-up and 11 patients listed as 'other' [discharge (2), did not return for final visit (1), sponsor discontinued patient (6), loss of IV access (1), withdrawal of consent (1)]

5 additional patients at site 2260 (South Africa) were discontinued from the study due to a cluster of fever/pyrexia. No conclusive cause was identified by the sponsor, which has attributed the events to concomitant conditions in the patient population at the site.

Table 17 Number of Patients with Treatment Emergent Adverse Events

Adverse Events	Micafungin Treatment Group						Total (n = 78)
	3 mg/kg			4.5 mg/kg			
	2 - 5 Years (n = 1)	6 - 11 Years (n = 13)	12 - 16 Years (n = 12)	2 - 5 Years (n = 31)	6 - 11 Years (n = 20)	12 - 16 Years (n = 1)	
Any TEAE	1 (100%)	9 (69.2%)	11 (91.7%)	25 (80.6%)	16 (80%)	0	62 (79.5%)
Drug-related TEAE	0	3 (23.1%)	5 (41.7%)	12 (38.7%)	8 (40%)	0	28 (35.9%)
Deaths	0	0	1 (8.3%)	0	2 (10%)	0	3 (3.8%)
SAE other than death	0	1 (7.7%)	3 (25%)	3 (9.7%)	2 (10%)	0	9 (11.5%)
Drug-related SAE	0	0	1 (8.3%)	1 (3.2%)	0	0	2 (2.6%)
TEAE leading to discontinuation of study drug	0	0	2 (16.7%)	1 (3.2%)	1 (5%)	0	4 (5.1%)
Drug-related TEAE leading to permanent discontinuation of	0	0	2 (16.7%)	1 (3.2%)	1 (5%)	0	4 (5.1%)

Adapted from Astellas study 2101 page 58.
All patients enrolled in the study who received at least one dose of micafungin (Safety Analysis Set)
Treatment-emergent adverse events occurred from first dose date to last dose date of study drug plus 3 days. SAE: serious adverse event(s); TEAE: treatment-emergent adverse event(s)

MO Comment: *Upon reviewer's analysis of the study data, the nine patients listed with SAE other than death appear to include the two patient deaths. No trends in age or dose dependency of AE were identified, although the small sample size limits analysis.*

In study 98-0-047, 93.3% of pediatric patients experienced any treatment emergent adverse event. 33.3% of pediatric patients had a treatment emergent adverse event related to study drug. 16.7% of pediatric patients died and 16.7% of pediatric patients also experienced an adverse event that led to the discontinuation of study drug. 6.7% of pediatric patients had an adverse event related to study drug that led to discontinuation. In the pivotal adult EC efficacy study 005, 77.7% of subjects experienced TEAE, 13.5% Serious TEAE, 6.2% of patients discontinued the study due to AE and 11.5% died. The most common TEAE reported were phlebitis (15.4%), fever (13.1%), diarrhea (10.4%), and pneumonia (9.6%). The safety profile of micafungin at 3-4.5 mg/kg dose in pediatric patients 2-<17 years is comparable to the micafungin safety profile in the adult patients

receiving 150 mg of micafungin for treatment of EC.

Table 18 Patient Deaths

Patient No.	Age (yrs)/ Sex	Days of Treatment /Day of Death	Primary Cause of Death	Relationship to Study Drug	Related to Fungal Infection	Contributing Conditions Leading to Death	Primary Underlying Disease
3 mg/kg Treatment Group							
00051245	16.5/F	11/12	Intracranial hemorrhage	Not related	No	None	Liver disease, autoimmune hepatitis
00051253†	16.9/F	22/43	Hepatic infarction, hemorrhagic pancreatitis, renal failure, respiratory failure	Not related	No	Heart transplant, pancreatitis, nonalcoholic steatohepatitis, ERCP stent placement	Heart disease, dilated cardiomyopathy
4.5 mg/kg Treatment Group							
12211203	9.5/M	10/15	Suspected pneumonia	Not related	No	None	HIV
12211207	10.2/F	7/8	Suspected pneumonia	Not related	No	None	HIV

Adapted from Astellas study 2101, p. 61
All patients enrolled in the study who received at least one dose of micafungin (Safety Analysis Set)
† Not included in clinical study database; information from safety database
ERCP: endoscopic retrograde cholangiopancreatography; HIV: human immunodeficiency virus

MO Comment: *Of the five pediatric patients (16.7%) that died in study 98-0-047, the causes of death included carcinoma, heart failure, leukemia, pneumonia, and respiratory failure.*

Of the four patients that died during study 2101, causes of death are listed in Table 14. The first patient had received a liver transplant during the study for her autoimmune hepatitis and worsening encephalopathy. She was also noted to have GI bleeding and severe thrombocytopenia at baseline. She had received the liver transplant two days prior to starting study drug, but experienced worsening of her mental status on day four and was found to have hyperdense lesions felt to be consistent with abscesses. Although coverage was broadened, on day 5 she was found to have a devastating intracranial bleed and medical support was withdrawn. Given the complex and serious concomitant medical conditions experienced by this patient, it is unlikely micafungin was the underlying cause of her intracranial bleed and decompensation.

The second patient's primary underlying disease was HIV and baseline medical conditions included increased LFTs, and pneumonia. His pneumonia was treated during the study and was considered resolved by day 5 of the study. On day 15, the patient's

mother reported the patient died of natural causes. The investigator suspected pneumonia as the underlying cause. Antiretroviral medications were not listed among concomitant medications.

The third patient's primary underlying disease was HIV with esophageal candidiasis. The investigator prematurely discontinued the study drug as there was no improvement in the candidiasis and the retroviral disease was worsening. On day 8, one day after study drug discontinuation, the patient deteriorated and appeared to have developed pneumonia. Ceftriaxone was started, but the patient died the same day. Antiretroviral medications were not listed among concomitant medications.

The fourth patient's primary underlying disease was dilated cardiomyopathy and was status post second heart transplant. The patient had multiple serious concomitant medical conditions including renal impairment, pseudocysts, history of acute rejection and sepsis, pancreatitis and pulmonary hypertension. Two days after the patient's last dose of study medication, the patient experienced worsening abdominal distension with decompensation. Imaging revealed increased pancreatic pseudocysts which were drained, however the patient developed a hepatic hemorrhage and acute renal failure. Shortly after, the family elected to pursue comfort measures only and the patient subsequently died. Given the patient's complex and serious medical history, it is unlikely that her death was secondary to the study drug.

Overall, these four deaths do not seem to be secondary to micafungin exposure. Although adverse events including anemia and thrombocytopenia have been associated with micafungin, no other serious coagulation issues have been reported. Patients 00051245 and 00051253 had extensive and complex medical histories, and it is unlikely that micafungin contributed to their deaths. Patients 12211203 and 12211207 both were diagnosed with HIV and pneumonia. Neither of these deaths is likely secondary to micafungin.

Table 19 Serious Adverse Events Other Than Death

Patient No.	Micafungin Treatment Days	Age (years) /Sex	MedDRA (v5.0) Preferred Term	Onset/ Stop Day	Outcome	Relationship to Study Drug	Primary Underlying Disease
3 mg/kg Treatment Group							
00051124	14	15.7/M	Intestinal perforation NOS	3/5	Recovered with residual effect	Not related	Non-Hodgkin's lymphoma
00051230	27	7.6/M	Klebsiella sepsis	16/19	Recovered no residual effect	Not related	Line sepsis
			Hyperglycaemia NOS	25/26	Recovered no residual effect	Not related	
00711241	8	16.3/M	Hypomagnesaemia	4/ongoing	Persistent condition	Possible	Acute myelogenous leukemia
			Ventricular tachycardia	4/4	Recovered no residual effect	Possible	
			Hypokalaemia	4/9			
			Hypocalcaemia	4/10			
4.5 mg/kg Treatment Group							
02491236	10	3.9/M	Haematemesis	24/27	Recovered no residual effect	Not related	Neuroblastoma
			Thrombocytopenia	24/43			
02491237	11	7.0/F	Hypokalaemia	9/13	Recovered no residual effect	Not related	Acute lymphocytic leukemia
02491239†	14	2.0/F	Candidiasis Hypokalaemia Hyponatraemia Hypophosphataemia	37/44 37/42 37/44 40/43	Recovered no residual effect	Not related	Dysmotility syndrome
04641247	11	2.1/M	Central line infection	21/30	Recovered no residual effect	Not related	Pneumonia
04641250	9	3.9/F	Febrile neutropenia	10/14	Recovered no residual effect	Not related	Acute myelogenous leukemia
18881118	10	5.8/M	Lymph node tuberculosis NOS	4/ongoing	Persistent condition	Not related	HIV
22601219	6	5.2/M	Infusion associated symptoms	6/6	Recovered no residual effect	Probable	HIV
24461251†	10	5.0/F	Device related sepsis‡	30/51	Recovered no residual effect	Not related	Short gut syndrome

Adapted from Astellas study 2101 report, p. 63
All patients enrolled in the study who received at least one dose of micafungin (Safety Analysis Set)
† Not included in clinical study database; information from safety database
‡ MedDRA (v14.1) term

MO Comment: *Drug-related SAEs occurred in two patients and included ventricular tachycardia, infusion associated symptoms, hypocalcaemia, hypokalaemia and hypomagnesaemia. Hypokalemia, hypomagnesaemia and infusion related symptoms are labeled adverse events.*

Table 20 TEAE Leading to Permanent Discontinuation of Study Drug

Patient No.	Micafungin Treatment Days	Age (years)/ Sex	MedDRA (v5.0) Preferred Term	Onset/ Stop Day	Outcome	Relationship to Study Drug
3 mg/kg Treatment Group						
00051127	6	14.9/F	Infusion associated symptoms	6/13	Recovered no residual effect	Possible
00711241	8	16.3/M	Hypomagnesaemia	4/ongoing	Persistent condition	Possible
4.5 mg/kg Treatment Group						
22601219	6	5.2/M	Infusion associated symptoms	6/6	Recovered no residual effect	Probable
22601224	7	6.5/F	Pyrexia	6/7	Recovered no residual effect	Probable

Adapted from Astellas study 2101 report, p. 66
All patients enrolled in the study who received at least one dose of micafungin (Safety Analysis Set)

MO Comment: *Most common adverse reaction resulting in micafungin discontinuation was infusion reaction.*

Table 21 Treatment Emergent Adverse Events Reported for At Least 3% of All Patients

MedDRA (v5.0) System Organ Class Preferred Term	Micafungin Treatment Group					Total (n = 78 †)
	3 mg/kg			4.5 mg/kg		
	2 - 5 Years (n = 1)	6 - 11 Years (n = 13)	12 - 16 Years (n = 12)	2 - 5 Years (n = 31)	6 - 11 Years (n = 20)	
Any TEAE	**1 (100%)**	**9 (69.2%)**	**11 (91.7%)**	**25 (80.6%)**	**16 (80%)**	**62 (79.5%)**
Blood and Lymphatic System Disorders	**1 (100%)**	**3 (23.1%)**	**4 (33.3%)**	**7 (22.6%)**	**3 (15%)**	**18 (23.1%)**
Anaemia NOS	0	1 (7.7%)	1 (8.3%)	2 (6.5%)	1 (5%)	5 (6.4%)
Anaemia NOS aggravated	1 (100%)	0	0	1 (3.2%)	2 (10%)	4 (5.1%)
Leukopenia NOS	0	1 (7.7%)	1 (8.3%)	2 (6.5%)	0	4 (5.1%)
Thrombocytosis	0	0	1 (8.3%)	2 (6.5%)	0	3 (3.8%)
Cardiac Disorders	**0**	**3 (23.1%)**	**2 (16.7%)**	**4 (12.9%)**	**0**	**9 (11.5%)**
Bradycardia NOS	0	1 (7.7%)	1 (8.3%)	3 (9.7%)	0	5 (6.4%)
Gastrointestinal Disorders	**1 (100%)**	**4 (30.8%)**	**6 (50%)**	**8 (25.8%)**	**4 (20%)**	**23 (29.5%)**
Abdominal pain aggravated	0	2 (15.4%)	1 (8.3%)	0	0	3 (3.8%)
Abdominal pain	0	1 (7.7%)	1 (8.3%)	0	2 (10%)	4 (5.1%)
NOS Vomiting NOS	0	1 (7.7%)	2 (16.7%)	6 (19.4%)	1 (5%)	10 (12.8%)

General Disorders and Administration Site Conditions	**1 (100%)**	**5 (38.5%)**	**5 (41.7%)**	**12 (38.7%)**	**8 (40%)**	**31 (39.7%)**
Infusion associated symptoms	0	1 (7.7%)	2 (16.7%)	4 (12.9%)	2 (10%)	9 (11.5%)
Infusion site pain	1 (100%)	1 (7.7%)	1 (8.3%)	2 (6.5%)	1 (5%)	6 (7.7%)
Mucosal inflammation NOS	0	1 (7.7%)	1 (8.3%)	0	1 (5%)	3 (3.8%)
Pain NOS	0	1 (7.7%)	1 (8.3%)	1 (3.2%)	1 (5%)	4(5.1%)
Pyrexia	0	3 (23.1%)	1 (8.3%)	8 (25.8%)	7 (35%)	19 (24.4%)
Rigors	0	3 (23.1%)	1 (8.3%)	2 (6.5%)	4 (20%)	10(12.8%)
Infections and Infestations	**0**	**3 (23.1%)**	**4 (33.3%)**	**6 (19.4%)**	**4 (20%)**	**17 (21.8%)**
Staphylococcal bacteremia	0	1 (7.7%)	1 (8.3%)	1 (3.2%)	0	3 (3.8%)
Investigations	**0**	**3 (23.1%)**	**3 (25.0%)**	**3 (9.7%)**	**3 (15%)**	**12 (15.4%)**
ALT increased	0	0	0	2 (6.5%)	1 (5%)	3 (3.8%)
AST increased	0	0	0	2 (6.5%)	1 (5%)	3 (3.8%)
GGT increased	0	0	0	2 (6.5%)	1 (5%)	3 (3.8%)
Metabolism and Nutrition Disorders	**1 (100%)**	**5 (38.5%)**	**6 (50.0%)**	**7 (22.6%)**	**5 (25%)**	**24 (30.8%)**
Dehydration	0	0	0	2 (6.5%)	1 (5%)	3 (3.8%)
Fluid retention	0	0	2 (16.7%)	0	1 (5%)	3 (3.8%)
Hyperglycaemia NOS	0	1 (7.7%)	0	2 (6.5%)	1 (5%)	4 (5.1%)
Hypocalcaemia	0	0	2 (16.7%)	1 (3.2%)	1 (5%)	4 (5.1%)
Hypokalaemia	1 (100%)	4 (30.8%)	1 (8.3%)	3 (9.7%)	2 (10%)	11 (14.1%)
Hypomagnesemia	0	1 (7.7%)	3 (25%)	3 (9.7%)	1 (5%)	8 (10.3%)
Hypophosphatemia	0	0	0	1 (3.2%)	3 (15%)	4 (5.1%)
Musculoskeletal and Connective Tissue Disorders	**0**	**1 (7.7%)**	**2 (16.7%)**	**1 (3.2%)**	**0**	**4 (5.1%)**
Arthralgia	0	0	2 (16.7%)	1 (3.2%)	0	3 (3.8%)
Respiratory, Thoracic and Mediastinal Disorders	**0**	**1 (7.7%)**	**3 (25.0%)**	**4 (12.9%)**	**4 (20.0%)**	**12 (15.4%)**
Respiratory	0	1 (7.7%)	1 (8.3%)	1 (3.2%)	1 (5.0%)	4 (5.1%)
Vascular Disorders	**0**	**0**	**5 (41.7%)**	**4 (12.9%)**	**0**	**9 (11.5%)**
Hypertension NOS	0	0	4 (33.3%)	2 (6.5%)	0	6 (7.7%)
Hypotension NOS	0	0	3 (25.0%)	0	0	3 (3.8%)
Psychiatric Disorders	**0**	**3 (23.0%)**	**1 (8.3%)**	**0**	**0**	**4 (5.1%)**
Anxiety	0	3 (23.0%)	1 (8.3%)	0	0	4 (5.1%)

Adapted from Astellas study 2101 report, p. 59
All patients enrolled in the study who received at least one dose of micafungin (Safety Analysis Set) Treatment-emergent adverse events occurred from first dose date to last dose date of study drug plus 3 days.
Within a SOC, the patient may have reported more than one type of adverse event.
† One patient in the 4.5 mg/kg, 12 to 16 years age cohort did not experience any TEAEs.
ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: gamma-glutamyltransferase; NOS: not otherwise specified; TEAE: treatment-emergent adverse event(s)

MO Comment: *Adverse events regardless of causality occurred in the majority of study patients. Although, clearance of/exposure to micafungin appears to be age dependent, no clear age/exposure response in the incidence of TEAE was identified.*

The frequency of some classes of events was higher in the 3 mg/kg group than in the 4.5 mg/kg group:

- Blood and lymphatic disorders: 3 mg/kg group, 8/26 (30.7%); 4.5 mg/kg group, 10/52 (19.2%)
- Cardiac disorders: 3 mg/kg group, 5/26 (19.2%); 4.5 mg/kg group, 4/52 (7.7%)
- Gastrointestinal disorders: 3 mg/kg group, 11/26 (42.3%); 4.5 mg/kg group, 12/52 (23.1%)
- Investigations: 3 mg/kg group, 6/26 (23.1%); 4.5 mg/kg group, 6/52 (11.5%)
- Metabolism and nutritional disorders: 3 mg/kg group, 12/26 (46.2%); 4.5 mg/kg group, 12/52 (23.1%)
- Musculoskeletal disorders: 3 mg/kg group, 3/26 (11.5%); 4.5 mg/kg group, 1/52 (1.9%)
- Vascular disorders: 3 mg/kg group, 5/26 (19.2%); 4.5 mg/kg group, 4/52 (7.7%)
- Psychiatric disorders: 3mg/kg group 4/26 (15.38%); 4.5 mg/kg group, 0/52 (0%)

MO Comment*: While overall frequency of broad categories of treatment-emergent adverse events appeared higher in the 3 mg/kg age group, several specific adverse events occurred more frequently in the 4.5 mg/kg group. These adverse events included elevation of transaminases and GGT and fever. Specific adverse events that occurred more frequently in the 3 mg/kg age group included hypokalemia, hypomagnesemia, hypertension, hypotension, anxiety, and aggravated abdominal pain. There was no evidence of a dose-dependent trend towards more AEs in either of the dosage groups. The 3 mg/kg group included more adolescent patients who were more likely be exposed to higher concentrations of micafungin, than the younger patients who demonstrated increased medication clearance.*

Drug-related TEAEs occurred in 28 patients and included anemia, ventricular tachycardia, abdominal pain NOS, diarrhea NOS, loose stools, vomiting NOS, infusion site associated symptoms, infusion site burning, infusion site phlebitis, pain NOS, pyrexia, rigors, AST/ALT increased, lactate increased, triglycerides increased, GGT increased, hypoalbuminemia, hypocalcaemia, hypokalaemia, hypomagnesaemia, hyponatraemia aggravated, hypophosphataemia, headache, proteinuria, cough, hypertension and phlebitis NOS.

MO Comment: *In study 98-0-047, two pediatric patients (6.7%) experienced treatment emergent adverse events related to study drug that led to discontinuation, which included elevated transaminases and rash.*

EFFICACY: Among patients with invasive candidiasis or candidemia who did not receive other systemic antifungal medication for more than one day during micafungin treatment, clinical success and mycological success were each reported for 14/16 (87.5%) patients. For patients with esophageal candidiasis and suspected candidiasis, clinical success was reported for 34/36 (94.4%) and 8/10 (80.0%) patients, respectively. Of the 38 patients with esophageal candidiasis, 10 had proven esophageal candidiasis and 28 had probable esophageal candidiasis. Among 10 patients with proven EC, 9 received micafungin at 4.5 mg/kg, a dose 50% greater than the sponsor's proposed dose for this indication. A single pediatric patient with proven EC who received 3 mg/kg dose had documented a successful clinical outcome at EOT. Endoscopic evaluation of cure has not been performed in this study.

MO Comment: *Although the sponsor is using efficacy data from this study to support micafungin efficacy in esophageal candidiasis in pediatric patients, it is difficult to conclude that the study provide sufficient supportive efficacy information for the indication of EC in pediatric patients, due to significant differences in doses of/exposures to micafungin and outcome assessment. Evidence of micafungin efficacy in EC comes from adequate and well controlled studies in adults and PK bridging approach,* (b) (4) *3 mg/kg, results in micafungin exposure similar to or greater than that of adults receiving 150 mg dose.*

CONCLUSIONS: Study 2101 was conducted in response to a PWR, in which the Division has requested a minimum of 8 evaluable patients per age cohort to examine the pharmacokinetics/safety of micafungin. However, only seven patients were evaluable for pharmacokinetic analysis in the 6 – 11 year age group. Astellas has therefore fallen short in fulfilling the study requirements as specified by the PWR. In the safety analysis group, which did enroll sufficient numbers of patients, no dose-dependent adverse reaction trends were appreciated. Pharmacokinetics analyses demonstrated increased clearance in younger patients, and increased exposure to study drug among older patients (6-<17y). The study was not designed to assess efficacy, and does not provide supportive evidence for the treatment of esophageal candidiasis in the pediatric population. The safety profile of micafungin at 3-4.5 mg/kg once daily in pediatric patients 2-<17 years is comparable to the micafungin safety profile in the adult population of patients with EC receiving 150 mg dose.

5.3.2 Study 2102

Study 2102: A Phase 1, Open-Label Study of the Safety and Pharmacokinetics of Repeated-Dose Micafungin (FK463) in Infants and Toddlers (≥ 4 Months to < 24 Months of Age) with Esophageal Candidiasis or Other Invasive Candidiasis

5.3.2.1 Methods

INVESTIGATORS: 6 investigators, 5 of whom enrolled patients

STUDY CENTERS: 6 centers, 5 enrolled patients (6 U.S.)

STUDY PERIOD: 22-October 2007 to 08-October 2009

OBJECTIVES: The objective of the study was to evaluate the pharmacokinetics and safety of intravenous (IV) micafungin (FK463) after repeated daily dosing at 4.5 mg/kg in infants and toddlers (≥ 4 months to < 24 months of age) with proven or probable esophageal candidiasis or other invasive candidiasis or suspected *Candida* infection.

METHODOLOGY: Prospective, multicenter, open-label, repeat-dose study.

NUMBER OF SUBJECTS: Nine patients were enrolled in the study, all of whom received at least one dose of the study medication.

STUDY DRUG: Micafungin was infused in normal saline at a dose of 4.5 mg/kg. The study drug lot number was 707057K. Each vial contained 50 mg of lyophilized micafungin and 200 mg lactose with citric acid and/or sodium hydroxide.

DURATION OF TREATMENT: Micafungin was administered at a daily dose of 4.5 mg/kg for injection over 1 hour at the same time every morning for a minimum of 10 consecutive days to a maximum of 14 consecutive days.

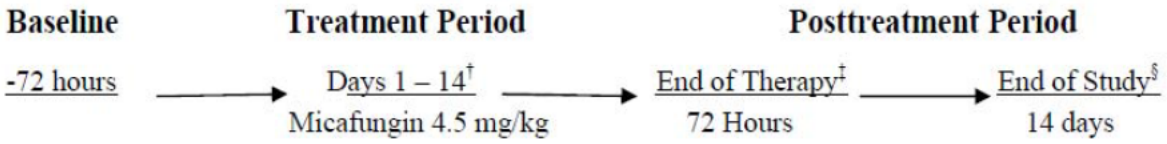
TREATMENT COMPLIANCE: Patients remained hospitalized until at least day 8 administration of IV micafungin. Patients discharged after day 8 returned for daily infusions of micafungin on an outpatient basis.

STUDY DESIGN: This was a prospective, multicenter, open-label, repeat-dose study to evaluate the pharmacokinetics and safety of micafungin in infants and toddlers (≥ 4 months to < 24 months of age). Serial blood samples were drawn on day 7 at predose ("0" hr) and 1, 2, 4 and 10 hours postdose. Single blood samples were trough analyte including micafungin and metabolites M1, M2 and M5, were drawn predose on days 4, 6 and 8. An end of therapy (EOT) visit was performed within 72 hours after the final micafungin infusion and an end of study (EOS) visit was performed 14 days (+/- 2 days) after the final micafungin infusion. For patients enrolled prior to the adoption of Amendment 2 which added a follow-up safety visit 14 days after the last dose of study

drug, EOS assessments were made at 3 days instead of 14 days after the final micafungin infusion; therefore, for these patients, EOS may have been the same as EOT.

Figure 2 Study 2102 Flow Diagram

Figure 1 Study Flow Diagram



† Patient could be dosed for a minimum of 10 to a maximum of 14 consecutive days.

‡ End of therapy (EOT) was the period between the last dose of study drug and up to 72 hours (3 days) after the last dose of study drug (i.e., if the patient received the maximum of 14 consecutive days of study drug then the EOT procedures could be performed up to day 17).

§ End of study (EOS) was 14 days after the last dose of study drug ± 2 days (i.e., if the patient received 14 consecutive days of study drug then EOS was day 28). For patients enrolled prior to the adoption of Amendment 2, EOS assessments were made at 3 days instead of 14 days after the end of therapy; therefore, for these patients, EOS may have been the same as EOT.

APPEARS THIS WAY ON ORIGINAL

written request (PWR) issued in May 2007 and most recently amended in August, 2012. The PWR stipulations were generally fulfilled by the study. The type of study, objectives, age groups, and study endpoints were adhered to as specified by the PWR.

SAMPLE SIZE: Infants and toddlers (≥ 4 months to < 24 months of age) with proven or probable esophageal candidiasis or other invasive candidiasis or suspected *Candida* infections were enrolled. Planned enrollment was approximately 8 patients.

INCLUSION CRITERIA: A patient was eligible for the study if all of the following applied:

1. IRB/IEC-approved written informed consent and privacy language as per national regulations (e.g., HIPAA Authorization for US sites) was obtained from the patient's parent(s) or legally authorized representative prior to any study-related procedures (including withdrawal of prohibited medications, if applicable).
2. Patient was ≥ 4 months to < 24 months of age.
3. Patient's parent(s) or legally authorized representative agreed to comply with the study requirements and with the concomitant medication restrictions.
4. Patient had sufficient venous access to permit administration of study medication, collection of pharmacokinetic samples and monitoring of laboratory safety variables.
5. Patient had **proven** or **probable** candidiasis as evidenced by 5a, 5b, 5c or 5d:
    a. Proven or probable esophageal candidiasis documented within 5 days prior to the first dose of study drug as follows:

i. Diagnosis of esophageal candidiasis by endoscopy (as per institution standard of care according to age) AND/OR presence of oropharyngeal candidiasis; AND clear signs/symptoms of esophagitis AND
ii. At least one clinical symptom of esophageal candidiasis with a grade > 0 at baseline
iii. Histological/cytological and culture confirmation of infection from esophageal brushings and biopsy must have been obtained if endoscopy was performed; however, the cytological and culture confirmation results could be pending at the time study drug was initiated. Histological results were to be available within 24 hours prior to first dosing.

b. Proven candidemia or other invasive candidiasis documented as follows
   i. A positive culture and/or histology from a sample obtained no more than 96 hours prior to the first dose of study medication (or positive culture within the last 4 weeks for chronic invasive candidiasis) AND
   ii. At least one typical clinical sign or symptom. Patients with positive signs or symptoms not listed in the protocol, but in the opinion of the Investigator were supportive of a fungal infection, could be enrolled with permission of the Medical Monitor.
   iii. For candidemia, preliminary evidence of yeast (by staining and microscopy of the blood culture sample) could be used to enroll the child; in these instances confirmation of *Candida* species must have been obtained within 1 week after first dosing.
   iv. For invasive candidiasis, culture results could be pending at the time of enrollment if histology/cytology revealed yeast.
c. Probable candidiasis
   i. A positive scan consistent with chronic, disseminated (hepatosplenic) candidiasis AND
   ii. Clinical signs or symptoms noted by the Investigator that were consistent with the above diagnosis.
d. Suspected *Candida* infection documented as follows:
   i. Patients who required broad spectrum antibiotics and were at risk for invasive *Candida* infection AND
   ii. Persistent fever of 100.4°F (38°C) for which there was no known etiology OR
   iii. A recurrent fever of > 100.4°F (> 38°C) on two measurements of temperature at least 3 hours apart or a single measurement of 101.3°F (38.5°C).

MO Comment: *The sponsor conducted a number of efficacy studies that are of relevance to the study under review: study 005 (pivotal adult study in esophageal candidiasis), study 2109 (supportive phase 2 adult study in study in esophageal candidiasis), study 003 (phase 2 adult dose finding study in EC) and study 047.*

Micafungin doses selected for evaluation in the study under review were thought to closely approximate exposures achieved at the approved 150 mg dose for EC in adults that was evaluated for efficacy and safety in studies 2109 and 005. Due to significant differences in design between the study under review and the pivotal efficacy studies for EC in adults the comparison of efficacy outcomes between the two studies is difficult. Study 98-0-047 was a phase 2 open-label noncomparative multinational study evaluating the efficacy of micafungin in the treatment of adult and pediatric patients diagnosed with candidemia or invasive candidiasis. Patients were started on a dose of 50 mg (1 mg/kg for patients <40 kg) or 100 mg (2 mg/kg for patients <40kg) for non-C. albicans. The dose could be increased in 50 mg increments to a maximum of 200 mg (4 mg/kg for patients <40kg) in the event of continued symptoms after five days of medication administration.

Inclusion criteria for study 98-0-047 included positive blood culture within 96 hours, biopsy with invasive fungal elements, characteristic lesions visualized endoscopically and confirmed by biopsy. Chronic disseminated candidiasis was defined by characteristic signs and symptoms as well as positive blood culture or biopsy. Patient with persistent or intermittent fever and abdominal imaging consistent with disseminated disease were also considered to have possible infection.

These inclusion criteria are more stringent than those observed by 9463-CL-2102 and do not rely upon clinical symptomatology. Study 98-0-047 does include patients with "typical clinical signs and symptoms" of candidemia or invasive candidiasis, but requires culture confirmation.

EXCLUSION CRITERIA: Patients were excluded from participation if any of the following applied:

1. Patient had evidence of significant liver disease, as defined by aspartate aminotransferase (AST), alanine aminotransferase (ALT), bilirubin or alkaline phosphatase > 5 times the upper limit of normal (ULN).
2. Patient had a concomitant medical condition that in the opinion of the Investigator and/or medical monitor precluded enrollment into the study.
3. Patient had history of anaphylaxis, hypersensitivity or any serious reaction to the echinocandin class of antifungals.
4. Patient had received treatment with an echinocandin within 1 week prior to first dosing.
5. Patient status was unstable and was unlikely to complete required study procedures.
6. Patient had participated in another clinical trial involving an investigational drug within 30 days or 5 half-lives of the drug, whichever is longer, prior to day 1 of the study, except for those trials involving primary cancer therapy.
7. Patient was previously enrolled in this study.
8. Patient had yeast or mold-like infection other than invasive candidiasis or candidemia.

9. Patient whose diagnosis of invasive candidiasis was based on evidence of infection limited to a positive culture for *Candida* sputum, or broncho-alveolar lavage, vascular catheter tip, or urinary catheter drainage. However, patients with a positive urine culture obtained via in/out catheterization or suprapubic aspiration, who had signs and symptoms of upper urinary tract disease, could be enrolled.

MO Comment: *Study 98-0-047 excluded patients with abnormal transaminases > 10x ULN and patients who required other systemic antifungal agents. They did not explicitly exclude patients with a diagnosis based urinary, BAL or sputum results, or yeast/mold infections.*

STUDY PROCEDURES: The micafungin dose of 4.5 mg/kg per day was used to approximate the exposure observed in adults at a dose of 150 mg/day. Micafungin was infused in normal saline over 1 hour (+/- 3 min) at a final concentration of 0.5 to 4.0 mg/mL; the maximum volume infused was not to exceed 100 mL. It was recommended that dose concentrations > 1.5 mg/mL be infused through a central catheter line to minimize the potential for infusion related toxicity. Micafungin was administered at approximately the same time every morning for a minimum of 10 consecutive days to a maximum of 14 consecutive days (per Investigator judgment). The use of concomitant systemic antifungal therapy (except for other echinocandins) was allowed at a stable, consistent dose during the study.

Table 22 Schedule of Assessments

PROCEDURES	Baseline	Study Day						
		1	2-6	7	8-10	11-14	EOT[a]	EOS[b]
Informed Consent	X							
Demographics and medical history	X							
Record clinical symptoms of EC, OC, or IC[c]	X[c,d]						X[c]	
Assessment of fungal infection[e]	X[d,e]						X[e]	
Physical examination	X[f]	X					X	
Weight	X[f]	X		X			X	X
Electrocardiogram[g]	X[f,g]	X[g]					X[g]	
Vital signs (BP, heart rate, body temperature), height[h]	X[f]	X	X	X	X	X	X	X
Clinical laboratory tests[i]	X[f,i]	X[i]				X[i]	X[i]	X[i]
Microbiology/histopathology[j]	X[j]							
Evaluation of inclusion/exclusion Criteria	X	X						
Antifungal and concomitant medication	X[k]	X	X	X	X	X	X	X
Adverse event recording		X	X	X	X	X	X	X
Micafungin dosing (infusion over 1 hr)[l]		X	X	X	X[l]	X[l]		
Pharmacokinetic Blood								
Predose ("0 hr")[n]			X	X	X			

1 hr; 1 mL/ sample				X				
2 hr; 1 mL/ sample				X				
4 hr; 1 mL/ sample				X				
10 hr; 1 mL/ sample				X				

Adapted from Astellas study 2102 report, p. 21
BP: blood pressure; EOT: end of therapy; EOS: end of study; EC: esophageal candidiasis; OC: oropharyngeal candidiasis; IC: invasive candidiasis.
[a] EOT visit occurred within 72 hours after the final micafungin dose was administered.
[b] EOS visit occurred 14 days (} 2 days) after the final micafungin dose was administered. For patients enrolled prior to the adoption of Amendment 2, EOS assessments were made at 3 days instead of 14 days after the end of therapy; therefore, for these patients, EOS may have been the same as EOT.
[c] Patient with esophageal candidiasis must have at least one clinical symptom of oropharyngeal candidiasis with a grade > 0 at baseline for enrollment
[d] Completed within 5 days prior to first dosing.
[e] Documentation of infection using institution standard of care.
[f] Completed within 72 hours prior to first dosing
[g] 12-lead ECG with 10 second rhythm strip were obtained within 72 hours prior to first dosing, once between day 4 and day 8 (within +/- 15 min of the end of the micafungin infusion) and at the EOT visit.
[h] Height (length) recorded once within 72 hours prior to first dosing. Vital signs were taken at baseline and twice daily (prior to the start of the infusion and within 1 hour postinfusion) during study drug therapy, at EOT and at EOS. On days when pharmacokinetic sampling was scheduled (days 4, 6, 7 and 8), predose vital signs were taken before pharmacokinetic blood draws.
[i] Clinical lab samples were collected within 72 hours prior to first dosing, once between day 2 and day 7, once between day 8 and day 14 (each weekly draw separated by at least three days), at the EOT visit and at the EOS visit. See Section 5.4.3.4 for lab variables measured.
[j] Tissue or fluid sample from infected sites for fungal culture stains and histopathologic examination if locus of infection was readily accessible for sampling and clinically indicated.
[k] Treatment associated with patient's underlying condition (including immunosuppressives, chemotherapy and antiinfectives) and any antifungals (oral, nonabsorbable and systemic) received in the 14 days prior to first dose of study drug were recorded. Use of all concomitant medications, both prescribed and over-the-counter, from baseline to EOS was recorded**.** Patient could not have received echinocandin therapy for 1 week prior to first dose or during the study.
[l] Micafungin administered for 10 to 14 days per Investigator clinical judgment. Patients could be discharged from the hospital after the day 8 administration of IV micafungin, but were required to return daily for remaining micafungin infusions.
[m] Serial blood samples for micafungin analysis following IV dosing of micafungin were collected relative to the start of the day 7 one-hour micafungin infusion. The first serial pharmacokinetic blood sample drawn was not to be collected from the same location used for study drug infusion.
[n] Predose sample was collected within 10 minutes prior to the start of infusion on days 4, 6, 7 and 8.

EVALUATION OF EFFICACY: This study was not designed to demonstrate efficacy, however a clinical assessment of fungal infection was captured. The investigator provided a clinical assessment of fungal infection at baseline and EOT. Information on the status of clinical signs and symptoms were recorded in the source document and eCRFs along with any additional supportive documentation (e.g., whether a negative culture, endoscopy or additional testing was obtained).

PHARMACOKNIETICS: The pharmacokinetic analyses were performed using model-independent, noncompartmental methods using analyte (micafungin, metabolite 1 [M1], metabolite 2 [M2] and metabolite 5 [M5]) concentration data. The primary pharmacokinetic parameters for micafungin were AUC_{tau} and C_{max} at steady state. The

same parameters were estimated for the micafungin metabolites when sufficient measurable concentrations were available. Other pharmacokinetic parameters (e.g., t., t_{max}, clearance and volume of distribution) were estimated for micafungin, with t_{max} estimated for all analytes.

REASONS FOR WITHDRAWAL: Reasons for withdrawal of a patient from the study included:

1. Patient did not fulfill inclusion or exclusion criteria
2. AE(s)
3. Withdrawal of consent
4. Patient was lost to follow-up
5. Protocol violation
6. Investigator felt it was in the patient's best interest
7. Sponsor elected to terminate the study
8. Patient required the use of a prohibited treatment or medication

Any patient terminating the study prior to completion had all EOT and EOS procedures completed unless consent was withdrawn.

***MO Comment**: Study 98-0-047 withdrew patients who required therapy with another systemic anti-fungal agent. Patient's lost to follow-up were not considered withdrawals.*

ADVERSE EVENTS: Any signs or symptoms present on day 1 before the first dose of study drug were recorded as baseline conditions in the medical history. AEs were recorded from the time of first dosing through the EOS visit. Baseline conditions that exacerbated during the study were recorded as AEs. AEs ongoing at the final visit were followed up for as long as necessary to adequately evaluate the patient's safety or until the event stabilized.

STATISTICS: Approximately 8 male and female infants and toddlers were enrolled into the study. This sample size was determined in order to assess the pharmacokinetics and safety of micafungin in the indicated population at the dose of 4.5 mg/kg for the treatment of esophageal candidiasis and other invasive candidiasis. The sample size chosen for this study was based upon precedent set by other studies of similar nature, and not on statistical considerations

- Safety analysis set (SAF): The SAF consisted of those enrolled patients who received at least 1 dose of micafungin. The SAF was used for summaries of demographic and baseline characteristics and all safety related variables.
- Pharmacokinetic Analysis Set (PKAS): The PKAS consisted of patients in the SAF for whom sufficient micafungin concentration data were available to facilitate derivation of at least 1 pharmacokinetic parameter

The M1 and M5 pharmacokinetic parameters were estimated using the scheduled time and a modification of elapsed time, where the scheduled 24-hour time was imputed as 24 (e.g., 24.5 hr was imputed as 24). Missing data were not imputed, except for the missing hour 24 analyte concentrations for Patient 04272003, which were imputed using the predose concentrations. Micafungin was assumed to have reached steady state.

EVALUATION OF SAFETY: Safety was assessed by evaluating the following variables:

- Extent of exposure to study drug
- Treatment-emergent adverse events (TEAEs)
- Clinical laboratory results (hematology and serum chemistry)
- Vital sign measurements (systolic and diastolic BP, temperature and heart rate)
- Physical examination findings
- ECG findings

PROTOCOL CHANGES: Protocol changes are included as follows. These changes did not affect PWR compliance.

- The addition of a safety visit 14 days after final dose of study drug.
- The modification of study criteria to allow enrollment of patients who previously participated in clinical trials that did not involves an investigational drug or were for primary cancer therapy.
- The addition of an ECG and GGT to the safety analysis
- Extend monitoring of AE from 3 days after last infusion to 14 days.
- Modification of inclusion criteria to allow patients with suspected *Candida* infection

RESULTS:

Table 23 Patient Disposition

Patient Disposition	**Micafungin 4.5 mg/kg**
End of Treatment	
Completed treatment	5 (55.6%)
Discontinued treatment	4 (44.4%)
Reason for discontinuation:	2 (22.2%)
Adverse event	2 (22.2%)
End of Study	
Completed study	7 (77.8%)
Discontinued study	2 (22.2%)
Reason for discontinuation:	
Death	1 (11.1%)
Lost to follow-up	1 (11.1%)

Adapted from Astellas study 2102 report, p 32

All patients enrolled in the study who received at least 1 dose of micafungin (Safety Analysis Set).

†Other reasons were 1) treatment failure and 2) fungal infection cleared by Day 8, patient was clinically stable and ready for hospital discharge.

The final diagnosis of the enrolling fungal infection was proven fungemia for 5 (55.6%) patients and suspected infection for 4 (44.4%) patients.

MO Comment: *Study 2102 had anticipated enrolling eight patients. Even with the exclusion of patient No. 00520006, they met the study goal. Only 55.6% of patients completed the prespecified study treatment. Two patients discontinued the study due to an adverse event including heart failure on day 10 of treatment and worsening liver function enzymes on day 8 of treatment. Two patients discontinued micafungin study treatment due to 'other' reasons, including discharge on day 8 of treatment and treatment failure on day 8 of treatment. Treatment protocol specified a minimum of ten days of treatment*

Of all patients in study 98-0-047, 62.6% completed study, 28.7% died and 5.1% were lost to follow-up. It should be noted that study 98-0-047 had a significantly longer duration of study drug. Of those that withdrew from the study, 18.8% was due to an adverse event.

Table 24 Demographics and Other Baseline Characteristics

Characteristic	Micafungin 4.5 mg/kg
Sex, n (%)	
Male	7 (77.8%)
Female	2 (22.2%)
Race, n (%)	
White	8 (88.9%)
Asian	1 (11.1%)
Ethnicity, n (%)	
Non-Hispanic or Latino	3 (33.3%)
Hispanic or Latino	6 (66.7%)
Age, months	
Mean (SD)	8.78
Median	(4.944)
Range	9.00
Weight, kg	
Mean (SD)	6.53
Median	(1.814)
Range	6.48

Adapted from Astellas study 2102 report, p 34

All patients enrolled in the study who received at least 1 dose of micafungin (Safety Analysis Set).

MO Comment: *Study 98-0-047 did not provide demographic information for pediatric patients. Of all enrolled patients, 54.8% were male and 60.0% were Caucasian, 20.4% were Mestizo and 15.2% Black.*

Prior to study drug therapy, 4 (44.4%) patients received non-systemic antifungal therapy and 7 (77.8%) patients received systemic antifungal therapy. During study drug therapy, 4 (44.4%) patients received non-systemic antifungal therapy and 4 (44.4%) patients received systemic antifungal therapy. After study drug therapy, 2 (22.2%) patients received nonsystemic antifungal therapy and 5 (55.6%) patients received systemic antifungal therapy.

Table 25 Summary of Study Drug Exposure

Parameter	Micafungin 4.5 mg/kg	
	Safety Analysis Set (n=9)	Pharmacokinetic Analysis Set (n=8)
Duration, days		
< 10	4 (44.4%)	3 (37.5%)
≥ 10	5 (55.6%)	5 (62.5%)
Mean (SD)	10.11 (2.205)	10.25 (2.315)
Median	10.00	10.00
Range	8.0 – 14.0	8.0 – 14.0
Cumulative Dose, mg		
Mean (SD)	279.8 (63.64)	281.1 (67.90)
Median	268.9	265.2
Range	216.0 – 414.0	216.0 – 414.0
Cumulative Dose, mg/kg		
Mean (SD)	44.44 (10.03)	45.13 (10.49)
Median	45.09	45.32
Range	32.2 – 64.4	32.2 – 64.4
Mean Daily Dose, mg		
Mean (SD)	28.72 (8.411)	28.58 (8.979)
Median	29.00	28.00
Range	17.0 – 41.5	17.0 – 41.5
Mean Daily Dose, mg/kg		
Mean (SD)	4.39 (0.218)	4.40 (0.231)
Median	4.51	4.51
Range	4.0 – 4.6	4.0 – 4.6

Adapted from Astellas study 2102 report, p. 36

All patients enrolled in the study who received at least 1 dose of micafungin (Safety Analysis Set).

All patients from the Safety Analysis Set for whom sufficient plasma micafungin concentration data were available to facilitate derivation of at least 1 pharmacokinetic parameter (Pharmacokinetic Analysis Set).

MO Comment: *Four (44.4%) patients received less than 10 days of study drug therapy and 5 (55.6%) received at least 10 days of study drug therapy. Reasons for discontinuation included: death, elevated LFTs, discharge, and treatment failure.*

Pharmacokinetic Results

Trough micafungin, M1 and M5 concentrations were measurable in all patient samples on days 4, 6, 7 and 8. Plasma micafungin concentrations from all 8 patients in the PKAS were used in the calculation of micafungin pharmacokinetic parameters (Table 26). Similarly, plasma M1 and M5 concentrations from all 8 patients were used in the calculation of M1 and M5 pharmacokinetic parameters [Table 27]. Plasma M2 pharmacokinetic parameters were not calculated due to the low plasma concentrations of this metabolite.

Table 26 Plasma Micafungin Pharmacokinetic Parameters on Day 7

Parameter		Micafungin 4.5 mg/kg (n=8)	Adult patients with Esophageal Candidiasis [Day 1]	Adult patients with Esophageal Candidiasis [Day 14]
AUC_{tau}, hr*mcg/mL	Mean (SD) CV% Median Range Geometric mean	299.422 (140.1897) 46.82 263.795 187.97 – 622.17 278.354	151 ± 45	167 ± 40
C_{max}, mcg/mL	Mean (SD) CV% Median Range Geometric mean	32.825 (22.7115) 69.19 21.700 18.20 – 84.80 28.286	11.6 ± 3.1	16.4 ± 6.5
$T_{1/2}$, hr	Mean (SD) CV% Median Range	11.078 (4.8574) 43.85 10.381 5.46 – 21.78	14.1 ± 2.6	15,2 ± 2.2
CL_{ss}/Wt, mL/hr/kg	Mean (SD) CV% Median Range Geometric mean	16.673 (5.2965) 31.77 16.411 7.25 – 24.23 15.793	20.4±5.5	17.82±4.8

Adapted from Astellas study 2102 report, p. 41

All patients in the Safety Analysis Set for whom sufficient plasma micafungin concentration data were available to facilitate the derivation of at least 1 pharmacokinetic parameter (Pharmacokinetic Analysis Set).

CV: coefficient of variation; CL_{ss}: total body clearance at steady state; CL_{ss}/Wt: weight normalized total body clearance at steady state;

Table 27 Plasma M1 and M5 Pharmacokinetic Parameters on Day 7, PKAS

Parameter		Micafungin 4.5 mg/kg (n=8)	
		M1 (n=8)	M5 (n=8)
AUC_{tau}, hr*mcg /mL	Mean (SD)	27.898 (20.4420)	68.794 (53.6256)
	CV%	73.2274	77.95
	Median	19.085	50.291
	Range	11.91 – 73.26	7.40 – 189.22
	Geometric mean	23.274	51.564
C_{max}, mcg/mL	Mean (SD)	1.332 (0.9086)	3.265 (2.2393)
	CV%	68.24	68.58
	Median	0.862	2.870
	Range	0.60 – 3.27	0.38 – 8.21
	Geometric mean	1.128	2.548
t_{max}, hr	Mean (SD)	9.750 (9.4529)	4.000 (2.7775)
	CV%	96.95	69.44
	Median	7.000	4.000
	Range	1.00 – 24.00	1.00 – 10.00

Adopted from Astellas study 2102 report, page 43

CV: coefficient of variation; PRc_{max}: C_{max}(M1 or M5)/C_{max}(micafungin); PR_{AUC}: AUC_{tau}(M1 or M5)/AUC_{tau} (micafungin).

MO Comment: *Table 7 demonstrates that in adults micafungin has longer half-live and lower C maxi as compared to young children. Young pediatric patients have clearance values approaching that of adult. At 4.5 mg/kg dose exposure to the study medication is higher than in adults at 150mg dose. In children relative proportions of M1 metabolite to parent micafungin exposure (AUC) was 9.3%. For the metabolite M5, the relative proportion was 23.0%. The adult population with esophageal candidiasis given micafungin at a dose of 150mg had relative proportions of 11% for M1, 2% for M2 and 12% for M5*

Safety Results

Table 28 Overview of Adverse Events

	Micafungin 4.5 mg/kg
Overall Adverse Events	
Overall adverse events during study	9 (100%)
Overall serious adverse events during study	5 (55.6%)
Deaths	1 (11.1%)

Treatment-emergent Adverse Events	
Treatment-emergent adverse events	9 (100%)
Treatment-emergent serious adverse events	3 (33.3%)
Treatment-emergent adverse events related to study drug	1 (11.1%)
Treatment-emergent adverse events leading to discontinuation of study drug	2 (22.2%)

Adapted from Astellas study 2102 report, p. 44

All patients enrolled in the study who received at least 1 dose of micafungin (Safety Analysis Set).

MO Comment: *In study 2102, one TEAE was considered related to study drug by the sponsor. This event occurred in a 19-month-old male with acute lymphocytic leukemia who experienced a worsening of liver function tests. The patient had elevated LFTs at baseline with an AST of 48 U/L and an ALT of 63 U/L. Treatment was discontinued on day 8 and on day 9 AST was 137 U/L and ALT was 143 U/L. On day 22, AST was 658 U/L and ALT was 476 U/L, The patient had a complex medical history, however this event could possibly be related to study drug administration.*

One patient died during the study; a 9-month-old white boy, died of cardiac failure on study day 11. The patient's primary underlying disease was hypoplastic left heart syndrome. He pulled out his central venous line and then developed shock and could not be resuscitated. His cause of death was documented as heart failure and bacteremia. It is unlikely to be related to the study drug.

The two adverse events that led to study drug discontinuation included the above episodes of elevated LFTs and death.

In study 98-0-047, 93.3% of pediatric patients experienced any treatment emergent adverse event. 33.3% of pediatric patients had a treatment emergent adverse event related to study drug. 16.7% of pediatric patients died and 16.7% of pediatric patients also experienced an adverse event that led to the discontinuation of study drug. 6.7% of pediatric patients had an adverse event related to study drug that led to discontinuation.

Of the five pediatric patients (16.7%) that died in study 98-0-047, the causes of death included carcinoma, heart failure, leukemia, pneumonia, and respiratory failure. In study 98-0-047, two pediatric patients (6.7%) experienced treatment emergent adverse events related to study drug that led to discontinuation, which included elevated transaminases and rash.

All patients experienced at least 1 TEAE. The more common types of SOCs were injury, poisoning and procedural complications (66.7%), investigations (66.7%), and general disorders and administration site conditions (55.6%). Only post-procedural pain was reported for more than 2 patients.

Table 29 Serious Adverse Events without an Outcome of Death

Patient No./ Micafungin Treatment Days	Age (months) /Sex	MedDRA (v. 5.0) Preferred Term (Investigator's Verbatim Term)	Onset/ Stop Day	Outcome	Relationship to Study Drug
00052006† Days 1-9	9/M	Oxygen saturation decreased (oxygen desaturation)	7/7	Recovered, no residual effect	Not related
		Hyperkalaemia (hyperkalemia)	7/7	Recovered, no residual effect	Not related
		Respiratory distress (respiratory distress)	7/7	Recovered, no residual effect	Not related
		Ventricular tachycardia (wide, complex ventricular tachycardia)	7/7	Recovered, no residual effect	Not related
		Bacteraemia (bacteremia)	11/11	Persistent condition at time of death	Not related
00052007 Days 1-8	4/M	Supraventricular tachycardia (supraventricular tachycardia)	5/6	Recovered, no residual effect	Not related
00052008 Days 1-13	11/F	Respiratory failure (respiratory decompensation) ‡	25/25	Recovered, no residual effect	Not related
02492004 Days 1-11	5/M	Haematochezia (bloody stools)	9/15	Recovered, no residual effect	Not related
		Pathological fracture (pathologic Bones) ‡	23/36	Recovered, no residual effect	Possibly related
04672005 Days 1-10	12/M	Staphylococcal bacteraemia (staphylococcus epidermidis bacteremia) ‡	22/34	Recovered, no residual effect	Not related

Adapted from Astellas study 2102 report, p 48
All patients enrolled in the study who received at least 1 dose of micafungin (Safety Analysis Set).
M: male; F: female;
† Patient 00052006 also had a serious adverse event of heart failure that lead to death.
‡ These were not treatment-emergent adverse events.

MO Comment: *Patient 00052006 ultimately died of cardiac failure and is discussed above. The above serious adverse events are not likely related to the study drug.*

Patient 00052007 had an underlying diagnosis of congestive heart failure with multiple cardiac anomalies including patent ductus arteriosus, subaortic ventricular septal defect, secundum atrial septal defect, atrial pacing and cardiomegaly. The patient had an abnormal ECG prior to initiation of study drug. Given the patient's complex cardiac history, it is unlikely the episode of SVT is secondary to study drug.

Patient 000520008 had a history of biliary atresia with end-stage liver disease status post liver transplant. The patient had multiple other concomitant conditions prior to study drug including respiratory failure. While re-taping the patient's endotracheal tube, the patient became hypoxic and required bagging. After repositioning the endotracheal tube, the event resolved. This event is not related to the study drug.

Patient 02492004 had an underlying diagnosis of coarctaction of the aorta, atrial septal

defect, ventricular septal defect, duodenal atresia with resection of small intestine, grossly bloody stools, g-tube placement, cholestasis secondary to parenteral nutrition and necrotizing enterocolitis. The patient developed bloody stool and was found to be infected with Clostridium difficile. This event is not related to the study drug. The patient also developed a pathological fracture secondary to osteopenia. Follow-up imaging did not identify callous formation, and the true existence of a fracture is questionable. This event was considered by the study investigator to be possibly related to study drug. The resection of small intestine and chronic illness can also lead to osteopenia and pathological fracture. It is unlikely this event was secondary to micafungin exposure.

Patient 04672005 had a history of short bowel syndrome with central line placement and developed Staphylococcus epidermidis bacteremia on day 22 and 25. This event is unlikely to be related to study drug.

Table 30 Treatment-emergent Adverse Events

MedDRA (v5.0) System Organ Class Preferred Term	**Micafungin 4.5 mg/kg (n=9)**
Any Adverse Event	**9 (100%)**
Cardiac Disorders	**4 (44.4%)**
Bradycardia NOS	1 (11.1%)
Cardiac failure NOS	1 (11.1%)
Supraventricular tachycardia	1 (11.1%)
Ventricular extrasystoles	1 (11.1%)
Ventricular tachycardia	2 (22.2%)
Congenital, Familial and Genetic Disorders	**1 (11.1%)**
Congenital intestinal malformation NOS	1 (11.1%)
Gastrointestinal Disorders	**4 (44.4%)**
Diarrhoea NOS	1 (11.1%)
Frequent bowel movements	1 (11.1%)
Gastrointestinal motility disorder NOS	1 (11.1%)
Haematochezia	1 (11.1%)
Impaired gastric emptying	1 (11.1%)
Vomiting NOS	1 (11.1%)
General Disorders and Administration Site Conditions	**5 (55.6%)**
Discomfort NOS	1 (11.1%)
Infusion site pain	1 (11.1%)
Oedema NOS	1 (11.1%)
Pyrexia	2 (22.2%)
Immune System Disorders	**1 (11.1%)**
Acquired hypogammaglobulinaemia	1 (11.1%)
Infections and Infestations	**2 (22.2%)**
Bacteraemia	1 (11.1%)
Clostridial infection NOS	1 (11.1%)
Enterococcal bacteraemia	1 (11.1%)
Staphylococcal bacteraemia	1 (11.1%)

MedDRA (v5.0) System Organ Class Preferred Term	**Micafungin 4.5 mg/kg (n=9)**
Injury Poisoning and Procedural Complications	**7 (77.8%)**
Feeding tube complication	1 (11.1%)
Hypothermia	1 (11.1%)
Medical device complication	1 (11.1%)
Post procedural pain	3 (33.3%)
Procedural site reaction	1 (11.1%)
Investigations	**6 (66.7%)**
Blood culture positive	1 (11.1%)
Blood phosphate decreased	1 (11.1%)
Blood triglycerides increased	1 (11.1%)
Fibrin D dimer increased	1 (11.1%)
Gamma-glutamyl transferase increased	1 (11.1%)
Liver function tests NOS abnormal	1 (11.1%)
Oxygen saturation decreased	1 (11.1%)
Metabolism and Nutrition Disorders	**3 (33.3%)**
Hyperkalaemia	1 (11.1%)
Hypoalbuminaemia	1 (11.1%)
Hypocalcaemia	1 (11.1%)
Hypoglycaemia NOS	2 (22.2%)
Hypokalaemia	2 (22.2%)
Hyponatraemia	1 (11.1%)
Hypoproteinaemia	1 (11.1%)
Psychiatric Disorders	**1 (11.1%)**
Agitation	1 (11.1%)
Reproductive System and Breast Disorders	**1 (11.1%)**
Scrotal swelling	1 (11.1%)
Respiratory, Thoracic and Mediastinal Disorders	**3 (33.3%)**
Atelectasis	1 (11.1%)
Dyspnoea NOS	1 (11.1%)
Nasal congestion	1 (11.1%)
Respiratory distress	1 (11.1%)
Tachypnoea	1 (11.1%)
Skin and Subcutaneous Tissue Disorders	**2 (22.2%)**
Dermatitis bullous	1 (11.1%)
Erythema	2 (22.2%)
Sweating increased	1 (11.1%)
Vascular Disorders	**1 (11.1%)**
Phlebothrombosis	1 (11.1%)

Adapted from Astellas study 2102 report, pp. 45-46
All patients enrolled in the study who received at least 1 dose of micafungin (Safety Analysis Set).
NOS: not otherwise specified.

MO Comment: *The total number of patients enrolled in 2102 was small, and makes meaningful conclusions regarding the safety of micafungin in this age group difficult. However, the data appears similar to previously reported adult data in the pivotal efficacy study for EC indication for micafungin 150 mg dose.*

Table 31 Adverse Events of Special Interest

Special Interest Category Preferred Term	**Micafungin 4.5 mg/kg (n=9)**
Any Adverse Event	**7 (77.8%)**
Cardiovascular	**4 (44.4%)**
Bradycardia NOS	1 (11.1%)
Supraventricular tachycardia	1 (11.1%)
Ventricular extrasystoles	1 (11.1%)
Ventricular tachycardia	2 (22.2%)
Hepatic	**2 (22.2%)**
Gamma-glutamyl transferase increased	1 (11.1%)
Liver function tests NOS abnormal	1 (11.1%)
Histamine Release	**2 (22.2%)**
Erythema	2 (22.2%)
Injection Site Reaction	**1 (11.1%)**
Infusion site pain	1 (11.1%)

All patients enrolled in the study who received at least 1 dose of micafungin (Safety Analysis Set).
NOS: Not otherwise specified.
Adapted from the study report, p. 50

EFFICACY: This study was not designed to evaluate micafungin efficacy and there were no protocol defined efficacy endpoints, however a clinical assessment of fungal infection was performed at baseline and EOT.

Five patients (Patient Nos. 02492002, 02492004, 02682001, 04272003 and 04672005), all of whom had a proven fungal infection at baseline, had a complete clinical response and eradication of their infection. Two patients (Patient Nos. 00052008 and 02492009) had a suspected infection at baseline and a complete clinical response. Patient No. 00052006 had a suspected infection at baseline and had a clinical response of “not successful”. Patient No. 00052007 had a suspected infection at baseline and had a clinical response of “not successful” and a mycological response of persistence. The patient had *Candida* infection of the blood on days 4 and 6 and discontinued the study on day 8.

CONCLUSIONS: Study 2102 was conducted in response to a PWR, which requested a minimum of 8 patients to examine the pharmacokinetics of micafungin in pediatric patients 4 months to 2 years of age. Astellas did enroll eight patients in 2102, and, thus, fulfilled the conditions outlined in the PWR. No dose-dependent adverse reactions trends were appreciated, and the safety profile was similar to that observed in adults and other pediatric studies. Pharmacokinetic analyses demonstrated increased micafungin clearance relative to adults. Children in other pharmacokinetic studies have also demonstrated increased clearance rates. The 4.5 mg/kg dose micafugnin exposure in children 4-24 month of age exceeded the exposures seen in the adult population given 150 mg doses.

5.3.1 Study 2103

Study 2103: A Phase 1 Open-Label Study of the Safety and Pharmacokinetics of Repeated-Dose Micafungin as Antifungal Prophylaxis in Children and Adolescents Undergoing Hematopoietic Stem Cell Transplantation

5.3.1.1 Methods

INVESTIGATORS: 13 investigators, 11 of whom enrolled patients

STUDY CENTERS: 13 sites, 11 of which enrolled patients (13 U.S.)

STUDY PERIOD: 16- Jan 2008 to 10-Mar 2009

OBJECTIVES: The objective of this study was to evaluate the pharmacokinetics and safety of intravenous (IV) micafungin after repeated daily dosing at either of 2 doses (1 mg/kg and 1.5 mg/kg) as prophylaxis in children and adolescents undergoing autologous, syngeneic, or allogeneic HSCT. Transplantation types may have included cord blood, peripheral stem cell, and bone marrow.

METHODOLOGY: Prospective, multi-center, open-label, repeat-dose pharmacokinetic study with two treatment arms

NUMBER OF SUBJECTS: 42 patients were enrolled in the study, 40 patients received study drug.

STUDY DRUG: IV micafungin was administered at a dose of 1.0 mg/kg to patients with a weight greater than or equal to 25 kg, or 1.5mg/kg to patients with a weight less than 25 kg. Patient received test drug as Mycamine in 50 mg/vial from lot number 707057K. Each vial contained 50mg of lyophilized micafungin and 200 mg of lactose with citric acid and/or sodium hydroxide. Micafungin was infused in dextrose in water or normal saline over 1 hour at a final concentration of 0.5 to 4.0 mg/mL. Maximum daily dose administered to any patient was 50 mg.

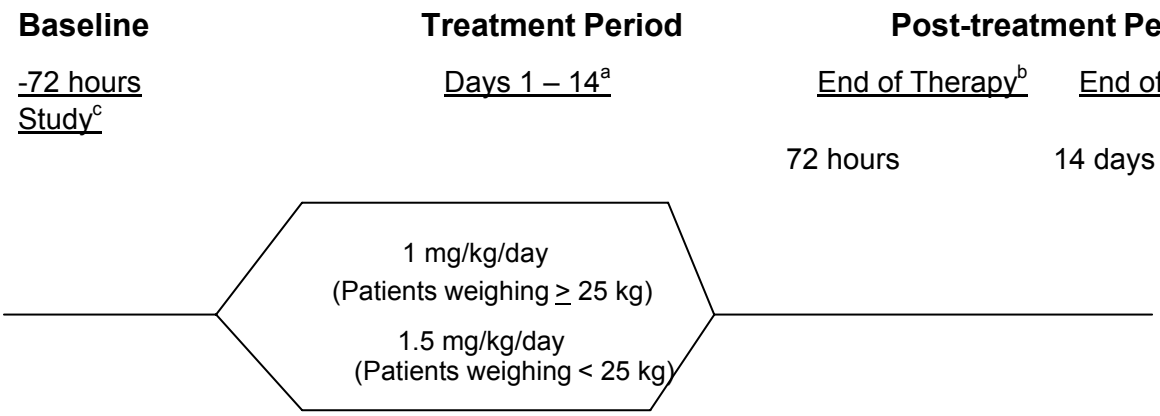
DURATION OF TREATMENT: Injections were given over one hour, once a day for 10 to 14 days. Micafungin was initiated within 48 hours of the start of the patient's transplant-related conditioning regimen.

TREATMENT COMPLIANCE: Study drug was administered by site personnel and documentation of administration was provided on the electronic case report form.

STUDY DESIGN: This was a prospective, multi-center, open-label, repeat-dose pharmacokinetic study with 2 treatment arms. Study enrollment was planned for a total of 32 patients based upon age as follows: children (4 months to < 24 months, 2 to 5 years, and 6 to 11 years of age) and adolescents (12 to 16 years of age).Micafungin

was administered by infusion over 1 hour, once a day for 10 to 14 days. End of therapy (EOT) procedures were conducted up to 72 hours (3 days) after the last dose of study drug. The duration of the study was approximately 24 to 28 days from day 1, with an end of study (EOS) visit performed 14 days (+/- 1 day) after the final micafungin infusion. For patients enrolled prior to the adoption of Amendment 2, EOS assessments were made at 3 days instead of 14 days after the end of treatment; therefore, for these patients, EOS may have been the same as EOT.

Figure 3 Study 2103 Flow Diagram



Adapted from Astellas study 2103 page 16

a. Patient could be dosed for a minimum of 10 to a maximum of 14 consecutive days.

b. End of therapy (EOT) was the period between the last dose of study drug and up to 72 hours (3 days) after the last dose of study drug (i.e., if the patient received the maximum of 14 consecutive days of study drug then the EOT procedures could be performed up to day 17).

c. End of study (EOS) was 14 days after the last dose of study drug +/- 1 day (i.e., if the patient received 14 consecutive days of study drug then EOS was day 28). For patients enrolled prior to the adoption of Amendment 2, assessments were made at 3 days instead of 14 days after the end of treatment; therefore, for these patients, EOS may have been the same as EOT.

MO comment: *The study was designed and conducted in response to the pediatric written request (PWR) issued in May 2007 and most recently amended in August, 2012. The PWR stipulations were generally fulfilled by the study. The type of study, objectives, age groups, and study endpoints were adhered to as specified by the PWR.*

SAMPLE SIZE: Children (4 months to < 24 months, 2 to 5 years, and 6 to 11 years) and adolescents (12 to 16 years) undergoing a HSCT were allowed to participate. Approximately 32 patients were planned to be enrolled into this study; 8 patients were planned for each of the 4 age strata.

INCLUSION CRITERIA: A patient was eligible for the study if all of the following applied:

1. An IRB-approved written Informed Consent and Assent (as applicable) and HIPAA Authorization were obtained from the patient (as able) and/or patient's parent/legally authorized representative prior to any study-related procedures.
2. Patient was > 4 months of age and < 16 years of age.
3. Patient had sufficient venous access to permit administration of study drug, collection of pharmacokinetic samples, and monitoring of laboratory safety variables.
4. Female patient of childbearing potential had a negative pregnancy test within 72 hours prior to the first dose of study drug, and if sexually active agreed to use an acceptable method of birth control per Investigator judgment for the duration of the study.
5. Patient (when able) and/or patient's parent/legally authorized representative agreed to comply with the study requirements and with the concomitant medication restrictions.
6. Patient planned to undergo a HSCT.

MO Comment: *The sponsor conducted an efficacy study that is of relevance to the study under review: study 050 (pivotal adult study in prophylaxis of Candida infections in HSCT. Micafungin doses selected for evaluation in the study under review was thought to closely approximate exposures achieved at the approved 50 mg dose for Candida prophylaxis in adults that was evaluated for efficacy and safety study 050. No significant difference exists between inclusion criteria for study 9463-CL-2103 and 98-0-050, which established efficacy of micafungin for fungal prophylaxis in HSCT patients.*

EXCLUSION CRITERIA: A patient was excluded from the study if any of the following applied:

1. Patient had evidence of significant liver disease, as defined by aspartate transaminase (AST), alanine transaminase (ALT) 10 times the upper limit of normal (ULN) and total bilirubin or alkaline phosphatase > 5 times the ULN.
2. Patient had a concomitant medical condition that in the opinion of the Investigator and/or medical monitor precluded enrollment into the study.
3. Patient with evidence of an active systemic or disseminated fungal infection prior to enrollment.
4. Patient had a history of anaphylaxis, hypersensitivity, or any serious reaction to the echinocandin class of antifungals [Mycamine (micafungin), Eraxis (anidulafungin) or Cancidas (caspofungin)].
5. Patient had received treatment with an echinocandin within 1 week prior to first dose of study drug.
6. Patient status was unstable and patient was unlikely to complete required study procedures.
7. Female patient was pregnant or nursing. Females of childbearing potential avoided becoming pregnant while receiving study drug.

8. Patient had participated in another clinical trial and/or had taken an investigational drug within 30 days prior to the first dose of study drug, except for those trials involving primary cancer therapy
9. Patient was previously enrolled in this study.

***MO Comment**: Differences in exclusion criteria between study 9463-CL-2103 and 98-0-050 included:*

1. *98-0-050 excluded patients with HIV and autologous transplants for nonhematological malignancies.*
2. *9463-CL-2103 excluded patients that were considered "unstable" and patients who had undergone treatment with an echinocandin within one week prior to first dose of micafungin.*
3. *9463-CL-2103 excluded patients with transaminases > 10x ULN and bilirubinemia/alkaline phosphatase > 5x ULN while 98-0-050 excluded patients with transaminases > 5x ULN and bilirubinemia > 2.5x ULN.*

No patients in 9463-CL-2103 were known to have HIV or received a transplant for a nonhematological malignancy.

STUDY PROCEDURES: Micafungin was dosed at 1 mg/kg in patients weighing > 25 kg, or at 1.5 mg/kg in patients weighing < 25 kg, with a maximum daily dose not to exceed 50 mg. Micafungin was initiated within 48 hours of the start of the patient's transplant-related conditioning regimen. Micafungin was infused in dextrose in water or normal saline over 1 hour at a final concentration of 0.5 to 4.0 mg/mL. It was recommended that micafungin concentrations greater than 1.5 mg/mL were administered via a central IV line. Micafungin was not to be administered with other drugs and a separate line was used if other drugs needed to be administered simultaneously.

Table 32 Schedule of Assessments

Schedul	Baseline	Treatment Period[a]		End of Therapy [b]	End of Study [c]
Study Day	(Within 72 hours prior to the first dose of	Days 1 to 10	Days 11 to 14	Within 72 hours after the last dose of	14 Days (+/- 1 day) after last dose
PROCEDURES					
Informed Assent/Consent	X				
Medical History/Baseline	X				
Demographics	X				
Fungal Assessment [d]	X			X	
Physical Examination [e]	X			X	
Vital Signs [f]	X	X	X	X	X
Clinical Laboratories [g]	X	X	X	X	X
Pregnancy Test [h]	X				

Electrocardiogram (ECG)[i]	X	X		X	
Micafungin infusion		X	X		
Adverse Events		X	X	X	X
Concomitant Medications [j]	X	X	X	X	X
Pharmacokinetics [k]		X			

Adapted from Astellas study 2103 report, page 23

[a] Per Investigator discretion, micafungin was administered for a minimum of 10 to a maximum of 14 consecutive days.

[b] The End of Therapy (EOT) visit was to occur within 72 hours (3 days) after the last dose of study drug. The following were required at EOT: physical exam, vital signs, clinical laboratories, ECG, adverse event (AE) assessment, and concomitant medications.

[c] End of Study (EOS) was 14 days after the last dose of study drug was infused (day 24-28, as appropriate). The following were required at EOS: vital signs, clinical laboratories, AE assessment and concomitant medications. For patients enrolled prior to the adoption of Amendment 2, EOS assessments were made at 3 days instead of 14 days after the end of treatment; for these patients, EOS may have been the same as EOT.

[d] Fungal infection assessment was performed at baseline and at EOT. Fungal assessments were performed a total of 2 times during the study.

[e] Physical examinations were performed at baseline and at EOT. Height (length) at baseline only; additional weights were obtained prior to micafungin infusion on days 1 and 7 and on days 10 to 14 (as appropriate, after last dose of study drug).

[f] Vital signs were taken at baseline and twice (prior to the start of the infusion and within 1 hour post-infusion) daily during therapy with study drug and at EOT and EOS. On days when pharmacokinetic sampling was scheduled, days 4, 6, 7 and 8, predose vital signs were taken before pharmacokinetic blood draws.

[g] Clinical laboratories were collected at baseline, twice during the Treatment Period (separated by at least 72 hours), at EOT and at EOS. Clinical laboratories were completed a total of 5 times during the study.

[h] Pregnancy testing at baseline on adolescent females of child-bearing potential was a precaution only to ensure that pregnant patients were not enrolled.

[i] 12 Lead ECG with a 10 second rhythm strip were obtained at baseline (within 72 hours prior to first dose), and once between days 4 and 8 (to be completed 15 minutes prior to the end of study drug infusion [45 minutes after the start] up to 15 minutes after the end of study drug infusion), and at EOT.

[j] Medications/treatment associated with patient's underlying condition (such as immunosuppressives, chemotherapy and anti-infectives; any antifungals [oral, non-absorbable and systemic] or radiation) received within 7 days prior to the first dose of study drug were recorded. Use of all concomitant medications, both prescribed and over-the-counter, from baseline to EOS was recorded.

[k] Micafungin trough concentration samples were taken predose (0 hour) on treatment days 4, 6 and 8. Serial pharmacokinetic samples were collected relative to the Treatment Period day 7 infusion: Predose ("0" hour), immediately (within 3 minutes) after the end of infusion ("1" hour), 2, 4 and 10 hours after the start of the infusion.

MO Comment: *98-0-050 required fungal surveillance cultures of anterior nares at baseline and then weekly. Fungal infection status was also revisited weekly during 98-0-050 compared to 9463-CL-2103 which only performed fungal assessments at baseline and after final dose of micafungin.*

EVALUATION OF EFFICACY: Although this study was not designed to prove efficacy, the children and adolescents in this study were immunocompromised and no clinically

significant fungal infection emerged during the 10 to 14 day micafungin administration period or in the 14 day follow-up.

MO Comment: *Patients in 9463-CL-2103 were permitted to receive systemic anti-fungal therapy while receiving micafungin. 98-0-050 did not allow other systemic anti-fungal agents and discontinued patients who required these agents.*

PHARMACOKINETICS: Pharmacokinetic profiles were assessed using analyte (micafungin, M1, M2, and M5) concentrations from serial blood draws that began prior to study drug administration on day 7. Pharmacokinetic parameters were calculated using noncompartmental analysis.

REASONS FOR WITHDRAWAL: Reasons for withdrawal of a patient from the study:

1. Did not fulfill inclusion or exclusion criteria.
2. Adverse event(s).
3. Patient withdrew assent.
4. Parent(s) or legally authorized representative withdrew consent.
5. Protocol violation.

Any patient terminating the study prior to completion had EOT and EOS evaluations completed unless consent was withdrawn.

MO Comment: *98-0-050 had different criteria for patient withdrawal, including neutrophil recovery to an ANC >/= 500, the development of a proven, probable or suspected fungal infection or death. The anticipated duration of therapy in 98-0-050 was significantly longer, which may account for these differences in withdrawal criteria.*

ADVERSE EVENTS: An AE could be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of study drug, whether or not related to the study drug. A laboratory abnormality that was associated with signs or symptoms, required a diagnostic evaluation (other than retesting) or therapeutic intervention, or led to discontinuation of study drug was considered an AE. A treatment-emergent adverse event (TEAE) was defined as an AE occurring at any time after the first dose of study drug through 3 days after the last dose of study drug. If a patient had more than 1 AE that coded to the same preferred term, the patient was counted only once for that preferred term. Similarly, if a patient had more than 1 AE within a system organ class category, the patient was counted only once in that system organ class category.

STATISTICS: Two populations were identified for analysis, as follows:

- Safety analysis set (SAF): The SAF consisted of those patients enrolled in the study who received at least 1 dose of micafungin. The SAF was the only analysis

set for any safety displays. The SAF was used for summaries of demographic and baseline characteristics and all safety and tolerability related variables.

- Pharmacokinetics analysis set (PKAS): The PKAS consisted of those patients from the SAF whose plasma micafungin concentration data were adequate for the derivation of at least 1 pharmacokinetic parameter. Patients with protocol violations had their data assessed by the pharmacokineticist on a patient by patient basis for inclusion of the patient in the PKAS. The PKAS was the only set for pharmacokinetic analyses.

EVALUATION OF SAFETY: Vital signs, an ECG, and routine blood work was collected throughout the study as part of the safety assessment.

PROTOCOL CHANGES: Changes to the protocol included the following:

- The addition of ECG to the safety assessment.
- The addition of an additional patient assessment 14 days after the final dose of study drug.

RESULTS: Forty-two patients were enrolled in the study. Two patients were registered in the study but did not receive study drug.

Table 33 Data Analysis Sets

Data Analysis Set	Number (%) of Patients by Treatment Group						
		1 mg/kg		1.5 mg/kg			
	No Drug (n=2)	6-11 Years (n=6)	12-16 Years (n=9)	4-< 24 Months (n=11)	2-5 Years (n=11)	6-11 Years (n=3)	Total (n=42)
SAF‡	0	6 (100%)	9 (100%)	11 (100%)	11 (100%)	3 (100%)	40 (95.2%)
PKAS§	0	6 (100%)	9 (100%)	11 (100%)	11 (100%)	3 (100%)	40 (95.2%)
Did not receive drug	2 (100%)	0	0	0	0	0	2 (4.8%)

Adapted from Astellas study 2103 report, page 35
‡SAF: safety analysis set, defined as all patients who received at least one dose of micafungin.
§PKAS: pharmacokinetic analysis set, defined as all patients for whom sufficient plasma micafungin concentration data was available to facilitate derivation of at least 1 pharmacokinetic parameter.

Table 34 Patient Disposition

Patient Disposition	Number (%) of Patients by Treatment Group					
	1 mg/kg		1.5 mg/kg			Total (n=40)
	6-11 Years (n=6)	12-16 Years (n=9)	4-< 24 Months (n=11)	2-5 Years (n=11)	6-11 Years (n=3)	
Completed study	6 (100%)	9 (100%)	11 (100%)	10 (90.9%)	3 (100%)	39 (97.5%)
Discontinued study	0	0	0	1 (9.1%)	0	1 (2.5%)
Reason for discontinuation:						
Adverse event	0	0	0	1 (9.1%)	0	1 (2.5%)
Died after completing study	0	0	0	1 (9.1%)	1 (33.3%)	2 (5%)

Adapted from Astellas study 2103 report, page 36
Patient base: safety analysis set (SAF), defined as all patients enrolled in the study who received at least 1 dose of micafungin.

MO Comment: *The study was intended to enrolled 32 patients in total, with 8 patients in each of the four age cohorts. Per Table 2, they met and exceeded these goals. 97.5% of patients completed therapy, with only one patient discontinuing therapy due to an adverse event of pruritus.*

Table 35 Demographics and Other Baseline Characteristics – SAF

Characteristic	Micafungin Treatment Group					Total (n=40)
	1 mg/kg		1.5 mg/kg			
	6-11 Years (n=6)	12-16 Years (n=9)	4-< 24 Months (n=11)	2-5 Years (n=11)	6-11 Years (n=3)	
Sex, n (%)						
Male	5 (83.3%)	7 (77.8%)	6 (54.5%)	6 (54.5%)	2 (66.7%)	26 (65.0%)
Female	1 (16.7%)	2 (22.2%)	5 (45.5%)	5 (45.5%)	1 (33.3%)	14 (35.0%)
Race, n (%)						
White	6 (100.0%)	7 (77.8%)	11 (100.0%)	9 (81.8%)	3 (100.0%)	36 (90.0%)
Black or African-American	0	2 (22.2%)	0	2 (18.2%)	0	4 (10.0%)
Ethnicity, n (%)						
Non-Hispanic	2 (33.3%)	8 (88.9%)	9 (81.8%)	9 (81.8%)	2 (66.7%)	30 (75.0%)
Hispanic or Latino	4 (66.7%)	1 (11.1%)	2 (18.2%)	2 (18.2%)	1 (33.3%)	10 (25.0%)
Age, years						
Mean ± SD	9.6 ± 1.34	14.6 ± 0.91	1.1 ± 0.43	3.4 ± 1.38	7.6 ± 1.95	6.5 ± 5.35
Median	9.5	14.7	1.1	2.8	6.7	5.1
Range	7.4 – 11.3	12.7 –	0.4 – 1.7	2.1 – 5.7	6.3 – 9.9	0.4 – 15.8
Weight, kg						
Mean ± SD	34.2 ± 3.93	59.8 ±	8.1 ± 1.47	14.8 ± 4.40	23.4 ± 1.57	26.7 ±
Median	33.2	13.00	8.5	13.3	22.9	21.02
Range	30.8 –	66.1	5.2 – 9.8	9.3 – 22.6	22.2 –	19.9

Adapted from Astellas study 2103 report, page 38
Patient base: safety analysis set (SAF), defined as all patients enrolled in the study who received at least 1 dose of micafungin.
SAF: safety analysis set; SD: standard deviation.

MO Comments: *98-0-050 reported 59.5% male participants and 91.1% Caucasian race overall. The pediatric population of study 98-0-050 consisted of 62.2% male and 88.9%Caucasian compared to 65.0% male and 90.0% Caucasian in 9463-CL-2103. It is unlikely these differences are significant. Mean age was 7.2 +/-4.65 yrs (0.6 – 15) and mean weight was 30.3 +/- 18.90 (6.1 – 95.0) in 98-0-050 versus 6.5 +/- 5.35 (0.4 – 15.8) yrs and 26.7 +/- 21.02 (5.2 – 75.1). 9463-CL-2103 sought to include patients >/= 4mo, while 98-0-050 only included patients >/= 6mos, which may have decreased 9463-CL-2103 age and weight range.*

Table 36 Summary of Study Drug Exposure – SAF/PKAS

Parameter	Micafungin Treatment Group					Total (n=40)
	1 mg/kg		1.5 mg/kg			
	6-11 Years (n=6)	12-16 Years (n=9)	4-<24 Months (n=11)	2-5 Years (n=11)	6-11 Years (n=3)	
Duration, days						
≥ 10	6 (100.0%)	9 (100.0%)	11 (100.0%)	11 (100.0%)	3 (100.0%)	40 (100.0%)
Mean ± SD	13.3 ± 1.63	13.2 ± 1.56	13.6 ± 1.21	12.2 ± 1.94	13.0 ± 1.73	13.1 ± 1.63
Median	14.0	14.0	14.0	13.0	14.0	14.0
Range	10.0 – 14.0	10.0 – 14.0	10.0 – 14.0	10.0 – 14.0	11.0 – 14.0	10.0 – 14.0
Cumulative Dose, mg						
Mean ± SD	457.6 ± 83.78	640.0 ± 90.42	165.1 ± 28.51	266.6 ± 75.73	458.8 ± 79.47	365.8 ± 195.0
Median	466.1	700.0	168.0	257.7	490.0	335.0
Range	330.0 - 587.6	500.0 - 700.0	112.0 - 201.6	159.0 - 392.0	368.5 - 518.0	112.0 - 700.0
Cumulative Dose, mg/kg						
Mean ± SD	13.4 ± 1.69	11.1 ± 2.28	20.4 ± 2.14	18.2 ± 2.58	19.5 ± 2.56	16.6 ± 4.34
Median	14.1	10.6	20.6	19.4	20.6	16.1
Range	9.9 – 14.3	6.7 – 14.4	14.7 – 23.7	15.0 – 21.2	16.6 – 21.4	6.7 – 23.7
Mean Daily Dose, mg						
Mean ± SD	34.3 ± 4.03	48.4 ± 3.97	12.2 ± 2.13	22.2 ± 6.76	35.2 ± 1.76	28.1 ± 14.31
Median	33.3	50.0	12.5	20.0	35.0	29.0
Range	30.0 – 42.0	38.0 – 50.0	8.0 – 14.5	13.5 – 34.0	33.5 – 37.0	8.0 – 50.0
Mean Daily Dose, mg/kg						
Mean ± SD	1.0 ± 0.02	0.8 ± 0.15	1.5 ± 0.07	1.5 ± 0.04	1.5 ± 0.03	1.3 ± 0.31
Median	1.0	0.8	1.5	1.5	1.5	1.5
Range	1.0 – 1.0	0.7 – 1.1	1.4 – 1.7	1.4 – 1.6	1.5 – 1.5	0.7 – 1.7

Adopted from Astellas study 2103 report, page 43
Patient base: safety analysis set, defined as all patients enrolled in the study who received at least 1 dose of micafungin. SAF: safety analysis set; SD standard deviation.

All patients in the SAF were also included in the PKAS. Therefore, study drug exposure for the PKAS was the same as for the SAF.

Pharmacokinetic Results

Table 37 Plasma Micafungin Pharmacokinetic Parameters on Day 7 – PKAS

Parameter		Micafungin Treatment Group							Adults 50mg Dose on Day 1	Adult 50mg Dose on Day 14
		1 mg/kg			1.5 mg/kg					
		6-11 Years (n=6)	12-16 Years (n=9)	Total (n=15)	4-< 24 Months (n=11)	2-5 Years (n=11)	6-11 Years (n=3)	Total (n=25)		
C_{max}, mcg/mL	Mean ± SD	6.7±0.91	5.6±1.15	6.0 ±1.19	8.1±2.83	8.6±4.88	8.7±1.29	8.4±3.67	4.1 ± 1.4	5.1 ± 1.0
	CV%	13.5	20.8	19.7	35.0	56.6	14.9	43.7		
	Median	6.9	5.4	5.9	7.1	7.3	9.1	7.3		
	Range	5.5-7.9	4.3-8.1	4.3-8.1	5.6-15.3	6.0-23.1	7.2-9.7	5.6-23.1		
	Geo. mean	6.7	5.5	5.9	7.7	7.9	8.6	7.9		
$t_{1/2}$, hr	Mean ± SD	14.7±6.98	13.1±1.68	13.7±4.44	11.5±2.17	11.1±1.32	15.2±3.00	11.8±2.27	14.9 ± 4.3	15.6 ± 2.8
	CV%	47.4	12.8	32.4	18.8	11.9	19.7	19.3		
	Median	11.8	12.8	12.5	11.5	11.1	14.6	11.5		
	Range	9.8-28.4	10.5-16.2	9.8–28.4	7.9-16.0	8.9-13.8	12.6-18.5	7.9-18.5		
	Geo. mean	13.7	13.0	13.3	11.4	11.0	15.0	11.6		
AUC_{tau}, mcg*hr/mL	Mean ± SD	77.9±16.24	65.4±11.2	70.4±14.35	77.3±11.45	76.0±14.93	113.6±	81.1±17.68	36 ± 9	54 ± 13
	CV%	20.8	17.1	20.4	14.8	19.7	13.04	21.8		
	Median	75.0	65.0	67.8	79.0	67.1	11.5	79.0		
	Range	60.8-107.6	51.4-84.4	51.4–107.6	59.6-99.3	62.8-106.7	112.7	59.6-127.1		
	Geo. mean	76.7	64.6	69.2	76.5	74.7	101.1-127.1	79.4		
CL_{ss}/Wt, (mL/hr)/kg	Mean ± SD	13.2±2.33	13.0±2.22	13.1 ±2.19	19.7±2.74	20.4±3.45	13.3±1.70	19.3±3.66	19.2 ± 5.9	18 ± 3.8
	CV%	17.6	17.2	16.7	13.9	16.9	12.7	19.0		
	Median	13.4	13.3	13.3	20.5	21.6	13.6	20.0		
	Range	9.3-16.0	10.2-16.7	9.3-16.7	14.6-24.1	14.2-24.0	11.6-14.9	11.6-24.1		
	Geo. mean	13.1	12.8	12.9	19.6	20.1	13.3	18.9		

Adapted from Astellas study 2103 page 52

MO Comment: *Table 7 demonstrates a dose proportional increase between the 1 and 1.5 mg/kg groups. However, again clearance is slower in pediatric patients 6-<17 years as compared to adults and younger children. The adult micafungin pharmacokinetic profile values at the 50 mg dose are approaching micafungin exposures for the 1 mg/kg group, rather than 1.5 mg/kg in pediatric patients. Due to slower clearance in pediatric patients 6-<17 years, Cmax and AUC are exceeding adult values.*

Relative proportions of M1 metabolite to parent micafungin exposure (AUC) for the 1mg/kg group were 9.4% (6 – 11 yrs), 8.3% (12 – 16 yrs) and 8.8% (total). Similar proportions for M1 metabolite were observed at 1.5 mg/kg dose in children. For M5 metabolite in the 1mg/kg group, relative proportions were 8.7% (6 -11 yrs), 9.2% (12 – 16 yrs) and 8.9 % (total). For the 1.5mg/kg group, relative proportions were 17.7% (4 – 24mos), 13.6% (2 – 5 yrs), 10.2% (6 – 11 yrs) and 15% (total). The adult population with esophageal candidiasis given micafungin at a dose of 150mg had relative proportions of 11% for M1, 2% for M2 and 12% for M5.

MO Comment: *Metabolite to parent ratios were similar between adult and pediatric patients receiving 150 mg and 1 mg/kg micafungin doses, respectively.*

Safety Results

Table 38 Overview of Adverse Events

	Micafungin Treatment Group					Total (n=40)
	1 mg/kg		1.5 mg/kg			
	6-11 Years (n=6)	12-16 Years (n=9)	4-< 24 Months (n=11)	2-5 Years (n=11)	6-11 Years (n=3)	
Adverse events	6 (100.0%)	9 (100.0%)	11 (100.0%)	11 (100.0%)	3 (100.0%)	40 (100.0%)
Drug-related adverse events	1 (16.7%)	3 (33.3%)	0	2 (18.2%)	1 (33.3%)	6 (15.0%)
Serious adverse events	0	2 (22.2%)	0	1 (9.1%)	1 (33.3%)	4 (10.0%)
Adverse events leading to discontinuation	0	0	0	1 (9.1%)	0	1 (2.5%)
Deaths	0	0	0	1 (9.1%)	1 (33.3%)	2 (5.0%)

Adapted from Astellas study 2103 report, page 56
Patient base: safety analysis set, defined as all patients who received at least 1 dose of micafungin.

All patients experienced at least 1 AE. The more common AEs were vomiting (72.5%), nausea (47.5%), and mucosal inflammation (45.0%). The incidence of AEs was generally similar for the two dose groups. However, more patients in the 1.5 mg/kg group had tachycardia (32.0%) than in the 1 mg/kg group (13.3%), and more patients in the 1.5 mg/kg group had increased body temperature (28.0%) and pyrexia (40.0%) than in the 1 mg/kg group (6.7% and 26.7%, respectively).

***MO Comment**: There were seven adverse events considered related to study drug administration; one led to study drug discontinuation. The event that led to discontinuation was an episode of moderate pruritus and rash that resolved after drug discontinuation. The other episodes that were thought to be possibly related to study drug included pyrexia, epistaxis, diarrhea (2), hypotension, subconjunctival hemorrhage and hypocalcemia. All events resolved without further complication.*

All patients in 98-0-050 also reported at least one adverse event while on study drug therapy. 20.5% of pediatric patients in 98-0-050 also reported at least one serious adverse event. 7.7% of pediatric patients in 98-0-050 experienced an adverse event that led to study drug discontinuation. The 3 pediatric patients in 98-0-050 who experienced an adverse event that led to study drug discontinuation included episodes of arthralgia, intracranial hemorrhage, meningitis and respiratory distress syndrome.

Table 39 Treatment-Emergent Adverse Events Reported for at Least 5% of Patients Overall

MedDRA (v. 5.0) System Organ Class Preferred Term	Micafungin Treatment Group					Total (n=40)
	1 mg/kg		1.5 mg/kg			
	6-11 Years (n=6)	12-16 Years (n=9)	4-< 24 Months (n=11)	2-5 Years (n=11)	6-11 Years (n=3)	
Any Adverse Event	**6 (100.0%)**	**9 (100.0%)**	**11 (100.0%)**	**11 (100.0%)**	**3 (100.0%)**	**40 (100.0%)**
Blood and Lymphatic System Disorders	**4 (66.7%)**	**3 (33.3%)**	**5 (45.5%)**	**7 (64.4%)**	**4 (66.7%)**	**23 (57.5%)**
Anaemia NOS	2 (33.3%)	2 (22.2%)	4 (36.4%)	4 (36.4%)	1 (33.3%)	13 (32.5%)
Febrile Neutropenia	0	2 (22.2%)	0	1 (9.1%)	0	3 (7.5%)
Neutropenia	1 (16.7%)	0	3 (27.3%)	1 (9.1%)	1 (33.3%)	6 (15.0%)
Thrombocytopenia	4 (66.7%)	2 (22.2%)	4 (36.4%)	7 (63.6%)	2 (33.3%)	19 (47.5%)
Cardiac Disorders	**0**	**3 (33.3%)**	**3 (27.3%)**	**5 (45.5%)**	**1 (33.3%)**	**12 (30.0%)**
Tachycardia NOS	0	2 (22.2%)	3 (27.3%)	4 (36.4%)	1 (33.3%)	10 (25.0%)
Gastrointestinal Disorders	**5 (83.3%)**	**9 (100.0%)**	**11 (100.0%)**	**10 (90.9%)**	**3 (100.0%)**	**39 (97.5%)**
Abdominal Pain NOS	4 (66.7%)	3 (33.3%)	0	2 (18.2%)	1 (33.3%)	10 (25.0%)
Diarrhoea NOS	3 (50.0%)	3 (33.3%)	2 (18.2%)	5 (45.5%)	2 (66.7%)	15 (37.5%)
Dyspepsia	2 (33.3%)	1 (11.1%)	0	0	0	3 (7.5%)
Loose Stools	1 (16.7%)	3 (33.3%)	3 (27.3%)	2 (18.2%)	0	9 (22.5%)
Nausea	4 (66.7%)	6 (66.7%)	4 (36.4%)	4 (36.4%)	1 (33.3%)	19 (47.5%)
Oral pain	0	1 (11.1%)	1 (9.1%)	0	0	2 (5.0%)
Perianal Erythema	0	1 (11.1%)	1 (9.1%)	2 (18.2%)	1 (33.3%)	5 (12.5%)
Pruritus ANI	1 (16.7%)	1 (11.1%)	0	1 (9.1%)	0	3 (7.5%)
Saliva Altered	1 (16.7%)	1 (11.1%)	0	0	0	2 (5.0%)
Vomiting NOS	5 (83.3%)	6 (66.7%)	9 (81.8%)	8 (72.7%)	1 (33.3%)	29 (72.5%)
General Disorders & Administration Site Conditions	**5 (83.3%)**	**9 (100.0%)**	**10 (90.1%)**	**8 (72.7%)**	**3 (100.0%)**	**35 (87.5%)**
Cather Site Erythema	0	0	1 (9.1%)	1 (9.1%)	0	2 (5.0%)
Catheter Site Pain	0	0	1 (9.1%)	1 (9.1%)	1 (33.3%)	3 (7.5%)
Chest Pain	0	3 (33.3%)	0	0	0	3 (7.5%)
Fatigue	2 (33.3%)	0	0	0	1 (33.3%)	3 (7.5%)
Infusion Associated Symptoms	1 (16.7%)	2 (22.2%)	0	0	0	3 (7.5%)
Mucosal Inflammation NOS	4 (66.7%)	5 (55.5%)	7 (63.6%)	5 (45.5%)	2 (66.7%)	23 (57.5%)
Oedema NOS	0	1 (11.1%)	1 (9.1%)	2 (18.2%)	1 (33.3%)	5 (12.5%)
Oedema Peripheral	1 (16.7%)	0	0	1 (9.1%)	0	2 (5.0%)
Pain NOS	3 (50.0%)	0	3 (27.3%)	3 (27.3%)	1 (33.3%)	10 (25.0%)
Pyrexia	2 (33.3%)	3 (33.3%)	8 (72.7%)	6 (54.5%)	2 (66.7%)	21 (52.5%)
Hepatobiliary Disorders	**1 (16.7%)**	**0**	**2 (18.2%)**	**1 (9.1%)**	**0**	**4 (10.0%)**
Hepatomegaly	0	0	2 (18.2%)	0	0	2 (5.0%)
Infections and Infestations	**2 (33.3%)**	**3 (33.3%)**	**3 (27.3%)**	**4 (36.4%)**	**1 (33.3%)**	**13 (32.5%)**
Bacteraemia	1 (16.7%)	0	1 (9.1%)	1 (9.1%)	0	3 (7.5%)
Colitis	1 (16.7%)	0	1 (9.1%)	0	0	2 (5.0%)
Pseudomembranous Engraftment Syndrome	0	0	0	1 (9.1%)	1 (33.3%)	2 (5.0%)
Injury, Poisoning and Procedural Compl.	**0**	**2 (22.2%)**	**4 (36.4%)**	**5 (45.5%)**	**0**	**11 (27.5%)**
Blister	0	1 (11.1%)	1 (9.1%)	0	0	2 (5.0%)
Transfusion Reaction	0	1 (11.1%)	2 (18.2%)	2 (18.2%)	0	5 (12.5%)

MedDRA (v. 5.0) System Organ Class Preferred Term	Micafungin Treatment Group					Total (n=40)
	1 mg/kg		1.5 mg/kg			
	6-11 Years (n=6)	12-16 Years (n=9)	4-< 24 Months (n=11)	2-5 Years (n=11)	6-11 Years (n=3)	
Investigations	**4 (66.7%)**	**4 (44.4%)**	**7 (63.6%)**	**4 (36.4%)**	**1 (33.3%)**	**20 (50.0%)**
ALT Incr.	2 (33.3%)	1 (11.1%)	3 (27.3%)	0	0	6 (15.0%)
AST Incr.	3 (50.0%)	1 (11.1%)	4 (36.4%)	1 (9.1%)	0	9 (22.5%)
Blood Bicarbonate Decr.	0	1 (11.1%)	1 (9.1%)	0	0	2 (5.0%)
Blood Bilirubin Incr.	1 (16.7%)	0	1 (9.1%)	0	1 (33.3%)	3 (7.5%)
Blood CO_2 Decr.	0	0	0	2 (18.2%)	0	2 (5.0%)
Cardiac Murmur NOS	0	0	1 (9.1%)	1 (9.1%)	0	2 (5.0%)
Faecal Occult Blood Positive	0	1 (11.1%)	2 (18.2%)	2 (18.2%)	0	5 (12.5%)
GGT	1 (16.7%)	1 (11.1%)	2 (18.2%)	1 (9.1%)	1 (33.3%)	6 (15.0%)
Weight Incr.	1 (16.7%)	0	1 (9.1%)	0	0	2 (5.0%)
Metabolism and Nutrition Disorders	**5 (83.3%)**	**6 (66.7%)**	**5 (45.5%)**	**7 (63.6%)**	**2 (66.7%)**	**25 (62.5%)**
Anorexia	3 (50%)	4 (44.4%)	3 (23.1%)	4 (36.4%)	2 (66.7%)	16 (40%)
Fluid Imbalance	1 (16.7%)	0	0	1 (9.1%)	0	2 (5%)
Fluid Overload	0	1 (11.1%)	1 (9.1%)	0	0	2 (5%)
Fluid Retention	0	2 (22.2%)	2 (18.2%)	0	0	4 (10%)
Hyperglycaemia NOS	2 (33.3%)	3 (33.3%)	1 (9.1%)	0	0	6 (15%)
Hypermagnesaemia	0	1 (11.1%)	0	1 (9.1%)	0	2 (5%)
Hypertriglyceridaemia	1 (16.7%)	0	1 (9.1%)	0	0	2 (5%)
Hypoalbuninaemia	1 (16.7%)	1 (11.1%)	0	0	1 (33.3%)	3 (7.5%)
Hypocalcaemia	4 (66.7%)	2 (22.2%)	1 (9.1%)	2 (18.2%)	1 (33.3%)	10 (25%)
Hypokalaemia	0	3 (33.3%)	2 (18.2%)	5 (45.5%)	1 (33.3%)	11 (27.5%)
Hypomagnesaemia	4 (66.7%)	1 (11.1%)	2 (18.2%)	0	0	7 (17.5%)
Hypophosphataemia	0	2 (22.2%)	2 (18.2%)	2 (18.2%)	0	6 (15%)
Hyponatremia	0	0	2 (18.2%)	1 (9.1%)	0	3 (7.5%)
Renal Disorders	**3 (50.0%)**	**3 (33.3%)**	**0**	**1 (9.1%)**	**0**	**7 (17.5%)**
Hematuria	2 (33.3%)	1 (11.1%)	0	0	0	3 (7.5%)
Musculoskeletal and Connective Tissue Disorders	**4 (66.7%)**	**3 (33.3%)**	**2 (18.2%)**	**1 (9.1%)**	**0**	**10 (25.0%)**
Pain in Jaw	2 (33.3%)	1 (11.1%)	0	0	0	3 (7.5%)
Pain in Limb	1 (16.7%)	2 (22.2%)	0	0	0	3 (7.5%)
Nervous System Disorders	**3 (50.0%)**	**4 (44.4%)**	**2 (18.2%)**	**3 (27.3%)**	**0**	**12 (30.0%)**
Dizziness	1 (16.7%)	3 (33.3%)	0	0	0	4 (10%)
Headache NOS	3 (50%)	2 (22.2%)	0	2 (18.2%)	0	7 (17.5%)
Psychiatric Disorders	**2 (33.3%)**	**2 (22.2%)**	**3 (27.3%)**	**2 (18.2%)**	**0**	**9 (22.5%)**
Anxiety	2 (33.3%)	0	0	0	0	2 (5%)
Irritability	0	0	2 (18.2%)	1 (9.1%)	0	3 (7.5%)
Hallucinations	0	1 (11.1%)	0	1 (9.1%)	0	2 (5%)
Respiratory, Thoracic and Mediastinal Disorders	**2 (33.3%)**	**5 (55.6%)**	**1 (9.1%)**	**4 (36.4%)**	**1 (33.3%)**	**13 (32.5%)**
Cough	2 (33.3%)	4 (44.4%)	0	2 (18.2%)	1 (33.3%)	9 (22.5%)
Epistaxis	0	3 (33.3%)	0	1 (9.1%)	0	4 (10%)
Hypoxia	0	2 (22.2%)	0	0	0	2 (5%)
Pharyngolaryngeal Pain	0	3 (33.3%)	0	1 (9.1%)	0	4 (10%)
Tachypnoea	0	0	1 (9.1%)	2 (18.2%)	0	3 (7.5%)

MedDRA (v. 5.0) System Organ Class Preferred Term	Micafungin Treatment Group					Total (n=40)
	1 mg/kg		1.5 mg/kg			
	6-11 Years (n=6)	12-16 Years (n=9)	4-< 24 Months (n=11)	2-5 Years (n=11)	6-11 Years (n=3)	
Skin & Subcutaneous Tissue Disorders	**3 (50%)**	**8 (88.9%)**	**8 (72.7%)**	**8 (72.7%)**	**3 (100%)**	**30 (75%)**
Alopecia	1 (16.7%)	2 (22.2%)	0	1 (9.1%)	1 (33.3%)	5 (12.5%)
Dermatitis Diaper	0	0	2 (18.2%)	1 (9.1%)	0	3 (7.5%)
Erythema	1 (16.7%)	2 (22.2%)	1 (9.1%)	1 (9.1%)	0	5 (12.5%)
Face Oedema	0	0	1 (9.1%)	2 (18.2%)	0	3 (7.5%)
Pruritus NOS	0	3 (33.3%)	1 (9.1%)	5 (45.5%)	0	9 (22.5%)
Rash NOS	2 (33.3%)	5 (55.6%)	3 (27.3%)	3 (27.3%)	3 (100%)	16 (40%)
Skin Disorder NOS	0	0	1 (9.1%)	1 (9.1%)	0	2 (5%)
Skin Hyperpigmentation	0	1 (11.1%)	2 (18.2%)	1 (9.1%)	0	4 (10%)
Urticaria NOS	1 (16.7%)	1 (11.1%)	1 (9.1%)	1 (9.1%)	0	4 (10%)
Vascular Disorders	**1 (16.7%)**	**3 (33.3%)**	**4 (36.4%)**	**4 (36.4%)**	**0**	**12 (30%)**
Hypertension NOS	1 (16.7%)	2 (22.2%)	4 (36.4%)	3 (27.3%)	0	10 (25%)
Hypotension NOS	1 (16.7%)	1 (11.1%)	0	0	0	2 (5%)
Petechiae	1 (16.7%)	0	2 (18.2%)	0	0	3 (7.5%)
Veno-occlusive Disease NOS	0	0	1 (9.1%)	1 (9.1%)	0	2 (5%)

Adapted from Astellas study 2103 report, page 57
Patient base: safety analysis set, defined as all patients who received at least 1 dose of micafungin. Events starting at any time after the first dose of study drug through the last dose of study drug plus 3 days . Within a system organ class, a patient may have reported more than 1 adverse event.
NOS: not otherwise specified; ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: gamma glutamyl transferase; Incr: increased; Decr: decreased.

Differences in the frequency of some classes of events existed between the 1 mg/kg and 1.5 mg/kg groups.

- Blood and lymphatic disorders: 1 mg/kg group, 7/15 (46.7%); 1.5 mg/kg group, 16/25 (64.0%)
- Cardiac disorders: 1 mg/kg group, 3/25 (20.0%); 1.5 mg/kg group, 11/25 (44.0%)
- Metabolism and nutritional disorders: 1 mg/kg group, 11/25 (73.3%); 4.5 mg/kg group, 14/25 (56.0%)
- Musculoskeletal disorders: 1 mg/kg group, 7/25 (46.7%); 1.5 mg/kg group, 5/25 (20.0%)
- Renal disorders: 1 mg/kg group, 6/25 (40.0%); 1.5 mg/kg group, 1/25 (4.0%)
- Respiratory disorders: 1 mg/kg group, 7/25 (46.7%); 1.5 mg/kg group, 6/25 (24.0%)
- Nervous System disorders: 1 mg/kg group 7/25 (46.7%); 1.5 mg/kg group, 5/25 (20.0%)

Specific adverse events that occurred more frequently in the 1.5 mg/kg group as compared to the 1.0mg/kg group included neutropenia, tachycardia, fever and tachypnea.

Table 40 Patient Deaths

Patient No./ Age (years)/ Sex	Days of Treatment /Day of Death	Primary Cause of Death	Relationship to Study Drug	Related to Fungal Infection	Contributing Conditions Leading to Death
1.5 mg/kg Treatment Group					
02493001/ 6/Female	1-11/ 41	Cardiorespiratory arrest	Not related	No	Respiratory distress Pulmonary hemorrhage Acute
02493006/ 5/Male	1-10/ 20	Multi organ failure	Not related	No	Veno-occlusive disease

Adapted from Astellas study 2103 report, page 61
Patient base: safety analysis set, defined as all patients who received at least 1 dose of micafungin. Both deaths occurred more than 3 days after the last dose of study drug and were therefore not treatment- emergent.

MO Comment: *Two patients died in study 2103. Subject 02493001 with an underlying diagnosis of ALL 15 days after the last dose of study medication developed respiratory distress with hemoptysis. She then developed progressive respiratory failure with coagulopathy and ultimately died. It is unlikely this event is secondary to the study drug. The second patient, subject 02493006, was diagnosed with AML. On day 12, he became bacteremic with E. coli, developed shock and died on day 20 despite maximum medical support. This event is not secondary to study drug therapy, as his underlying immune dysfunction and overwhelming sepsis likely resulted in his death.*

Five pediatric patients (12.8%) died in 98-0-050. The adverse events reported associated with the death included cardiac arrest, pneumonia, cerebral infarct, intracranial hemorrhage and meningitis. None of these deaths were considered related to study drug by the investigator.

Table 41 Serious Adverse Events without an Outcome of Death

Patient No./ Micafungin Treatment Days	Age (years)/ Sex	MedDRA (v. 5.0) Preferred Term (Investigator's Verbatim Term)	Onset/ Stop Day	Outcome	Relationship to Study Drug
1 mg/kg Treatment Group					
04643029 Days 1-14	15/Male	Hypersensitivity NOS (allergic reaction to stem cell infusion)	7/9	Recovered, no residual effect	Not related
04643037 Days 1-14	14/Male	Septic shock (septic shock)	11/22	Recovered, no residual effect	Not related
1.5 mg/kg Treatment Group					
01253013 Days 1-14	6/Male	Graft versus host disease (GVHD) Engraftment syndrome (engraftment syndrome)	17/cont. 17/24	Persistent condition Recovered, no residual effect	Not related Not related

Adapted from Astellas study 2103, report, page 62
Patient base: safety analysis set (SAF), defined as all patients who received at least 1 dose of micafungin. Cont.: continuing; NOS: not otherwise specified; GVHD: graft versus host disease.

MO Comment: *Three patients experienced four serious adverse events that did not result in death. Patient 04643029 had an underlying diagnosis of ALL. The patient experienced an episode of hives, chest pain, facial edema and hypertension while receiving his allogeneic bone marrow transplant. The infusion was stopped, but resumed the next day. Upon resumption of the BMT infusion, the patient again experienced a similar allergic reaction. This event is unlikely to be related to the study drug, but rather secondary to the stem cell transplant.*

Patient 04643037 was diagnosed with ALL. The patient developed septic shock secondary to S. viridans and was treated with antimicrobials and replacement of his central line. This event is not considered to be related to study drug.

The third subject, patient 01253013, had an underlying diagnosis of ALL. After completing study drug therapy, the patient had an episode of respiratory distress with rash. Study reports a diagnosis of metapneumovirus and engraftment syndrome/GVHD. These events are not considered related to study drug.

CONCLUSIONS: Study 2103 was conducted in response to a PWR, which requested a minimum of 8 patients per age cohort to examine the pharmacokinetics of micafungin. Astellas succeeded in enrolling at least eight patients in each of the four age cohorts, and satisfied the requirement specified by the PWR. The safety profile of micafungin in pediatric patients 2-<17 years at 1-1.5 mg/kg was similar to previous pediatric and adult studies. A dose proportional increase in AUC and Cmax of micafungin was observed between the 1 and 1.5 mg/kg groups. Micafungin clearance is slowest in pediatric patients 6-<17 years as compared to adults and younger children. The adult micafungin pharmacokinetic profile values at the 50 mg dose are approaching micafungin exposures for the 1 mg/kg group, rather than 1.5 mg/kg in pediatric patients. Due to slower clearance in pediatric patients 6-<17 years, Cmax and AUC are exceeding adult values.

5.3.1 Study 2104

Study 2104: A Phase 1 Open-Label Study of the Safety and Pharmacokinetics of Repeated-Dose Micafungin in Neonates

5.3.1.1 Methods

INVESTIGATORS: 7 investigators, 5 of whom enrolled subjects

STUDY CENTERS: 7 sites, 5 of which enrolled subjects (7 U.S.)

STUDY PERIOD: 10-Aug 2007 to 31-Oct 2007

OBJECTIVES: To evaluate the safety and pharmacokinetics of intravenous micafungin in neonates (greater than 48 hours of age and up to day of life [DOL] 120) with suspected candidemia or invasive candidiasis.

METHODOLOGY: Multicenter, open-label study

NUMBER OF SUBJECTS: 13 patients enrolled in study, all of whom completed study drug therapy. One patient in the 7 mg/kg/day treatment group was inadvertently dosed 10 mg/kg/day and was not included in the PKAS.

STUDY DRUG: : IV micafungin dextrose of normal saline was administered at a dose of 7 mg/kg to patients with a weight greater than or equal to 1000 g, or 10 mg/kg to patients with a weight less than 1000 g. Patient received test drug as Mycamine in 50 mg/vial from lot number 707057K. Each vial contained 50mg of lyophilized micafungin and 200 mg of lactose with citric acid and/or sodium hydroxide. Maximum daily dose administered to any patient was 150 mg.

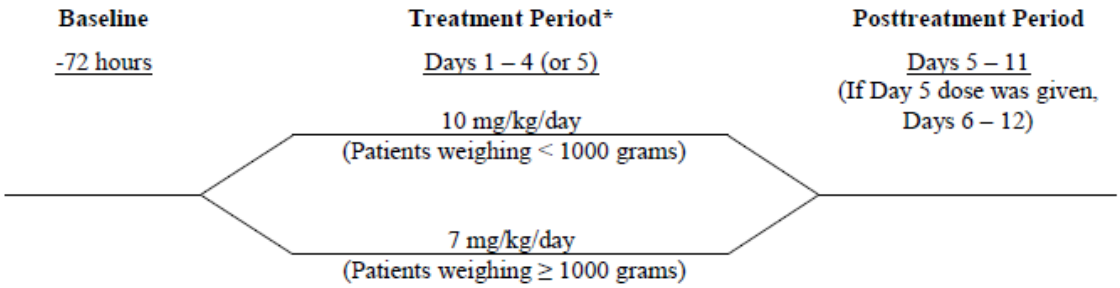
DURATION OF TREATMENT: Patient received micafungin for 4 or 5 consecutive days

TREATMENT COMPLIANCE: Study drug was administered by site personnel and documentation of administration was provided on the eCRF.

STUDY DESIGN: This was a multicenter, open-label study to evaluate the safety and pharmacokinetics of intravenous (IV) micafungin in infants with suspected candidemia or invasive candidiasis. Approximately 12 patients (6 weighing <1000 grams and 6 weighing ≥ 1000 grams) who were greater than 48 hours of age and up to day of life (DOL) 120 were planned for study enrollment. Patients were assigned to a dosing regimen based on body weight; patients <1000 grams were assigned to receive 10 mg/kg per day and patients ≥ 1000 grams were assigned to receive 7 mg/kg per day for 4 or 5 consecutive days, as appropriate. The end of study for each patient was 7 days after the last dose of study drug.

Figure 4 Study 2104 Flow Diagram

Figure 1: Study Flow Diagram



* If a patient had a documented fungal infection, continued micafungin therapy using the study drug supply was permitted beyond Day 4 or 5 at the discretion of the Investigator. If micafungin therapy was continued, additional doses were not to be administered until after the final pharmacokinetic sample was drawn. If another echinocandin was used, it was not to be initiated until after the completion of the last dose of micafungin.

Adopted from Astellas study 2104 report, page 14

***MO comment**: The study was conducted in response to the PWR issued in May 2007 and most recently amended in August 2012. The study was to collect PK data in neonates to determine the appropriate dose for neonatal candidiasis efficacy study, study 5 of the PWR.*

SAMPLE SIZE: Study enrollment was planned for a total of 12 infants who were greater than 48 hours of age and up to day of life (DOL) 120 at the time of administration of micafungin. The lower requirement of greater than 48 hours was needed so that unstable newly-born infants were not enrolled. Complications at this age are numerous and the infant would be too unstable to subject them to the study procedures, specifically pharmacokinetic sampling. The upper age limit was chosen because at this age the incidence of neonatal candidiasis declines.

INCLUSION CRITERIA: An infant was eligible for the study if all of the following applied:

1. Informed consent and HIPAA authorization of the infant's parent or legally authorized representative was obtained prior to study entry.
2. The infant was greater than 48 hours and up to DOL 120 at the time of initial study drug dosing.
3. The infant had sufficient venous access to permit study drug dosing.
4. The infant was suspected to have a systemic *Candida* infection and appropriate cultures (blood with or without urine/CSF) were obtained at the time of study entry.

***MO Comment:** For the indication of candidemia and other invasive candidiasis the sponsor conducted several efficacy studies: 192 (pivotal dose ranging active control efficacy study in IC), 2108 (supportive adequate and well controlled efficacy study) and study 047 (uncontrolled study of micafungin in invasive candidiasis, including EC). Studies 2108 and 047 enrolled pediatric patients.*

Enrollment criteria for study 2108 included candidemia or IC with characteristic signs and symptoms and confirmed by culture or histology. Cultures had to be obtained within 4 days of study drug administration. These inclusion criteria are more stringent than those observed by 9463-CL-2104 which only requires clinical suspicion of Candida infection.

EXCLUSION CRITERIA: An infant was excluded from participation if any of the following applied:

1. The infant had a history of anaphylaxis, hypersensitivity, or any serious reaction to the echinocandin class of antifungals (Mycamine [micafungin], Eraxis [anidulafungin] or Cancidas [caspofungin])
2. The infant was previously enrolled in this study.
3. The infant had received an echinocandin within one month prior to study entry.
4. The infant had a concomitant medical condition which, in the opinion of the investigator and/or medical adviser, may have created an unacceptable additional risk.
5. The infant had a life expectancy of less than 96 hours.

MO Comment: *Study 2108 excluded patients with abnormal transaminases, a sole diagnosis of isolated oropharyngeal or esophageal candidiasis without evidence of invasive infection, fungal infections other than candidiasis*

STUDY PROCEDURES: Administration of micafungin was initiated after inclusion/exclusion criteria were met. Micafungin was infused in dextrose in water or normal saline over one hour. The final micafungin concentration in solution was 0.5 mg/mL to 4.0 mg/mL, dependent on the volume restrictions of the patient. Micafungin concentrations greater than 2.0 mg/mL were given through central venous access or a midline peripherally inserted catheter (PIC). The tubing was flushed and the exact time of micafungin administration (start and stop times) was documented. Micafungin was not to be mixed with other drugs and a separate line was used if any other drugs needed to be administered simultaneously. An in-line filter was unnecessary. The infusion was rate controlled by using appropriate infusion (syringe) pumps. Micafungin was administered every 24 hours for 4 days. All Post treatment Period procedures were then completed within 72 hours after the last dose of micafungin (see Section 5.4.3.4, for reporting requirements). Increase or reduction in dose of micafungin was not permitted.

Table 42 Schedule of Assessments

Assessments	Baseline (-72 hr to predose)	Treatment Period t				Posttreatment Period Days 5-11 t
		Day 1	Day2	Day3	Day 4 (5)	
Informed consent	X					
Medical history/baseline Conditions	X					
Sterile body fluid cultures	X					
Vital signs§	X	X	X	X	X	X
Physical examination	X					X
Weight	X					
Micafungin infusion (1 hr)		X	X	X	X	
Adverse events tt		X	X	X	X	X
Concomitant medications tt	X	X	X	X	X	
Clinical laboratories§§	X	X				X
Pharmacokinetics					X	X

Adapted from Astellas study 2104 report, page 20

if a patient had a documented fungal infection, continued micafungin therapy using the study drug supply was permitted beyond Day 4 or 5 at the discretion of the Investigator. If continued micafungin therapy was used, additional doses were not to be given until after the final pharmacokinetic sample was drawn. If another echinocandin was used, it should have been initiated after the completion of the last dose of study drug. All Posttreatment Period procedures were then completed within 72 hours after the last dose of study drug.

if a Day 5 infusion was given, the posttreatment period was Days 6-12. Patients who prematurely discontinued from the study completed the posttreatment procedures no more than 72 hours after the final dose of study drug.

§Vital signs were taken at Baseline and twice daily (prior to start of infusion and within one hour postinfusion) on Days 1-4 (or Day 5, as appropriate). On Day 4 (or Day 5, as appropriate), vital signs were taken prior to pharmacokinetic blood draws.

The physical examination during the posttreatment period was performed on Day 5 only (within 72 hours after the last dose).

tt Adverse events were assessed and recorded throughout the treatment period and up to 72 hours after the last dose of micafungin.

U Antifungal medication, both systemic and topical, administered within 7 days prior to enrollment and concomitantly with study drug was recorded.

§§Hematology (hemoglobin, hematocrit, RBC, WBC, platelets and differentials) and serum chemistries (BUN, calcium, serum creatinine, potassium, sodium, magnesium, chloride and bicarbonate) were collected at Baseline (within 72 hours prior to first dose), once during the treatment period (Days 1-4), and once during the posttreatment period (within 72 hours after the last dose). At a minimum, serum AST, ALT, alkaline phosphatase and total bilirubin were obtained at Baseline (within 72 hours prior to first dose) and posttreatment (within 72 hours after last dose). Serum albumin was obtained at any one time throughout the entire study.

Serial pharmacokinetic assay samples were collected relative to the treatment period Day 4 infusion: within 1 hour prior to the start of infusion, immediately (within 3 minutes) after the end of infusion (1 hour), 2-4 hours after the start of infusion, 8-12 hours after the start of infusion, and 20-24 hours after the start of infusion (or Day 5). If a pharmacokinetic profile was not obtained relative to the Day 4 infusion, a patient may have received a Day 5 infusion and the pharmacokinetic profile was then obtained relative to this infusion.

EVALUATION OF EFFICACY: No statistical comparison of efficacy of the two dose groups was planned or conducted.

MO Comment: *Overall pediatric efficacy in study 2108 was similar to that of adults. However, the neonatal population demonstrates increased rates of Candida dissemination and CNS infection compared to the adult population. This limits extrapolation of efficacy data from the adult population. In study 2108, the neonatal subgroup was small, and the study was not sufficiently powered to allow for determination of efficacy for the pediatric subgroup.*

PHARMACOKINETICS: The 24-hour pharmacokinetic profiles were assessed using plasma micafungin concentrations from serial blood draws that began prior to study drug administration on Day 4. The area under the plasma micafungin concentration-time first moment curve from t=0 hour (time of dosing) to 24 hours postinfusion start (AUC_{tau}), maximum observed plasma micafungin concentration (C_{max}) and t_{max}, clearance at steady state (CL_{ss}) and volume of distribution at steady-state (Vd_{ss}) were calculated using noncompartmental methods.

REASONS FOR WITHDRAWAL: Reasons for withdrawal of an infant from the study included the following:

1. Did not fulfill inclusion or exclusion criteria
2. Adverse event(s)
3. Parent(s) or legally authorized representative withdrew consent
4. Protocol violation

MO Comment: *Study 2108 withdrew patients if the diagnosis of invasive candidemia could not be confirmed, death, and loss to follow-up.*

ADVERSE EVENTS: An adverse event could therefore have been any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of study drug, whether or not related to the study drug. Adverse events were assessed and recorded throughout the treatment period and up to 72 hours after the last dose of micafungin. All adverse events were followed for one week post-treatment

STATISTICS: Two populations were identified for analysis, as follows:

- Safety analysis set (SAF): The SAF consisted of all patients enrolled in the study who received at least one dose of micafungin. The SAF was the only analysis set used for any safety displays. The SAF was used for summaries of demographic and baseline characteristics and all safety- and tolerability-related variables.
- Pharmacokinetics analysis set (PKAS): The PKAS consisted of all patients from the SAF for whom sufficient plasma micafungin concentration data was available to facilitate derivation of at least one pharmacokinetic parameter. Patients with

protocol violations were assessed by the pharmacokineticist on a patient by patient basis for inclusion in the PKAS. All pharmacokinetic analyses were conducted only on the PKAS.

EVALUATION OF SAFETY: Vital signs, blood work as listed in Table 1, and an ECG were assessed as the safety evaluation.

PROTOCOL CHANGES: No significant protocol changes occurred during the study.

RESULTS:

Table 43 Data Analysis Sets

Data Analysis Set	Number(%) of Patients by Micafungin Treatment		
	7 mg/kg/day Body weight 1000 g (n=7)	10 mg/kg/day Body weight < 1000 g (n=6)	Overall (n=l3)
Safety analysis set (SAF) :t	7 (100.0%)	6 (100.0%)	13 (100.0%)
Pharmacokinetics analysis set	6 (85.7%)	6 (100.0%)	12 (92.3%)

Adapted from Astellas study 2104 report, p. 30 Patient base: all enrolled patients.
t One patient (04274004) in the 7 mg/kg/day treatment group was inadvertently dosed 10 mg/kg/day, and therefore, was excluded from the PKAS.
t All patients enrolled in the study who received at least one dose of micafungin.
§ All patients from the SAF for whom sufficient plasma micafungin concentration data was available to facilitate derivation of at least one pharmacokinetic parameter.

MO Comment: *The study aimed to enroll 12 patients. 13 patients were enrolled, although only 12 were evaluable due to a dosing error. Study 2108 enrolled 52 patients into the micafungin arm, who received study drug for a mean of 17 days, range 3 to 42. No dose changes were made in the <4 week age group. The average dose for the patients less than two years old was 2.4mg/kg.*

Table 44 Summary of Demographic and Baseline Characteristics – SAF

Characteristic	Micafungin Treatment Group		
	7 mg/kg/dayt Body weight ≥1000 g (n = 7)	10 mg/kg/day Body weight < 1000 g (n = 6)	Overall (n = 13)
Sex, n (%)			
Male	2 (28.6%)	4 (66.7%)	6 (46.2%)
Female	5 (71.4%)	2 (33.3%)	7 (53.8%)
Race, n (%)			
White	4 (57.1%)	5 (83.3%)	9 (69.2%)
Black or African-American	3 (42.9%)	1 (16.7%)	4 (30.8%)
Ethnicity, n (%)			
Non-Hispanic or Latino	4 (57.1%)	1 (16.7%)	5 (38.5%)
Hispanic or Latino	3 (42.9%)	5 (83.3%)	8 (61.5%)
Age, days			
Mean±SD	44.1 ± 37.35	7.5 ± 5.54	27.2± 32.74
Median	33.0	6.5	18.0
Range	13-119	3-18	3-119
Gestation Age, weeks			
Mean±SD	29.6 ± 5.50	24.7± 0.82	27.3 ± 4.68
Median	28.0	24.5	25.0
Range	25-40	24-26	24-40
Weight, g			
Mean±SD	2101 ± 1360	687.7 ± 106.7	1449± 1211
Median	1430	670.0	1210
Range	1210-4500	540-850	540-4500

Adapted from Astellas study 2104 page 32
Patient base: safety analysis set (SAF), defined as all patients who received at least 1 dose of micafungin. SD: standard deviation
T One patient (04274004) in the 7 mg/kg/day treatment group was inadvertently dosed 10 mg/kg/day.

MO Comment: *In the Full Analysis Set of Study 2108, the mean age of patients was 4.0 years± 5.1, 65.4% of patients were male, 57.7% of patients were Caucasian, 11.5% were black and 30.8% were listed as other ethnicities.*

A majority (85.7%) of patients in the 7 mg/kg per day group had received prior systemic antifungal therapy, compared to 16.7% of patients in the 10 mg/kg per day group. A higher percentage (57.1%) of patients in the 7 mg/kg per day group received concomitant systemic antifungal medication (amphotericin B or fluconazole) during treatment, compared with 16.7% of patients in the 10 mg/kg per day group. A similar percentage of each group received concomitant nystatin therapy (42.9%, 7 mg/kg/day group; 33.3%, 10 mg/kg/day group).

Table 45 Summary of Study Drug Exposure-SAF

Parameter	Micafungin Treatment Group		
	7 mg/kg/day[t] Body weight ≥1000 g (n=7)	10 mg/kg/day Body weight < 1000 g (n=6)	Overall (n=13)
Duration, days			
4 days	2 (28.6%)	5 (83.3%)	7 (53.8%)
5 days	5 (71.4%)	1 (16.7%)	6 (46.2%)
Mean± SD	9.14 ± 10.574	4.17 ± 0.408	6.85 ± 7.915
Median	5.00	4.00	4.00
Range	4.0-33.0	4.0-5.0	4.0-33.0
Cumulative Dose, mg			
Mean± SD	183.77 ± 299.859	28.24 ± 4.839	111.99 ± 226.892
Median	49.38	28.80	34.00
Range	28.0-852.0	21.6-34.0	21.6-852.0
Cumulative Dose, mg/kg			
Mean± SD	65.84 ± 76.321	41.18 ± 4.890	54.46 ± 55.552
Median	35.08	40.00	40.00
Range	23.1-236.7	36.4-50.7	23.1-236.7
Mean Daily Treatment Dose, mg			
Mean± SD	14.59 ± 8.429	6.79 ± 1.118	10.99 ± 7.241
Median	9.88	6.63	8.50
Range	7.0-27.0	5.4-8.5	5.4-27.0
Mean Daily Treatment Dose, mg/kg			
Mean± SD Median Range	7.16 ± 1.459	9.87 ± 0.387	8.41 ± 1.763
	7.00	10.00	9.09
	5.8-10.2	9.1-10.1	5.8-10.2

Adapted from Astellas study 2104, report, page 35
Patient base: safety analysis set (SAF), defined as all patients who received at least 1 dose of micafungin. SD: standard deviation
t One patient (04274004) in the 7 mg/kg/day treatment group was inadvertently dosed 10 mg/kg/day.

MO Comment: *100% of patients completed the stated study duration of 4-5 days of therapy. PKAS data was not significantly different from SAF data and is not included.*

Pharmacokinetics Results: No micafungin concentration data were excluded from the pharmacokinetic analyses for patients who received their assigned dosing regimen. All plasma micafungin concentration and pharmacokinetic parameter data from Patient 04274004 in the 7 mg/kg per day treatment group were excluded from the descriptive statistics because this patient was inadvertently dosed at 10 mg/kg/day. The pharmacokinetic sampling was performed relative to the start of infusion on Day 4. One patient (7 mg/kg/day treatment group) was atypical, compared to the other infants, in that she was 119 days old and weighed 4.5 kg. This patient had a substantially higher AUC (643.2 mcg·h/mL) than that seen in the smaller infants who received 7 mg/kg. The corresponding clearance for this patient was 0.18 mL/min/kg, which was well below the median clearance of 0.45 mL/min/kg for the 7 mg/kg dose group. While the mean AUCs

of the 7 mg/kg and 10 mg/kg groups are similar (307.6 and 307.9 mcg·h/mL, respectively), the 7 mg/kg mean is strongly influenced by the higher AUC of patient 04274009. Apart from this patient, the plasma concentration profiles of the 7 mg/kg patients a group are lower than those of the 10 mg/kg patients, as reflected in the median AUC values of 258.1 and 291.2 mcg·h/mL, respectively [Table 46].

Table 46 Plasma Micafungin Pharmacokinetic Parameters – PKAS

Parameter	Micafungin Treatment Group			Adult Patients 100 mg dose
	7 mglkg/dayt Body weight 1000 g (n=6)	10 mg/kg/day Body weight < 1000 g (n=6)	Overall (n=12)	
Cmax•				
Mean ±SD **mcg/mL**	26.6 ± 11.02	28.1 ± 9.25	27.3 ± 9.74	10.1 ± 2.6
Median	23.3	24.9	23.4	
Range	17.4-48.1	19.2-39.9	17.4-48.1	
CV%	41.5	32.9	35.6	
Geometric mean	25.1	26.9	26.0	
***t 1/2* h**				
Mean ±SD	11.39 ± 3.489	10.64 ± 3.192	11.01 ± 3.212	16.9 ± 4.4
Median	11.30	10.43	10.55	
Range	6.88-15.41	7.66-16.39	6.88-16.39	
CV%	30.6	30.0	29.2	
Geometric mean	10.92	10.28	10.60	
AUCtau mcg*h/mL				
Mean ±SD	307.6 ± 173.72	307.9 ± 100.62	307.8 ± 135.35	115 ± 25
Median	258.1	291.2	275.2	
Range	162.6-643.2	185.3 – 460.5	162.6-643.2	
CV%	56.5	32.7	44.0	
Geometric mean	276.8	294.4	285.5	
CLss/Wt, mL/min/kg				
Mean ±SD	0.44 ± 0.153	0.58±0.169	0.51 ±0.171	0.301 ± 0.086
Median	0.45	0.57	0.51	
Range	0.18-0.59	0.37-0.82	0.18-0.82	
CV%	35.1	29.1	33.6	
Geometric mean	0.41	0.56	0.48	

Adapted from Astellas study 2104 report, page 39
Patient base: pharmacokinetic analysis set (PKAS), defined as all patients who received at least 1 dose of micafungin who had sufficient plasma concentrations of micafungin to calculate at least 1 pharmacokinetic parameter. SD: standard deviation. CV: coefficient of variation.
t Excludes 1 patient (04274004) in the 7 mg/kg/day treatment group who was inadvertently given 10 mg/kg/day.
t Calculated using the following 2 serial timepoints, 8-12 hand 20-24 h after infusion start.

MO Comment: *The pharmacokinetic results in* Table 46 *demonstrate that Cmax, half-life and clearance rates are similar in both dose/weight groups. Compared to adult values, the neonatal population demonstrated increased clearance rates, but higher exposure to micafungin at the doses studied.*

Table 47 Overview of Adverse Events

	Micafungin Treatment Group		
	7 mg/kg/day[t] Body weight	10 mg/kg/day Body weight	Overall (n=13)
Adverse events	6 (85.7%)	6 (100.0%)	12 (92.3%)
Drug-related adverse events	2 (28.6%)	1 (16.7%)	3 (23.1%)
Serious adverse events	2 (28.6%)	2 (33.3%)	4 (30.8%)
Adverse events leading to discontinuation	0	0	0
Deaths	0	0	0

Adapted from Astellas study 2104, report page 41
Patient base: safety analysis set (SAF), defined as all patients who received at least 1 dose of micafungin. Within a system organ class, a patient may have reported more than 1 adverse event.
t One patient (04274004) in the 7 mg/kg/day treatment group was inadvertently dosed 10 mg/kg/day.
t The serious adverse events for 1 patient began 5 days after treatment and were not treatment emergent.

MO Comment: *92.3% of patients experienced an adverse event; 3 patients experienced adverse events related to the study drug. No adverse event resulted in early discontinuation. Drug-related adverse events included infusion site phlebitis, increase alkaline phosphatase and hypokalaemia.*

In study 2108, 92.3% of pediatric patients experienced any adverse event. 36.5% of these adverse events were considered by the sponsor to be related to the study drug. 28.8% of pediatric patients had a serious adverse event and 3.8% of patients discontinued study drug due to adverse events. 25% of patients in the micafungin treatment arm died, primarily in the post-treatment phase,

Of the 13 patients in study 2108 that died, the causes of death included cardiac arrest (3),sepsis (1), shock (1), autoimmune hemolytic anemia (1), arrhythmia (1), coagulation disorder (1), embolus (1), ALL (1), pneumonia (1) and vascular disorder (1).

Table 48 All Treatment-Emergent Adverse Events

MedDRA (v. 5.0) System Organ Class Preferred Term	Micafungin Treatment Group		
	7 mg/kg/day[t] Body weight ≥1000 g (n=7)	10 mg/kg/day Body weight <1000 g (n=6)	Overall (n=I3)
Any Adverse Event	**6 (85.7%)**	**6 (100%)**	**12 (92.3%)**
Blood and Lymphatic System Disorders			
Anaemia NOS	1 (14.3%)	0	1 (7.7%)
Cardiac Disorders			
Pulmonary Oedema NOS	1 (14.3%)	1 (16.7%)	2 (15.4%)
Cong enital, Familial and Genetic Disorders			
Patent Ductus Arteriosus	0	2 (33.3%)	2 (15.4%)
Endocrine Disorders			
Adrenal Insufficiency NOS	1 (14.3%)	0	1 (7.7%)
Gastrointestinal Disorders			
Abdominal Distention	1 (14.3%)	0	1 (7.7%)
Bowel Sounds Abnormal	1 (14.3%)	0	1 (7.7%)
Vomiting NOS	2 (28.6%)	0	2 (15.4%)
General Disorders and Administration Site Conditions			
Infusion Associated Symptoms	0	1 (16.7%)	1 (7.7%)
Infusion Site Phlebitis	1 (14.3%)	0	1 (7.7%)
Infusion Site Swelling	1 (14.3%)	0	1 (7.7%)
Lethargy	1 (14.3%)	0	1 (7.7%)
Oedema NOS	0	1 (16.7%)	1 (7.7%)
Hepatobiliary Disorders			
Jaundice NOS	1 (14.3%)	0	1 (7.7%)
Infections and Infestations			
Enterococcal Sepsis	0	1 (16.7%)	1 (7.7%)
Osteomyelitis NOS	0	1 (16.7%)	1 (7.7%)
Sepsis NOS	0	1 (16.7%)	1 (7.7%)
Subdural Empyema	1 (14.3%)	0	1 (7.7%)
Injury, Poisoning and Procedural Complications			
Abrasion NOS	0	1 (16.7%)	1 (7.7%)
Laceration	0	1 (16.7%)	1 (7.7%)
Medical Device Complication	0	1 (16.7%)	1 (7.7%)
Investigations			
Blood Alkaline Phosphatase NOS	1 (14.3%)	0	1 (7.7%)
Increased	1 (14.3%)	0	1 (7.7%)
Blood Calcium Decreased	0	1 (16.7%)	1 (7.7%)
Blood Chloride Decreased	1 (14.3%)	1 (16.7%)	2 (15.4%)
Blood Creatinine Increased	1 (14.3%)	0	1 (7.7%)
Blood Triglycerides Increased	1 (14.3%)	0	1 (7.7%)
Blood Urea Increased	1 (14.3%)	0	1 (7.7%)
C-Reactive Protein Increased	0	1 (16.7%)	1 (7.7%)
Cardiac Murmur NOS	0	1 (16.7%)	1 (7.7%)
Neutrophil Toxic Granulation Present	1 (14.3%)	0	1 (7.7%)
Oxygen Saturation Decreased	1 (14.3%)	0	1 (7.7%)
Platelet Count Decreased	1 (14.3%)	0	1 (7.7%)
White Blood Cell Count Increased			

MedDRA (v. 5.0) System Organ Class Preferred Term	Micafungin Treatment Group		
	7 mg/kg/day[t] Body weight ≥1000 g (n=7)	10 mg/kg/day Body weight <1000 g (n=6)	Overall (n=I3)
Metabolism and Nutrition Disorders			
Electrolyte Imbalance	0	1 (16.7%)	1 (7.7%)
Hyperglycaemia NOS	1 (14.3%)	0	1 (7.7%)
Hyperkalaemia	0	1 (16.7%)	1 (7.7%)
Hypokalaem ia	1 (14.3%)	0	1 (7.7%)
Musculoskeletal and Connective Tissue Disorders			
Osteopenia	1 (14.3%)	0	1 (7.7%)
Nervous System Disorders			
Subarachnoid Haemorrhage Neonatal	0	1 (16.7%)	1 (7.7%)
Renal and Urinary Disorders			
Oliguria	0	1 (16.7%)	1 (7.7%)
Pyelocaliectasis NOS	1 (14.3%)	0	1 (7.7%)
Renal Impairment NOS	1 (14.3%)	1 (16.7%)	2 (15.4%)
Respiratory, Thoracic and Mediastinal Disorders			
Atelectasis	1 (14.3%)	0	1 (7.7%)
Pneumothorax NOS	0	1 (16.7%)	1 (7.7%)
Respiratory Distress	0	2 (33.3%)	2 (15.4%)
Skin and Subcutaneous Tissue Disorders			
Dermatitis Diaper	1 (14.3%)	0	1 (7.7%)
Dermatitis NOS	1 (14.3%)	0	1 (7.7%)
Skin Disorder NOS	1 (14.3%)	1 (16.7%)	2 (15.4%)
Skin Necrosis	0	1 (16.7%)	1 (7.7%)
Vascular Skin Condition NOS	1 (14.3%)	1 (16.7%)	2 (15.4%)
Vascular Disorders			
Hypotension Aggravated	0	1 (16.7%)	1 (7.7%)
Hypotension NOS	0	1 (16.7%)	1 (7.7%)
Poor Peripheral Circulation	0	1 (16.7%)	1 (7.7%)

Adapted from Astellas study 2104 report, page 42
Patient base: safety analysis set (SAF), defined as all patients who received at least 1 dose of micafungin. Within a system organ class, a patient may have reported more than 1 adverse event.
NOS: not otherwise specified.
t One patient (04274004) in the 7 mg/kg/day treatment group was inadvertently dosed 10 mg/kg/day.

Table 49 Serious Adverse Events

Patient No./ Micafungin Treatment Days	MedDRA (v.5.0) Preferred Term (Investigator's Verbatim Term)	Onset/ Stop Day	Outcome	Relationship to Study Drug
7 mg/kg/day Treatment Group				
02494008H Days 1-4	Brain neoplasm NOS (massive left hemispheric brain tumor)	9/ 9	Recovered	Not related
	Convulsions NOS (seizures)	9/18	Recovered	Not related
04674001t Days 1-33	Blood alkaline phosphatase NOS ncreased (elevated alkaline phosphatase)	17/ continued	Persistent condition	Possibly related
10 mg/kg/day Treatment Group				
02494010t Days 1-4	Osteomyelitis NOS (Osteomyelitis)	7I continued	Persistent condition	Not related
02494012t Days 1-4	Patent ductus arteriosus (surgical PDA [patent ductus arteriosusl)	3/3	Recovered	Not related

Adapted from Astellas study 2104 report, page 45
Patient base: safety analysis set (SAF), defined as all patients who received at least 1 dose of micafungin. NOS: not otherwise specified. PDA: patent ductus arteriosus.
t The serious adverse events for Patient 02494008 began 5 days after treatment and therefore, were not treatment emergent.

MO Comment: *The serious adverse events of brain neoplasm, osteomyelitis and patent ductus arteriosus are not related to the study drug as these are serious underlying medical conditions. The elevated alkaline phosphatase could possibly be related to the study drug as other blood electrolyte and liver enzyme levels have been elevated with micafungin administration.*

In study 2108, 28.8% of patients experienced a serious adverse event. These events included sepsis (6), shock (2), cardiac arrest (2) and renal failure (2). The sponsors felt that the two episodes of renal failure were possibly related to micafungin administration.

CONCLUSIONS: Study 2104 was conducted in response to a PWR, which requested a minimum of 6 patients per weight cohort to examine the pharmacokinetics of micafungin. Astellas succeeded in enrolling at least six patients in each of the two cohorts, and satisfied the requirement as specified by the PWR. The safety profile was similar to previous pediatric and adult studies. Compared to the 100 mg adult dose, neonates demonstrated increased clearance rates, and overall increase in micafungin exposure (Cmax and AUC).

6 Review of Efficacy

Efficacy Summary

6.1 Indication

Micafungin (FK463), an echinocandin antifungal is approved for the treatment of adult patients with candidemia, acute disseminated candidiasis, *Candida* peritonitis and abscesses, esophageal candidiasis (EC), and for the prophylaxis of *Candida* infections in adult patients undergoing hematopoietic stem cell transplant (HSCT). The current application contains micafungin efficacy and safety data in pediatric patients ages 4 months to 16 years. While some efficacy data in infants less than 4 months are available, an efficacy study in neonates and young infants < 4 months of age with invasive candidiasis is currently ongoing.
As presented in the following table, these indications were approved based on the results from 5 pivotal clinical trials (192, 2108, 005, 2109, 050) in adults along with data from other supportive studies.

Table 50 Basis for the Approval of Micafungin in Adult Patients for the Indications of Invasive Candidiasis, Esophageal Candidiasis, and Prophylaxis of *Candida* Infections in HSCT Recipients

Adult Patient Indication	Pivotal Study	Comment
Invasive Candidiasis, Candidemia	Protocol 192 Protocol 2108	Efficacy of micafungin 100 mg was comparable (non-inferior) to caspofungin in Protocol192 (71% vs. 63%); and to Ambisome in Protocol 2108 (57% vs. 60%)
Esophageal Candidiasis	Protocol 005 Protocol 2109	Efficacy of micafungin 150 mg comparable (non-inferior) to fluconazole in Protocol 005 (88% in both arms) Dose dependent efficacy of micafungin at 50 mg, 100 mg, and 150 mg also demonstrated in Protocol 2109: 67%, 77% and 90%, respectively. Efficacy for micafungin 150 mg comparable to fluconazole 90% vs. 87%
Prophylaxis of Invasive *Candida* Infections in HSCT Recipients	Protocol 50	Efficacy of micafungin 50 mg superior to fluconazole 400 mg in Protocol 050, 81% vs. 74%, (95% CI 1.5%, 12.5%)

The data presented in the following tables are based on a review of the medical literature, primarily population-based studies. These summary data provide an overview of the similarities between the adult and pediatric patient population with respect to the epidemiology and mortality for the two indications (candidemia and esophageal candidiasis). Esophageal candidiasis remains a relatively rare condition in pediatric patients, and there are limited to no population-based epidemiology data available for different pediatric age groups. It should also be noted that there was limited discussion of differences between younger children/toddlers (3-24 months of age) and older

children/adolescents (2-17 years of age) in the reviewed literature; nevertheless, where available, these data are provided with the understanding that epidemiological data in pediatric patients ranging from 3 to 24 months of age are limited, as invasive fungal infections are less common in this age group.

Table 51 Comparative Overview of the Indication of Candidemia and Other *Candida* Infections in Adults and Children of Different Ages

Age Group	Risk Factors	Microbiology	Clinical Presentation & Pathogenesis
Adults	Risk factors include the following: • Immunosuppression • Use of broad-spectrum antibiotics • Central venous catheters • Hyperalimentation • Major surgery, specifically abdominal surgery/perforation • Malignancy or HSCT • Solid organ transplantation • Neutropenia • Hemodialysis	• Most common organisms in adults (>15 years) include: *C. albicans* (50-55%), *C. glabrata* (17-23%), *C. tropicalis* (10-11%), & *C. parapsilosis* (12%)	• *Candida* is the 4th most common bloodstream isolate (BSI) in adults • Incidence per 100,000 admissions (95% CI) is 30 (26-34). • Most common sites of dissemination include kidney (90%), lung (37%), eye (3-28%), brain (4-15%), liver/spleen (5-7%), & heart (<1%)
Children & Adolescents (2-17 Years)	Risk factors include the following: (essentially as above): • Immunosuppression • Use of broad-spectrum antibiotics • Central venous catheters • Hyperalimentation • Abdominal surgery/perforation • Malignancy or HSCT • Solid organ transplantation • Neutropenia • Hemodialysis	• Most common organisms in children & adolescents (2-15 years) include: *C. albicans* (55%), *C. parapsilosis* (21%), *C. tropicalis* (10%), & *C. glabrata* (3%)	• *Candida* is the 3rd most common bloodstream isolate (BSI) in children & adolescents • Incidence per 100,000 admissions (95% CI) is 47 (40-54) • Most common sites of dissemination in pediatric patients (including neonates) include lung (58%), liver (23%), brain (12-19%), kidney (5-16%), heart (5-8%), eye (3-8%), and spleen (0-8%) • Relative to adults, candidemia is associated with greater incidence of septic shock (20% versus 11%), longer duration of candidemia persistence, and a greater median number of positive blood cultures
Infants & Toddlers (4-24 Months)	• Similar risk factors are anticipated though data not readily available for this specific age group	• Data not readily available for this specific age group • Most common organisms in the youngest patients (<1 year) include: *C. albicans* (60%), *C. parapsilosis (24%),* *C. tropicalis (7%), &* *C. glabrata (3%)*	• Data not readily available for this age group

Age Group	Risk Factors	Microbiology	Clinical Presentation & Pathogenesis
Neonates and young infants (0-<4 months)	• Risk factor are different in the neonatal population: • Gestational age • Birth weight • Prolonged rupture of membranes • H2 blockers • Intubation • Third-generation cephalosporins	• Most common organism were: *C. albicans* (58%), *C. parapsilosis* (34%), *C. tropicalis* (4%), *C. lusitaniae* (2%), and *C. glabrata* (2%)	• In neonates incidence per 100,000 admissions (95% CI) is 150 (130-160) and, numerous organ systems can be involved • There is a 49% concordance with urinary involvement in candidemia. • 10-50% develop Candida meningitis, and yet 25-50% of those patients who develop meningitis have negative blood cultures

Mortality: Candidemia across different ages in children and adults continues to be associated with substantial morbidity and mortality. While it is not possible to determine mortality rates in all prespecified age ranges from the literature, several studies have assessed overall mortality rates due to invasive candidiasis. In summary, mortality rates are highest in patients with severe comorbidities, regardless of age. One analysis of pediatric (ages 3 months to 18 years) versus adult populations with invasive candidiasis reported crude mortality rates of 16% and 31%, respectively. However, crude mortality rates are not the same as candidiasis-attributable mortality. Candidiasis was responsible for between 13% and 97% of deaths in studies that analyzed attributable mortality. One study reported 97% and 93% attributable mortality for adults and pediatrics, respectively. Another reported 50% attributable mortality in neonates. Variability among reported rates is partially due to the patient's co-morbid conditions (e.g. organ transplant, HIV, cancer, etc.) and length of reported follow-up in each study. Nevertheless, the reported mortality ranges are generally consistent across ages with the exception of neonates, who have lower mortality (13 – 19%).

MO comment: *In comparative study of micafungin versus Ambisome for candidemia in adults and children, the subgroup of all pediatric subjects had the following species distribution: C. albicans (32%), C. parapsilosis (27%), C. tropicalis (22%), C. krusei and guilliermondii (4% each), while in neonates (0-<4 weeks) the species background was as follows: C. parapsilosis (26%), and C. tropicalis (23%), C. albicans (17%), and C. lipolytica (13%).*

As shown in the table below, the risk factors, microbiology, and clinical presentation in patients with esophageal candidiasis are also sufficiently comparable among adult and pediatric patients. Differences in risk factors or microbiology between the adult and pediatric patients are not clinically significant. Although the classic symptoms of esophageal candidiasis are the same across the different age groups, nausea and vomiting are more commonly reported in the pediatric population. This could be attributable to the anatomical differences in the size of the esophageal lumen among the different age groups.

Table 52 Comparative Overview of the Indication of Esophageal Candidiasis in Adults and Children of Different Ages

Age Group	Risk Factors	Microbiology	Clinical Presentation & Pathogenesis
Esophageal Candidiasis			
Adults	Risk factors include the following: • HIV infection, especially if low CD4 count (~85-90%) • Cytotoxic chemotherapy for hematologic malignancy or HSCT • High-dose corticosteroids or other immuno-suppressive therapy • Neutropenia	• Most common organism in adults (>15 years) is *C. albicans* (~95%), with ~25% as mixed infections of *C. albicans* and other organisms • Non-albicans *Candida* involvement without concurrent *C. albicans* infection is rarely seen (<5%)	• Mean age usually 35-40 years • Concomitant thrush is frequently seen (up to 90% of cases) • Classic symptoms include dysphagia, odynophagia, & retrosternal pain • Esophageal candidiasis in adults is the second most common AIDS-defining disease after PCP pneumonia • Death seen in ~6% of patients, but rarely associated with esophageal candidiasis. It is instead attributed to underlying conditions (i.e., AIDS)
Children & Adolescents (2-17 Years)	• Risk factors, essentially as above, include the following: • HIV infection (>80%), especially with low CD4 count (median 11/μL) • Cytotoxic chemotherapy for hematologic malignancy or HSCT • High-dose corticosteroids or other immuno-suppressive therapy (6-8%) • Neutropenia The strongest associated risk factors are prior oropharyngeal candidiasis, low CD4 count, and low CD4 percentage	• In the largest series, all patients had *C. albicans* (100%)	• Mean age of 5.8 years (range 0.2 to 17 years in 1 series) • Concomitant thrush is frequently seen (up to 95% of cases) • Classic symptoms: dysphagia, odynophagia, & retrosternal pain. Fever is relatively infrequent, but nausea and vomiting are seen. Up to 12% of children present with dehydration, requiring hospitalization and reflecting the acuity of esophageal candidiasis in some children • Esophageal candidiasis is a common cause of fungal infection in pediatric AIDS patients, seen in 8% of HIV-infected patients in one series from the 1990s • Death is seen in ~10%, but rarely associated with esophageal candidiasis. It is instead attributed to underlying conditions (i.e., AIDS)
Infants & Toddlers (4-24 Months)	• Though data not specifically available for this age group, similar risk factors are anticipated as in older children (a case series included patients as young as 2 months, but risk factor in this younger age group were not discussed)	• Data not available for this specific age group (a case series included patients as young as 2 months, but microbiological differences in this younger age group were not discussed)	• Data not available for this specific age group (A case series included patients as young as 2 months, but the specific differences in the clinical presentation in this younger age group were not mentioned.)

Indication of prophylaxis of *Candida* infection in patients undergoing HSCT is similar between adults and various pediatric age groups as the major risk factor (i.e., neutropenia in the setting of myeloablative therapy for hematopoietic stem cell transplantation [HSCT]) is the same across the adult and pediatric patient populations. Furthermore, if these patients were to go on to develop a breakthrough infection with

Candida species while on antifungal therapy, their clinical presentation would be as described above, in the included tables for the other two indications.

6.1.1 Methods

Clinical data from four pediatric PK/safety studies (2101, 2102, 2103, and 2104) were reviewed in the current supplemental NDA submission. The summary efficacy data from previously reviewed safety/efficacy adult/pediatric studies: 2108 and 050 are included in the efficacy section of this review to support the proposed pediatric dosing regimen for the following indications:

- Prophylaxis of *Candida* Infections in Patients Undergoing Hematopoietic Stem Cell Transplantation
- Treatment of Candidemia and the following invasive C*andida* infections: intra-abdominal abscesses, and peritonitis.
- Treatment of Esophageal Candidiasis

In addition, three pediatric PK studies (2101, 2102, and 2103) were also reviewed by the Clinical Pharmacology Reviewer, Dr. Dakshina Chilukuri, to examine micafungin exposure in pediatric patients ages 4 months - <17 years at the proposed dosing regimen of 1 mg/kg, 2 mg/kg and 3 mg/kg and compare it to micafungin exposure at the approved regimens of 50 mg, 100 mg, and 150 mg in adults. As the applicant is not seeking an indication of neonatal candidiasis (b) (4) and the comparative efficacy study in this indication is currently ongoing, the data from study 2104 (PK/safety) are included in the integrated safety analysis of micafungin use in pediatric patients, even though approval of micafungin use in pediatric patients 3 months and younger is not being considered.

6.1.2 Demographics

The table on the following page provides demographic information for pediatric patients in the trials of micafungin.

Table 53 Demographic and Baseline Characteristics (All Pediatric Patients Treated with Micafungin)

Characteristic	Study 2108	Study 050	PK studies (2101, 2102, 2103, 2104)	Other studies	Total Pediatric Patients	Total Adult Patients
	Invasive candidiasis	Prophylaxis	Invasive candidiasis, esophageal candidiasis, *Candida* prophylaxis	Invasive candidiasis, esophageal candidiasis, deep mycoses, *Candida* prophylaxis	All	All
	N = 56	N = 43	N = 140	N = 240	N = 479	N = 2748
Gender: n (%)						
Female	19 (33.9)	20 (46.5)	64 (42.4)	112 (46.7)	215 (55.1)	1412 (43.8)
Male	37 (66.1)	23 (53.5)	76 (57.6)	128 (53.3)	264 (44.9)	1815 (56.2)
Race: n (%)						
White	33 (58.9)	37 (86)	85 (60.7)	164 (68.3)	319 (66.6)	1809 (56.1)
Black	6 (10.7)	4 (9.3)	52 (37.1)	39 (16.3)	101 (21.1)	853 (26.4)
Asian/Pacific Islander	12 (21.4)	2 (4.7)	2 (1.4)	31 (12.9)	47 (9.8)	300 (9.3)
Other	5 (8.9)	0	1 (0.7)		12 (2.5)	265 (8.2)
Age:						
<4mos	20 (35.7)	0	13 (9.3)	35 (14.6)	68 (14.2)	
4 to 23 months	10 (17.9)	5 (11.6)	20 (14.3)	13 (5.4)	48 (10.0)	
2 to <6 years	8 (14.3)	9 (20.9)	43 (30.7)	48 (20.0)	108 (22.5)	
6 to 11 years	10 (17.9)	15 (34.9)	42 (30.0)	73 (30.4)	140 (29.2)	
12 to <17 years	8 (14.3)	14 (32.6)	22 (15.7)	71 (29.6)	115 (24.0)	
Mean ± SD	4.5±5.3	8.7±4.9	6.1±4.9	7.3±5.7	6.7±5.4	45.9±15.8
Min - Max	0 - 16	0.6 - 16	0 - 16	0 - 17	0 - 17	17 - 92
Weight:						
Mean ± SD	16.6±17.1	35.1±25.4	21.9±18.1	29±22	26±21.3	65.9±20.3
Median	9.5	24.5	15.6	25.5	21.2	62.9
Min - Max	0.9 - 75	5.9 – 117.9	0.5 – 75.1	0.6 -134.7	0.5-134.7	18-265.0

MO comment: *Demographic characteristics of the adult and pediatric populations varied substantially with respect to age and weight. Pediatric patients were more likely to be females as compared to adults. Racial distribution was similar between adult and pediatric patients.*

6.1.3 Subject Disposition

Table 54 Subject Disposition, ISS

	Study 2108	Study 050	PK studies (2101, 2102, 2103, 2104)	Other studies	Total Pediatric Patients	Total Adults
Indications studied	**Invasive candidiasis**	**Prophylaxis**	**Invasive candidiasis, esophageal candidiasis, *Candida* prophylaxis**	**Invasive candidiasis, esophageal candidiasis, *Candida* prophylaxis**	**All Pediatric Patients**	**All**
Patient disposition	**N = 56**	**N = 43**	**N = 140**	**N = 240**	**N = 479**	**N = 2748**
Received Study Therapy	56 (100)	43 (100)	140 (100)	240 (100)	479 (100)	2748 (100)
Completed Study Therapy	41 (73.2)	27 (62.8)	116 (82.8)	149 (62.1)	333 (69.5)	1938 (70.5)
Discontinued Prematurely	15 (26.8)	16 (27.2)	24 (17.2)	91 (38)	146 (30.5)	810 (29.5)
Lack of efficacy	7 (12.5)	12 (27.9)		41 (17.1)	60 (12.5)	242 (9.9)
Adverse Experience	2 (3.5)	3 (7)	7 (5)	35 (14.6)	47 (9.9)	342 (13.5)
Other	4 (10.7)	1 (2.3)	17 (12.1)	15 (6.3)	39 (8.1)	196 (7.1)
Underlying Disease						
Hematologic malignancy	11 (19.6)		25 (17.9)	91 (37.9)	127 (26.5)	252 (9.2)
HIV			36 (25.7)	6 (2.5)	42 (8.8)	992 (36.1)
BMT	2 (3.5)	43 (100)	16 (11.4)	64 (26.7)	125 (26.1)	628 (22.9)
Other	43 (76.8)		63 (45)	66 (27.5)	172 (35.9)	875 (31.8)
Diagnosis						
Deep Mycoses				20 (8.3)	20 (4.2)	105 (3.8)

	Study 2108	Study 050	PK studies (2101, 2102, 2103, 2104)	Other studies	Total Pediatric Patients	Total Adults
Invasive Aspergillosis				78 (32.5)	78 (16.3)	250 (9.1)
Invasive Candidiasis/ Candidemia	56 (100)		13 (9.2)	68 (28.3)	137 (28.6)	964 (35.1)
Esophageal candidiasis			87 (62.1)		87 (18.2)	895 (32.6)
Prophylaxis		43 (100)	40 (28.6)	74 (30.8)	157 (32.8)	534 (19.4)
Baseline Neutropenia	7 (13.5)	8 (18.6)	6 (4.3)	123 (51.3)	144 (30.1)	227 (8.3)

MO comment: *Disposition of patients was similar between the pediatric and adult patients. Seventy percent of pediatric and adult patients completed study therapy. Rate of micafungin discontinuation due to adverse events was lower among pediatric patients (10%) as compared to adults (14%).*
Pediatric and adult patient populations are fairly close in their make up with respect to underlying conditions and the nature of fungal disease. The differences worth noting are the higher percentage of adult patients with HIV relative to children, while hematologic malignancies were more common in children than in adults. Also, more pediatric patients received micafungin for invasive aspergillosis treatment and for prophylaxis; while in adults, esophageal candidiasis and candidemia predominated. It is not surprising that a greater proportion of pediatric patients had baseline neutropenia as compared to adults given the prevalence of hematologic malignancy in the pediatric patient population.

6.1.4 Analysis of Primary Endpoint(s)

Invasive Candidiasis

Of two clinical trials evaluating efficacy of micafungin at a 100-mg dose (2 mg/kg in patients ≤ 40 kg) for invasive candidiasis only one included pediatric patients. In the pediatric substudy of the invasive candidiasis study 2108, micafungin at 2 mg/kg/day IV once daily with protocol allowable dose escalation to 4 mg/kg was compared to Ambisome at 3 mg/kg/day with allowable dose increases up to 5 mg/kg/day. A total of 106 pediatric patients ages 0-15 years were administered study treatments: 52 on micafungin arm and 54 on the Ambisome arm. The patients on micafungin arm were slightly older (average 4 vs. 2.2 years) and less likely to be neutropenic (13% versus 24%), and more likely to be in the ICU (57.7% vs. 40.7%) as compared to patients on Ambisome arm. Other patient characteristics were similar between two groups. Primary efficacy endpoint was treatment success at the end of therapy. Treatment success was similar between the two study arms; however, the study was not powered to detect the differences in outcomes between the study treatments for pediatric subgroup. The treatment success in the pediatric patients (66.7%) was similar to adult patients treated with micafungin (74.1%) within this trial.

Table 55 Treatment Success at End of Blinded Therapy (Investigator Assessment)

Parameter Variable	Micafungin 100 mg	Ambisome
Full Analysis Set	**n = 52**	**n = 54**
Success	33 (63.5%)	34 (63%)
Treatment difference [**95.0% CI**]	0.5% **[-19.8%, 20.8%]**	
Modified Full Analysis Set	**n = 48**	**n = 50**
Success at EOT	32 (66.7%)	32 (64%)
Treatment difference [**95.0% CI**]	2.7% **[-18.2%, 22.6%]**	
Success at 12 week post treatment	29 (60.4%)	32 (64%)
Treatment difference [**95.0% CI**]	-3.6% **[-24.8%, 17.7%]**	
Per Protocol Set (Primary analysis)	**n = 41**	**n = 42**
Success	32 (78%)	31 (73.8%)
Treatment difference [**95.0% CI**]	4.2% **[-16.5%, 25%]**	

As the sponsor was seeking a fixed dosing regimen for the indication of invasive candidiasis in adults, the FDA analyses considered patients requiring dose escalation as a treatment failure in the primary efficacy assessment. In that analysis, similar rates of successful treatment were achieved in micafungin-treated pediatric (52.1%) and adult patients (56.7%). Response rate in the subgroup of patients with candidemia were numerically similar between the treatment arms and adult and pediatric patients; however, neutropenic pediatric patients were successfully treated with micafungin in 83% of the cases while success in adults was much lower (34.4%). The reverse was true for the other forms of invasive candidiasis: the successful outcome was achieved in 47.5% of adults and in 25% of children. Mycological eradication rates were numerically similar between the study arms in the pediatric substudy and between adults and children. The treatment success at the end of therapy in the adult patients with invasive candidiasis in the pivotal efficacy study 192 was 66%. Given the small number of

pediatric patients with invasive candidiasis treated with micafungin, subgroup analyses in this age group relative to adults should be interpreted with caution.

Prophylaxis of *Candida* infections in Patients Undergoing a Hematopoietic Stem Cell Transplant

Of the three clinical trials evaluating the 50 mg dose micafungin (1 mg/kg in patients ≤ 40 kg), only one trial enrolled pediatric patients for the prophylaxis of fungal infections after undergoing hematopoietic stem cell transplant, study 98-0-050. The pediatric substudy includes a total of 84 patients less than 16 years old (age range 6 months to 17 years; mean age 7 years). Thirty nine pediatric patients received micafungin while 45 received fluconazole. Prophylaxis success rates in pediatric patients in the micafungin arm were numerically higher than in the fluconazole arm (69.2% vs. 53.3%), but these success rates in the pediatric subpopulation were numerically lower than in adults for both study groups (81.1% vs. 75.7%). The applicant attributed the lower success rates in pediatric patients in both groups to the higher proportion of allogeneic transplant recipients (95.5% pediatric patients vs. 45% adults), which are known to do worse than those receiving autologous transplants (success rates of 71.4% vs. 89.2%, respectively, in adult patients).

Table 56 Candida Infection Prophylaxis Outcomes in Adults and Pediatric HSCT Patients, All treated, Study 98-0-50

Outcome of Prophylaxis	**Mycamine 50 mg/day (n=425)**		**Fluconazole 400 mg/day (n=457)**	
	Adults n=382 (%)	Pediatric Patients n=43 (%)	Adults n=409 (%)	Pediatric Patients N=48 (%)
Success*	312 (81.7)	31 (72.1)	311 (76)	26 (54.2)
95% CI	(77.8, 85.6)	[58.7%, 85.5%]	(71.9, 81.2)	[40.1%, 68.3%]
Failure:	70 (18.3)	12 (27.9)	98 (24)	22 (45.8)
All Deaths†	13 (3.4)	5 (11.6)	20 (4.9)	6 (12.5)
Proven/probable fungal infection prior to death	0 (0.0)	1 (2.3)	3 (0.7)	0
Proven/probable fungal infection (not resulting in death) †	6 (1.5)	0	5 (1.2)	3 (6.3)
Suspected fungal infection ‡	46 (12.1)	7 (16.3)	70 (17.1)	13 (27.1)
Lost to follow-up	5 (1.3)	0	3 (0.7)	0

Esophageal Candidiasis

Study 98-0-047, an open-label, non-comparative study for the treatment of invasive candidiasis, included a total of 30 pediatric patients, 4 of whom (age range 3-9 years) had endoscopically documented esophageal candidiasis. These patients received micafungin at doses 1 to 2.1 mg/kg/day for a total of 17-42 days. All four patients had documented clinical success (complete or partial clinical response). Three of these four patients had complete clearing of esophageal lesions at the end of therapy; endoscopy was contraindicated in the fourth patient and response was based upon clearing of all clinical symptoms. None of these patients relapsed.

Study 9463-CL-2101, a phase 1 open label study of safety and pharmacokinetics of micafungin in children with esophageal and other invasive candidiasis, enrolled a total of 38 pediatric patients with esophageal candidiasis. These patients received 2 dosing regimens of micafungin 3 mg/kg and 4.5 mg/kg with mean duration of study treatment of 10.3 days. Endoscopy was not required in this study to confirm a successful outcome. All patients in 3 mg/kg dose group achieved clinical success: complete (5/6) and partial (1/6) clinical response at the end of therapy. Similar findings were recorded in the 4.5 mg/kg dose group: overall 93.3% clinical success (complete response in 22/30 and partial in 6/30 patients).

MO comment: *While the treatment outcome was reported for the number of pediatric patients with esophageal candidiasis, the adequacy of the study design (open label), outcome assessment (clinical resolution, no endoscopic confirmation) and range of doses used preclude the reviewer from considering these data as adequate to support the indication of treatment of esophageal candidiasis in pediatric patients. Therefore, the evidence of micafungin efficacy in this indication comes from the adequate and well controlled studies in adults and the selection of the appropriate pediatric dose based that results in the exposures similar to that achieved in adults at 150 mg dose approved for this indication.*

6.1.5 Analysis of Secondary Endpoints(s)

Not applicable

6.1.6 Other Endpoints

Not applicable

6.1.7 Subpopulations

Pediatric populations in efficacy studies were too small to allow for comprehensive age, race, gender, dose-response, or indication-specific efficacy subgroup analyses.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The micafungin pediatric development program is considered to be based on extrapolation of efficacy from adults to pediatrics for the approved indications with the exception of neonatal candidiasis, a form of invasive candidiasis that is sufficiently different from the invasive candidiasis in adults. Therefore, the proposed pediatric dosing regimens for prophylaxis of *Candida* infections in HSCT recipients, esophageal candidiasis, and candidemia result in the exposures that are similar to those achieved in adults at the doses approved for above indications.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Not applicable

6.1.10 Additional Efficacy Issues/Analyses

Not applicable

7 Review of Safety

Safety Summary

Overall, micafungin dosed from 1 mg/kg/day up to 3 mg/kg/day has been shown to be safe in the pediatric population. The C_{max} and AUC were higher in the pediatric population compared to the adults with a concern for higher incidence of adverse events. In comparing overall clinical trial safety data between the pediatric and the adult population and between the micafungin and the comparator treatment groups, an overall similar profile of adverse events was observed.

The incidence of deaths in the pediatric patient population treated with micafungin was similar to the comparator groups (Ambisome, fluconazole) and lower than in the adult population. Across the 11 pediatric studies, a total of 15.9% (76/479) of patients died: 10 deaths (2.1%) occurred during study drug treatment and 66 deaths (13.8%) occurred during the posttreatment period. The causes of death in the pediatric patients were similar to that observed in adult studies, where the major causes of deaths were: respiratory failure (1.7% vs. 1.6%), aspergillosis (1.7% vs. 1.0%), intracranial hemorrhage (1.0% vs. 0.7%), septic shock (0.8% vs. 1.8%), multi-organ failure (0.6% vs. 1.3%), and sepsis (0.4% vs. 2.5%). Deaths in micafungin-treated pediatric patients were not considered to be related to the study drug.

In the micafungin clinical safety database 43/479 (9.0%) pediatric patients and 373/2748 (13.6%) adult patients experienced a treatment-emergent adverse experience (TEAE) that led to study discontinuation. In pediatric patients, the most common TEAE leading to study discontinuation were acute respiratory distress syndrome (0.8%), respiratory failure (0.6%), pulmonary hemorrhage (0.6%), and hemorrhage intracranial (0.6%) led to study discontinuation. In adult patients, the most common TEAEs that led to study discontinuation were septic shock (1.1%), sepsis (0.8%), respiratory failure (0.8%), and multi-organ failure (0.8%).

The most common SAEs in pediatric and adult patients were sepsis (3.8% versus 2.3%), respiratory failure (2.9% versus 3.1%), acute respiratory distress syndrome (2.5% versus 0.4%), respiratory distress (2.3% versus 0.7%), and septic shock (0.6% versus 1.8%), respectively.

The most common treatment emergent adverse experiences among pediatric and adult subjects treated with micafungin were vomiting (30.5% vs. 21.1%), diarrhea (22.1% versus 25.0%), pyrexia (21.5% vs. 19.8%), nausea (19.0% vs. 22.3%), hypokalemia (18.2% vs. 17.8%), mucosal inflammation (16.7% versus 13.1%), abdominal pain (15.9% versus 9.0%), thrombocytopenia (14.6% versus 15.9%), hypertension (13.6% versus 6.3%), headache (13.4% versus 15.9%). Vomiting was the most common TEAE (>20%) reported at all micafungin dose levels. Rash and infusion reactions were higher in the pediatric population compared to adults (11.5% and 5% versus 8.3% and 1.5%, respectively).

No demographic factors were identified with regards to micafungin safety.

No dose or exposure response in the assessment of micafungin safety (AEs and laboratory abnormalities) in pediatric patients was observed.

Postmarketing events observed in pediatric patients have already been described in the micafungin product labeling.

7.1 Methods

Table 57 Summary of Cumulative Subject Population

	Micafungin	Fluconazole	Caspofungin	AmBisome	Placebo	Total
Adult Volunteers	520	0	0	0	14	534
Adult Patients	2748	739	345	265	51	4148
Pediatric Patients	479	48	0	56	0	583
TOTAL	3747	787	345	321	65	5265

All randomized/enrolled subjects who received at least 1 dose of study drug
Adapted from the summary of clinical safety p. 11

This safety review was conducted using an integrated micafungin safety database that includes eleven studies that enrolled a total of 479 pediatric patients: protocols 043, 046, 047, 050, 063, 2101, 2102, 2103, 2104, 2108, and FP01. Additionally postmarketing safety assessments were made based on the data submitted by the applicant in the supplemental NDA.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Table 58 Summary Overview of the Pediatric Studies

Study Number	Study Title	Total Pediatric Patients†

(Phase)		
Candidemia or Invasive Candidiasis		
98-0-047 (Phase 2)	An Open-Label, Non-Comparative Study of FK463 in the Treatment of Candidemia or Invasive Candidiasis	55
99-0-063 (Phase 1)	Pharmacokinetic, Safety, and Tolerance Study of Three Dose Levels of Micafungin (FK463) in Premature Infants	13‡
FG-463-21-08-CR-02§ (Phase 3)	A Multicentre, Double Blind, Comparative, Randomized Study to Evaluate the Efficacy and Safety of Micafungin (FK463) versus Liposomal Amphotericin B (AmBisome®) in the Treatment of Invasive Candidiasis and Candidemia in Pediatric Patients	112 total 56 micafungin¶ 56 AmBisome
9463-CL-2102§ (Phase 1)	A Phase 1, Open-Label Study of the Safety and Pharmacokinetics of Repeated-Dose Micafungin (FK463) in Infants and Toddlers (≥ 4 Months to < 24 Months of Age) with Esophageal Candidiasis or Other Invasive Candidiasis	9
9463-CL-2104§ (Phase 1)	A Phase 1, Open-Label Study of the Safety and Pharmacokinetics of Repeated-Dose Micafungin in Neonates	13
9463-CL-2101§ (Phase 1)	A Phase 1, Open-Label Study of the Safety and Pharmacokinetics of Repeated-Dose Micafungin (FK463) in Children (2-5 Years and 6-11 Years) and Adolescents (12-16 Years) with Esophageal or Other Invasive Candidiasis	78
Prophylaxis		
98-0-050§ [NIAID MSG 46] (Phase 3)	A Phase 3, Randomized, Double-Blind, Comparative Trial of Micafungin (FK463) Versus Fluconazole for the Prophylaxis of Fungal Infections in Patients Undergoing a Hematopoietic Stem Cell Transplant	91 Total 43 micafungin 48 fluconazole
98-0-043 (Phase 1)	A Phase 1 Study to Determine the Safety and Pharmacokinetics of FK463 in Febrile Neutropenic Pediatric Patients	74††
9463-CL-2103§ (Phase 1)	A Phase 1 Open-Label Study of the Safety and Pharmacokinetics of Repeated-Dose Micafungin (FK463) as Antifungal Prophylaxis in Children and Adolescents Undergoing Hematopoietic Stem Cell Transplantation	40
Invasive Aspergillosis		
98-0-046 (Phase 2)	An Open-Label, Non-Comparative Study of Micafungin (FK463) in the Treatment of Invasive Aspergillosis	78
Deep Seated Mycosis due to *Aspergillus* or *Candida*		
FJ-463-FP01 (Phase 3)	A Phase III Study of FK463 in the Treatment of Deep Mycosis in Pediatric Patients—Multicenter Uncontrolled Open-label Study	20
Total Number of Patients Treated with Micafungin		**479**

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

†† A total of 77 patients were enrolled and received at least 1 dose of study drug; 17 year olds enrolled in Study 98-0-043 were not counted as pediatric patients.
Adapted from the sponsor's clinical summary of safety, p. 7

7.1.2 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The safety data were pooled across 11 clinical trials that enrolled pediatric patients. Overall, the pediatric safety database included 479 pediatric patients who received at least one dose of micafungin. Incidence of adverse events and laboratory abnormalities was compared between the pediatric and adult safety populations and within various subgroups within the pediatric population.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Table 59 Demographics Comparison Between Adults and Pediatric Patients Exposed to Micafungin in Clinical Trials

	Pediatric Patients (n = 479)		Adult Patients (n = 2748)		Total (n = 3227)	
Parameter Category	**n**	**%**	**n**	**%**	**n**	**%**
Sex						
Male	264	55.1	1551	56.4	1815	56.2
Female	215	44.9	1197	43.6	1412	43.8
Race						
White	319	66.6	1490	54.2	1809	56.1
Black	101	21.1	752	27.4	853	26.4
Asian	47	9.8	253	9.2	300	9.3
Other	12	2.5	252	9.2	264	8.2
Unknown	0	0	1	0	1	0
Region						
North America	349	72.9	1068	38.9	1417	43.9
Central America	0	0	6	0.2	6	0.2
South America	39	8.1	493	17.9	532	16.5
Europe	9	1.9	278	10.1	287	8.9
Asia	31	6.5	228	8.3	259	8.0
Africa	50	10.4	665	24.2	715	22.2
Australia	1	0.2	10	0.4	11	0.3
Age group						
0 – 4 weeks	37	7.7	--	--	37	1.1
5 weeks – 120 days	31	6.5	--	--	31	1.0

	Pediatric Patients (n = 479)		Adult Patients (n = 2748)		Total (n = 3227)	
121 days – < 2 years	48	10.0	--	--	48	1.5
2 – 5 years	108	22.5	--	--	108	3.3
6 – 11 years	140	29.2	--	--	140	4.3
12 – 16 years	115	24.0	--	--	115	3.6
> 16 years	--	--	2748	100	2748	85.2
Underlying disease						
Hematologic malignancy (no bone marrow transplant)	127	26.5	252	9.2	379	11.7
Bone marrow transplant	125	26.1	628	22.9	753	23.3
Human immunodeficiency virus	42	8.8	992	36.1	1034	32.0
Other	172	35.9	875	31.8	1047	32.4
Missing	13	2.7	1	0	14	0.4
Neutropenia at baseline						
No	328	68.5	2513	91.4	2841	88.0
Yes	144	30.1	227	8.3	371	11.5
Not assessed	7	1.5	8	0.3	15	0.5
Indication						
Invasive candidiasis	174	36.3	854	31.1	1028	31.9
Esophageal candidiasis	42	8.8	1002	36.5	1044	32.4
Invasive aspergillosis	80	16.7	251	9.1	331	10.3
Prophylaxis	157	32.8	534	19.4	691	21.4
Deep mycosis	20	4.2	105	3.8	125	3.9
Other	6	1.3	2	0.1	8	0.2

Modified from Sponsor's Summary of clinical safety p.12-13

MO comment: *As compared to adults, a greater proportion of pediatric patients exposed to micafungin were Caucasians, had neutropenia at baseline, hematologic malignancy as underlying disease, and invasive aspergillosis as the reason for trial enrollment.*

7.2.2 Explorations for Dose Response

The overall mean number of days of micafungin exposure was 19.8 (24.8 for children; 18.9 for adults), and the overall range was 1 – 681 days (1 – 681 days for children; 1 – 340 days for adults). Of the 479 micafungin-treated pediatric patients, 104 (21.7%) received micafungin for 1-6 days, 100 (20.9%) received micafungin for 7-10 days, 96 (20.0%) received micafungin for 11-14 days, 95 (19.8%) received micafungin for 15-28 days, 49 (10.2%) received micafungin for 29-56 days, and 35 (7.3%) received micafungin for more than 56 days.

Among 479 micafungin-treated pediatric patients, 192 (40.1%) received ≥2 mg/kg and 108 (22.5%) received ≥3 mg/kg for 7 or more days. One hundred sixty-nine (35.3%)

and 91 (19.0%) micafungin-treated pediatric patients received ≥2 mg/kg and ≥3 mg/kg for 10 or more days, respectively. The table below further summarizes the drug exposure for the highest proposed doses (2 and 3 mg/kg) in pediatric patients for those patients treated for at least 7 or 10 days by age group.

Table 60 Drug Exposure for More than 7 Days in Micafungin-treated Pediatric Patients

Age Group	Total n = 479		≥ 2 mg/kg for ≥ 7 days n = 192		≥ 2 mg/kg for ≥ 10 days n = 169		≥ 3 mg/kg for ≥ 7 days n = 108		≥ 3 mg/kg for ≥10 days n = 91	
	n	%	n	%	n	%	n	%	n	%
0 – 4 weeks	37	7.7	16	8.3	15	8.9	2	1.9	2	2.2
5 weeks – 120 days	31	6.5	15	7.8	14	8.3	3	2.8	2	2.2
121 days – < 2 years	48	10	20	10.4	16	9.5	10	9.3	6	6.6
2 – 5 years	108	22.5	53	27.6	46	27.2	34	31.5	29	31.9
6 – 11 years	140	29.2	59	30.7	50	29.6	43	39.8	37	40.7
12 – 16 years	115	24	29	15.1	28	16.6	16	14.8	15	16.5

Adapted from Summary of Clinical Safety p.12

MO comment: *Pediatric patients received micafungin at greater average daily dose on mg/kg basis and for longer duration of time as compared to the adult patient population.*

Dose response was assessed in respect to the incidence of adverse events, serious adverse events, adverse events resulting in the study drug discontinuation, as well as causes of death and incidence of laboratory abnormalities. Analyses of dose response are included in Section 7.5 of this review.

7.2.3 Special Animal and/or In Vitro Testing

Juvenile/neonatal rat studies were performed by the applicant in response to EMA concern regarding foci of altered hepatocytes (FAH) during prolonged (13 weeks) exposure to micafungin at 4-8 times highest human exposure. These studies were previously submitted to the IND 55,322 on 2/22/2011 and were reviewed by Pharmacology-Toxicology reviewer Dr. Owen McMaster. His review of the data submitted suggests that it appears that pups exposed to micafungin in early postnatal period are at no greater risk of developing FAH after prolonged (13 weeks) exposure to micafungin at the 32 mg/kg dose, resulting in exposures 8 times greater than the maximum human therapeutic exposure.

A 120-day safety update included information on a single non-GLP in vitro study evaluating hemolytic potential of 3 micafungin lots on rabbit blood. The study has been completed in October 2012, but study report has yet to be submitted to the NDA. The sponsor has provided a summary that there were not differences between the lots in the

hemolytic properties of micafungin. The potential for hemolysis with micafungin is well described in the currently approved Mycamine PI.

7.2.4 Routine Clinical Testing

Routine clinical testing while on study treatment included evaluation of the parameters potentially affected by the medication, such as: complete blood count, and comprehensive metabolic panel.

7.2.5 Metabolic, Clearance, and Interaction Workup

Evaluation of micafungin metabolites and clearance was performed in pediatric PK/safety studies.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The following target organs/effects were identified for micafungin and are described in the prescribing information: hepatic effects, hemolysis, histamine release, and injection site reaction. These findings are similar to those observed for the other approved echinocandins, caspofungin and anidulafungin, and are well-documented in the approved prescribing information. No new pharmacological class effects have been identified.

7.3 Major Safety Results

7.3.1 Deaths

Across the 11 pediatric studies, 76 (15.9%) of 479 patients died: 10 deaths (2.1%) occurred during study drug treatment and 66 deaths (13.8%) occurred during the posttreatment period. The primary cause of death for the pediatric patients were adverse events in Infections and Infestations (5.2%) and Respiratory, Thoracic and Mediastinal Disorders (4.0%) SOCs. The most common TEAEs reported as the primary cause of death overall in pediatric patients were respiratory failure (1.7%), aspergillosis (1.5%), and intracranial hemorrhage (1.0%), while the most common TEAEs reported as the primary cause of death overall in adult patients were sepsis (1.9%), septic shock (1.8%), respiratory failure (1.6%), and multi-organ failure (1.3%). No deaths in pediatric patients were considered by an investigator to be related to micafungin therapy. Mortality in the pediatric patients (15.9%) was lower than in the adult patients (22.5%).

7.3.2 Serious Adverse Events

Overall, the frequency of SAEs was similar between pediatric patients (27.8%; 133/479) and adult patients (27.7%; 760/2748). The table below summarizes the most common SAEs (≥ 1% of patients). There were no SAEs in the pediatric patients or adult patients

overall that exceeded 5%. The most common SAEs in the pediatric and adult patients were sepsis (3.8% versus 2.3%), respiratory failure (2.9% versus 3.1%), acute respiratory distress syndrome (2.5% versus 0.4%), respiratory distress (2.3% versus 0.7%), and septic shock (0.6% versus 1.8%), respectively.

Table 61 Frequency of Serious Adverse Events (> 1%) (All Micafungin-treated Patients)

MedDRA (v. 12.0) System Organ Class Preferred Term	All Micafungin-Treated Pediatric Patients (n = 479)	All Micafungin-Treated Adult Patients (n = 2748)
Any SAE	**133 (27.8%)**	**760 (27.7%)**
Blood and Lymphatic System Disorders	**22 (4.6%)**	**33 (1.2%)**
Febrile neutropenia	9 (1.9%)	16 (0.6%)
General Disorders and Administration Site Conditions	**23 (4.8%)**	**82 (3.0%)**
Multi-organ failure	5 (1%)	32 (1.2%)
Pyrexia	7 (1.5%)	23 (0.8%)
Infections and Infestations	**49 (10.2%)**	**284 (10.3%)**
Bacteremia	8 (1.7%)	16 (0.6%)
Septic shock	3 (0.6%)	50 (1.8%)
Sepsis	18 (3.8%)	63 (2.3%)
Pneumonia	5 (1%)	39 (1.4%)
Nervous System Disorders	**19 (4.0%)**	**57 (2.1%)**
Hemorrhage intracranial	5 (1.0%)	3 (0.1%)
Convulsion	9 (1.9%)	13 (0.5%)
Renal and Urinary Disorders	**19 (4.0%)**	**62 (2.3%)**
Renal failure	8 (1.7%)	32 (1.2%)
Renal failure acute	5 (1%)	14 (0.5%)
Respiratory, Thoracic and Mediastinal Disorders	**45 (9.4%)**	**197 (7.2%)**
Respiratory failure	14 (2.9%)	86 (3.1%)
Respiratory distress	11 (2.3%)	20 (0.7%)
Hypoxia	6 (1.3%)	6 (0.2%)
Acute respiratory distress syndrome	12 (2.5%)	11 (0.4%)
Vascular Disorders	**17 (3.5%)**	**67 (2.4%)**
Hypotension	8 (1.7%)	36 (1.3%)

Adapted from Sponsor's ISS/Summary of Clinical Safety p.39

MO comment: *Although, the overall incidence of SAEs was similar between pediatric and adult micafungin safety populations, some differences in the profile of the adverse events existed: nervous system disorders (seizures and intracranial hemorrhage) and respiratory distress were more common in children.*

7.3.3 Dropouts and/or Discontinuations

Nine percent (43/479) of pediatric patients and 13.6% (373/2748) of adult patients experienced a TEAE that led to study discontinuation. In pediatric patients, the most common TEAEs that led to study discontinuation were acute respiratory distress syndrome (0.8%), respiratory failure (0.6%), pulmonary hemorrhage (0.6%), and hemorrhage intracranial (0.6%). In adult patients, the most common TEAEs that led to study discontinuation were septic shock (1.1%), sepsis (0.8%), respiratory failure (0.8%), and multi-organ failure (0.8%).

MO comment: *Drug discontinuations due to adverse events were less common in pediatric patients as compared to adults. No specific adverse event stood out in pediatric patients as an adverse reaction of particular concern.*

7.3.4 Safety Results from Randomized Controlled Trials of Micafungin

In study 2108, candidemia and other invasive *Candida* infections, 56 subjects were exposed to micafungin at doses of 1.3 to 7.8 mg/kg. Micafungin exhibited a favorable safety profile as compared to AmBisome 3-5 mg/kg. The number of adverse events was overall similar between 2 study groups; however, fewer subjects on micafungin group experienced serious adverse events during treatment, infusion reactions, histamine-mediated reactions, renal and hepatic events.

In study 98-0-50 no clinically meaningful differences between safety profile of micafungin and fluconazole or differences between adults and pediatric patients were observed.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The majority of micafungin exposed pediatric (92%) and adult patients (91%) have experienced treatment emergent adverse events. The following table presents the incidence of common treatment emergent adverse events.

Table 62 Frequency of Common (> 10%) Treatment-emergent Adverse Events (Overall) (All Micafungin-treated Patients)

MedDRA (v. 12.0) System Organ Class Preferred Term	**All Micafungin-treated Pediatric Patients (n = 479)**	**All Micafungin-treated Adult Patients (n = 2748)**
Any TEAE	**439 (91.6%)**	**2497 (90.9%)**
Blood and Lymphatic System Disorders	**161 (33.6%)**	**923 (33.6%)**
Thrombocytopenia	70 (14.6%)	436 (15.9%)
Anemia	63 (13.2%)	323 (11.8%)
Neutropenia	61 (12.7%)	387 (14.1%)
Gastrointestinal Disorders	**285 (59.5%)**	**1542 (56.1%)**
Vomiting	146 (30.5%)	579 (21.1%)
Diarrhea	106 (22.1%)	686 (25.0%)
Nausea	91 (19%)	613 (22.3%)
Abdominal pain	76 (15.9%)	248 (9%)
Constipation	34 (7.1%)	311 (11.3%)
General Disorders and Administration Site Conditions	**256 (53.4%)**	**1242 (45.2%)**
Pyrexia	103 (21.5%)	544 (19.8%)
Mucosal inflammation	80 (16.7%)	361 (13.1%)
Metabolism and Nutrition Disorders	**231 (48.2%)**	**1140 (41.5%)**
Hypokalemia	87 (18.2%)	488 (17.8%)
Hypomagnesaemia	51 (10.6%)	371 (13.5%)
Nervous System Disorders	**120 (25.1%)**	**821 (29.9%)**
Headache	64 (13.4%)	436 (15.9%)
Skin and Subcutaneous Tissue Disorders	**197 (41.1%)**	**786 (28.6%)**
Rash	55 (11.5%)	230 (8.4%)
Pruritis	54 (11.3%)	139 (5.1%)
Vascular Disorders	135 (28.2%)	702 (25.5%)
Hypertension	65 (13.6%)	173 (6.3%)

Modifed from the clinical summary of safety, p. 15-17

MO comment: *Although the overall incidence of TEAE was similar between adults and children exposed to micafungin, abdominal pain, mucositis, rash, hypertension, and pruritis were more common in children than in adults. Among adverse events of interest with incidence of 5-10%, elevations in ALT and AST, hyperbilirubinemia were higher in pediatric patients as compared to adults (9%, 9% and 6% versus 5%, 5% and 3%, respectively).*

Dose/exposure analysis for common AEs

Five TEAEs (pyrexia, infusion related reaction, hypokalemia, vomiting, and diarrhea) were each reported with a frequency greater than 5% in at least 1 dose group. The frequency of individual TEAEs did not increase with increasing dose. Notably, of the pediatric patients who received a mean daily dose ≥ 4 mg/kg, 4 of the 5 related TEAEs

of infusion-related reaction were reported in study 9463-CL-2101 and all 7 of the related TEAEs of pyrexia were reported in study 9463-CL-2101.

MO comment: *These events were investigated by the applicant. The investigation revealed no conclusive cause for the cluster of fever/pyrexia adverse events at site 2260 in South Africa. Drug product, both retained samples and product retrieved from the clinical sites, met product quality requirements. The most likely attributable cause of the clustered events was thought to be related to the concomitant conditions in the patient population at the site. DSI has been consulted to further evaluate the site.*

AEs of Special Interest
The following adverse events were considered adverse events of special interest and had been identified as associated with micafungin use in adults: hepatic events, renal events, infusion/histamine mediated reactions, hemolytic events, injection site reactions. The sponsor identified SMQs associated with the above events and the tables below report the incidence of these events in adult and pediatric patients exposed to micafungin.

Table 63 Hepatic Events

SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	Pediatric Patients (n = 479)	Adult Patients (n = 2748)
ALL SYSTEMS	ANY AE	151 (31.5%)	649 (23.6%)
EYE DISORDERS	ANY AE	6 (1.3%)	15 (0.5%)
	OCULAR ICTERUS	6 (1.3%)	15 (0.5%)
GASTROINTESTINAL DISORDERS	ANY AE	6 (1.3%)	33 (1.2%)
	ASCITES	6 (1.3%)	31 (1.1%)
HEPATOBILIARY DISORDERS	ANY AE	62 (12.9%)	183 (6.7%)
	CHOLESTASIS	2 (0.4%)	9 (0.3%)
	HEPATIC FAILURE, acute, chronic	4 (0.8%)	20 (0.7%)
	HEPATIC FUNCTION ABNORMAL	2 (0.4%)	7 (0.3%)
	HEPATITIS, Hepatitis toxic, cytolytic, ischemic	1 (0.2%)	13 (0.5%)
	HEPATOMEGALY	26 (5.4%)	13 (0.5%)
	HEPATOSPLENOMEGALY	4 (0.8%)	6 (0.2%)
	HYPERBILIRUBINAEMIA	28 (5.8%)	84 (3.1%)
	HYPERTRANSAMINASAEMIA	1 (0.2%)	0
	JAUNDICE	10 (2.1%)	45 (1.5%)
	LIVER DISORDER	1 (0.2%)	5 (0.2%)
	HEPATOTOXICITY	0	4 (0.1%)
IMMUNE SYSTEM DISORDERS	ANY AE	1 (0.2%)	2 (0.1%)
	ACUTE GRAFT VERSUS HOST	1 (0.2%)	2 (0.1%)

SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	Pediatric Patients (n = 479)	Adult Patients (n = 2748)
	DISEASE IN LIVER		
INVESTIGATIONS	ANY AE	87 (18.2%)	443 (16.1%)
	ALANINE AMINOTRANSFERASE INCREASED	45 (9.4%)	132 (4.8%)
	AMMONIA INCREASED	3 (0.6%)	1 (0%)
	ASPARTATE AMINOTRANSFERASE INCREASED	43 (9.0%)	142 (5.2%)
	BILIRUBIN CONJUGATED INCREASED	3 (0.6%)	15 (0.5%)
	BLOOD ALKALINE PHOSPHATASE INCREASED	17 (3.5%)	151 (5.5%)
	BLOOD BILIRUBIN INCREASED	13 (2.7%)	83 (3.0%)
	BLOOD BILIRUBIN UNCONJUGATED INCREASED	2 (0.4%)	0
	GAMMA-GLUTAMYLTRANSFERASE INCREASED	20 (4.2%)	24 (1.0%)
	HEPATIC ENZYME INCREASED	5 (1.0%)	40 (1.5%)
	INTERNATIONAL NORMALISED RATIO INCREASED	1 (0.2%)	13 (0.5%)
	LIVER FUNCTION TEST ABNORMAL	11 (2.3%)	40 (1.5%)
	PROTHROMBIN TIME PROLONGED	9 (1.9%)	15 (0.5%)
	UROBILIN URINE PRESENT	3 (0.6%)	1 (0%)
	TRANSAMINASES INCREASED	0	19 (0.7%)
METABOLISM AND NUTRITION DISORDERS	ANY AE	25 (5.2%)	76 (2.8%)
	HYPOALBUMINAEMIA	25 (5.2%)	76 (2.8%)
NERVOUS SYSTEM DISORDERS	ANY AE	0	3 (0.1%)
	ASTERIXIS	0	1 (0%
	HEPATIC ENCEPHALOPATHY	0	2 (0.1%)

Additional TEAE in the hepatic SOC that were seen in adults, but not in pediatric patients treated with micafungin were: hepatic cirrhosis (2), hepatic steatosis (1), liver tenderness (1), hepatic lesion (1), and portal hypertension (1).

MO comment: *The SMQ for hepatic events identified that the incidence of the hepatic events was numerically higher in pediatric patients as compared to adults, primarily due to liver enzyme elevations. Hepatic events of particular concern: hepatitis and liver failure were equally uncommon in both groups. Hepatotoxicity as a TEAE was reported only in adults. Additional analyses of changes from baseline in pediatric patients were performed relative to dose received and no dose response was observed.*

Table 64 Hemolytic TEAE

SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	Pediatric Patients (n = 479)	Adult Patients (n = 2748)
ALL SYSTEMS	ANY AE	10 (2.1%)	48 (1.7%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	ANY AE	0	6 (0.2%)
	HAEMOLYSIS	0	2 (0.1%)
	HAEMOLYTIC ANAEMIA	0	4 (0.1%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	ANY AE	9 (1.9%)	37 (1.3%)
	TRANSFUSION REACTION	9 (1.9%)	37 (1.3%)
INVESTIGATIONS	ANY AE	0	6 (0.2%)
	ANTI-ERYTHROCYTE ANTIBODY POSITIVE	0	1 (<0.1%)
	HAEMOGLOBIN URINE PRESENT	0	4 (0.1%)
	RETICULOCYTE COUNT INCREASED	0	1 (<0.1%)
RENAL AND URINARY DISORDERS	ANY AE	1 (0.2%)	0
	HAEMOGLOBINURIA	1 (0.2%)	0

MO comment: *No differences in the incidence of hemolytic TEAE in hemolytic SMQ analysis were observed between adults and children exposed to micafungin.*

Table 65 Histamine TEAE

SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	Pediatric Patients (n = 479)	Adult Patients (n = 2748)
ALL SYSTEMS	ANY AE	215 (44.9%)	1082 (39.4%)
CARDIAC DISORDERS	ANY AE	3 (0.6%)	44 (1.6%)
	CARDIAC ARREST	2 (0.4%)	24 (0.9%)
	CARDIO-RESPIRATORY ARREST	1 (0.2%)	20 (0.7%)
EYE DISORDERS	ANY AE	11 (2.3%)	30 (1.1%)
	CONJUNCTIVITIS	3 (0.6%)	17 (0.6%)
	EYE OEDEMA	2 (0.4%)	0
	EYE SWELLING	2 (0.4%)	7 (0.3%)
	EYELID OEDEMA	4 (0.8%)	6 (0.2%)
GASTROINTESTINAL DISORDERS	ANY AE	18 (3.8%)	60 (2.25)
	LIP OEDEMA	0	1 (<0.1%)
	LIP SWELLING	0	1 (<0.1%)
	MOUTH ULCERATION	2 (0.4%)	10 (0.4%)
	OEDEMA MOUTH	1 (0.2%)	1 (<0.1%)
	STOMATITIS	15 (3.1%)	44 (1.6%)
	SWOLLEN TONGUE	0	5 (0.2%)
GENERAL DISORDERS	ANY AE	26 (5.4%)	134 (4.9%)

SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	Pediatric Patients (n = 479)	Adult Patients (n = 2748)
AND ADMINISTRATION SITE CONDITIONS	CHEST DISCOMFORT	1 (0.2%)	33 (1.2%)
	FACE OEDEMA	9 (1.9%)	24 (0.9%)
	OEDEMA	17 (3.5%)	83 (3%)
	SENSATION OF FOREIGN BODY	0	1 (<0.1%)
IMMUNE SYSTEM DISORDERS	ANY AE	1 (0.2%)	4 (0.1%)
	ANAPHYLACTIC REACTION	0	4 (0.1%)
	ANAPHYLACTOID REACTION	1 (0.2%)	0
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	ANY AE	0	2 (0.1%)
	ANAPHYLACTIC TRANSFUSION REACTION	0	2 (0.1%)
INVESTIGATIONS	ANY AE	1 (0.2%)	7 (0.3%)
	BLOOD PRESSURE DECREASED	0	7 (0.3%)
	BLOOD PRESSURE DIASTOLIC DECREASED	1 (0.2%)	0
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	ANY AE	0	7 (0.3%)
	GENITAL ULCERATION	0	5 (0.2%)
	VAGINAL ULCERATION	0	1 (<0.1%)
	VULVAL ULCERATION	0	1 (<0.1%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	ANY AE	103 (21.5%)	496 (18%)
	ACUTE RESPIRATORY FAILURE	0	9 (0.3%)
	ASTHMA	0	4 (0.1%)
	BRONCHIAL OEDEMA	0	1 (<0.1%)
	BRONCHOSPASM	4 (0.8%)	27 (1%)
	CHOKING	1 (0.2%)	2 (0.1%)
	CHOKING SENSATION	0	1 (<0.1%)
	COUGH	47 (9.8%)	209 (7.6%)
	DYSPNOEA	20 (4.2%)	168 (6.1%)
	HYPERVENTILATION	0	3 (0.1%)
	LARYNGEAL OEDEMA	1 (0.2%)	1 (<0.1%)
	RESPIRATORY ARREST	1 (0.2%)	8 (0.3%)
	RESPIRATORY DISTRESS	25 (5.2%)	42 (1.5%)
	RESPIRATORY FAILURE	16 (3.3%)	96 (3.5%)
	SNEEZING	1 (0.2%)	2 (0.1%)
	STRIDOR	2 (0.4%)	1 (<0.1%)
	THROAT TIGHTNESS	1 (0.2%)	1 (<0.1%)
	WHEEZING	10 (2.1%)	52 (1.9%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	ANY AE	128 (26.7%)	502 (18.3%)
	ANGIOEDEMA	0	1 (<0.1%)
	BLISTER	3 (0.6%)	15 (0.5%)
	DERMATITIS BULLOUS	1 (0.2%)	1 (<0.1%)
	DERMATITIS EXFOLIATIVE	0	2 (0.1%)
	DRUG ERUPTION	7 (1.5%)	6 (0.2%)
	ERYTHEMA	22 (4.6%)	72 (2.6%)
	GENERALISED ERYTHEMA	2 (0.4%)	8 (0.3%)

SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	Pediatric Patients (n = 479)	Adult Patients (n = 2748)
	PERIORBITAL OEDEMA	6 (1.3%)	9 (0.3%)
	PRURITUS	54 (11.3%)	139 (5.1%)
	PRURITUS ALLERGIC	1 (0.2%)	4 (0.1%)
	PRURITUS GENERALISED	3 (0.6%)	8 (0.3%)
	RASH	55 (11.5%)	226 (8.2%)
	RASH ERYTHEMATOUS	1 (0.2%)	13 (0.5%)
	RASH GENERALISED	4 (0.8%)	18 (0.7%)
	RASH PRURITIC	7 (1.5%)	28 (1%)
	SKIN EXFOLIATION	3 (0.6%)	19 (0.7%)
	SWELLING FACE	5 (1%)	15 (0.5%)
	URTICARIA	24 (5%)	34 (1.2%)
VASCULAR DISORDERS	Any AE	49 (10.2%)	302 (11%)
	CARDIOVASCULAR INSUFFICIENCY	0	2 (0.1%)
	FLUSHING	10 (2.1%)	58 (2.1%)
	HYPOTENSION	40 (8.4%)	247 (9.0%)
	SHOCK	1 (0.2%)	11 (0.4%)

MO comment: *Even though the overall incidence of the events under histamine reactions SMQ was similar between adults and children, differences in the profile of the histamine mediated adverse reactions between adults and pediatric patients were notable. The incidence of rash, urticaria, and pruritis was higher in pediatric patients as compared to adults.*

Table 66 Infusion Reactions

SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	Pediatric Patients (n = 479)	Adult Patients (n = 2748)
ALL SYSTEMS	ANY AE	37 (7.7%)	90 (3.3%)
CARDIAC DISORDERS	ANY AE	1 (0.2%)	0
	TACHYCARDIA	1 (0.2%)	0
EAR AND LABYRINTH DISORDERS	ANY AE	0	1 (<0.1%)
	VERTIGO	0	1 (<0.1%)
GASTROINTESTINAL DISORDERS	Any AE	3 (0.6%)	9 (0.3%)
	DIARRHOEA	1 (0.2%)	0
	NAUSEA	0	8 (0.3%)
	VOMITING	2 (0.4%)	4 (0.1%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	ANY AE	27 (5.6%)	67 (2.4%)
	CHILLS	1 (0.2%)	8 (0.3%)
	HYPOTHERMIA	0	3 (0.1%)

SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	Pediatric Patients (n = 479)	Adult Patients (n = 2748)
	INFUSION RELATED REACTION	24 (5%)	40 (1.5%)
	IRRITABILITY	1 (0.2%)	1 (<0.1%)
	OEDEMA PERIPHERAL	0	1 (<0.1%)
	PYREXIA	5 (1%)	17 (0.6%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	ANY AE	1 (0.2%)	2 (0.1%)
	PROCEDURAL HYPERTENSION	0	2 (0.1%)
	PROCEDURAL HYPOTENSION	1 (0.2%)	0
INVESTIGATIONS	ANY AE	2 (0.4%)	0
	BODY TEMPERATURE DECREASED	1 (0.2%)	0
	BODY TEMPERATURE INCREASED	1 (0.2%)	0
METABOLISM AND NUTRITION DISORDERS	ANY AE	0	2 (0.1%)
	HYPOGLYCAEMIA	0	1 (<0.1%)
	HYPONATRAEMIA	0	1 (<0.1%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	ANY AE	0	1 (<0.1%)
	BACK PAIN	0	1 (<0.1%)
NERVOUS SYSTEM DISORDERS	ANY AE	0	5 (0.2%)
	DIZZINESS	0	1 (<0.1%)
	HEADACHE	0	1 (<0.1%)
	SOMNOLENCE	0	2 (0.1%)
	TREMOR	0	1 (<0.1%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	ANY AE	0	5 (0.2%)
	BRONCHOSPASM	0	1 (<0.1%)
	DYSPNOEA	0	3 (0.1%)
	SNEEZING	0	1 (<0.1%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	ANY AE	6 (1.3%)	12 (0.4%)
	DERMATITIS	0	1 (<0.1%)
	DERMATITIS ALLERGIC	0	1 (<0.1%)
	DRUG ERUPTION	5 (1%)	1 (<0.1%)
	ERYTHEMA	0	1 (<0.1%)
	HYPERHIDROSIS	1 (0.2%)	2 (0.1%)
	RASH	0	4 (0.1%)
	RASH MORBILLIFORM	0	1 (<0.1%)
	RASH PRURITIC	0	1 (<0.1%)
VASCULAR DISORDERS	ANY AE	1 (0.2%)	3 (0.1%)
	FLUSHING	0	1 (<0.1%)
	HYPERTENSION	1 (0.2%)	1 (<0.1%)
	HYPOTENSION	0	1 (<0.1%)

MO comment: *SMQ analysis of infusion reactions showed that most individual events were rare in pediatric patients. Overall, events in this SMQ are more common in pediatric patients receiving micafungin as compared to adults. Notable individual events were infusion-related reactions and drug eruption, occurring more frequently in pediatric patients than in adults.*

Table 67 Injection Site Reactions

SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	Pediatric Patients (n = 479)	Adult Patients (n = 2748)
ALL SYSTEMS	ANY AE	81 (16.9%)	275 (10%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	ANY AEs	81 (16.9%)	275 (10%)
	APPLICATION SITE VESICLES	1 (0.2%)	0
	CATHETER RELATED COMPLICATION	17 (3.5%)	29 (1.1%)
	CATHETER SITE DISCHARGE	0	6 (0.2%)
	CATHETER SITE EROSION	1 (0.2%)	3 (0.1%)
	CATHETER SITE ERYTHEMA	15 (3.1%)	54 (2%)
	CATHETER SITE HAEMATOMA	0	4 (0.1%)
	CATHETER SITE HAEMORRHAGE	3 (0.6%)	24 (0.9%)
	CATHETER SITE INFLAMMATION	2 (0.4%)	15 (0.5%)
	CATHETER SITE OEDEMA	1 (0.2%)	3 (0.1%)
	CATHETER SITE PAIN	15 (3.1%)	43 (1.6%)
	CATHETER SITE PHLEBITIS	0	3 (0.1%)
	CATHETER SITE PRURITUS	1 (0.2%)	4 (0.1%)
	CATHETER SITE RASH	1 (0.2%)	1 (<0.1%)
	CATHETER SITE RELATED REACTION	6 (1.3%)	22 (0.8%)
	CATHETER SITE SWELLING	1 (0.2%)	4 (0.1%)
	CATHETER THROMBOSIS	9 (1.9%)	33 (1.2%)
	IMPLANT SITE HAEMORRHAGE	0	1 (<0.1%)
	INFUSION SITE ERYTHEMA	0	4 (0.1%)
	INFUSION SITE EXTRAVASATION	3 (0.6%)	5 (0.2%)
	INFUSION SITE HAEMORRHAGE	0	2 (0.1%)
	INFUSION SITE INDURATION	0	1 (<0.1%)
	INFUSION SITE INFLAMMATION	0	5 (0.2%)
	INFUSION SITE IRRITATION	0	2 (0.1%)
	INFUSION SITE OEDEMA	0	1 (<0.1%)
	INFUSION SITE PAIN	9 (1.9%)	11 (0.4%)
	INFUSION SITE PHLEBITIS	1 (0.2%)	17 (0.6%)
	INFUSION SITE SWELLING	1 (0.2%)	0
	INFUSION SITE THROMBOSIS	1 (0.2%)	10 (0.4%)
	INFUSION SITE URTICARIA	1 (0.2%)	1 (<0.1%)

SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	Pediatric Patients (n = 479)	Adult Patients (n = 2748)
	INFUSION SITE VESICLES	1 (0.2%)	0
	INJECTION SITE DISCOLOURATION	1 (0.2%)	0
	INJECTION SITE ERYTHEMA	1 (0.2%)	0
	INJECTION SITE HAEMATOMA	0	4 (0.1%)
	INJECTION SITE HAEMORRHAGE	2 (0.4%)	0
	INJECTION SITE PAIN	0	3 (0.1%)
	INJECTION SITE PHLEBITIS	1 (0.2%)	3 (0.1%)
	INJECTION SITE REACTION	0	2 (0.1%)
	MECHANICAL COMPLICATION OF IMPLANT	0	1 (<0.1%)
	PUNCTURE SITE PAIN	1 (0.2%)	0
	VENIPUNCTURE SITE INFLAMMATION	1 (0.2%)	0
	VESSEL PUNCTURE SITE HAEMATOMA	1 (0.2%)	1 (<0.1%)
	VESSEL PUNCTURE SITE HAEMORRHAGE	0	2 (0.1%)
	VESSEL PUNCTURE SITE PAIN	1 (0.2%)	3 (0.1%)

MO comment: *SMQ analysis of injection site reactions was unrevealing. Although the incidence of any TEAE under this query was 7% higher in pediatric patients as compared to adults, extreme difficulty in maintaining IV access in pediatric patients might have played a big role in the observed discrepancy.*

Table 68 Renal TEAE

SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	Pediatric Patients (n = 479)	Adult Patients (n = 2748)
ALL SYSTEMS	ANY AE	72 (15%)	364 (13.2%)
INVESTIGATIONS	ANY AEs	46 (9.6)	198 (7.2%)
	BLOOD CREATININE INCREASED	15 (3.1%)	113 (4.1%)
	BLOOD UREA INCREASED	22 (4.6%)	88 (3.2%)
	CREATININE RENAL CLEARANCE DECREASED	1 (0.2%)	2 (0.1%)
	PROTEIN URINE PRESENT	3 (0.6%)	5 (0.2%)
	URINE OUTPUT DECREASED	18 (3.8%)	48 (1.7%)
RENAL AND URINARY DISORDERS	ANY AEs	34 (7.1%)	180 (6.6%)
	ACUTE PRERENAL FAILURE	0	4 (0.1%)
	ANURIA	0	6 (0.2%)
	AZOTAEMIA	0	9 (0.3%)
	OLIGURIA	2 (0.4%)	21 (0.8%)

SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	Pediatric Patients (n = 479)	Adult Patients (n = 2748)
	PROTEINURIA	4 (0.8%)	12 (0.4%)
	RENAL FAILURE	21 (4.4%)	87 (3.2%)
	RENAL FAILURE ACUTE	6 (1.3%)	41 (1.5%)
	RENAL FAILURE NEONATAL	1 (0.2%)	0
	RENAL IMPAIRMENT	0	8 (0.3%)
	RENAL TUBULAR DISORDER	0	1 (<0.1%)
	RENAL TUBULAR NECROSIS	0	2 (0.1%)
	TUBULOINTERSTITIAL NEPHRITIS	0	2 (0.1%)
SURGICAL AND MEDICAL PROCEDURES	ANY AEs	0	2 (0.1%)
	HAEMODIALYSIS	0	2 (0.1%)

MO comment: *No significant differences were observed between adults and pediatric patients with respect to the incidence of the renal adverse events SMQ analysis*

7.4.2 Laboratory Findings

There were no clinically meaningful differences between the adult and pediatric populations in the frequency of shifts in laboratory parameters to low or high. There were also no differences in shifts of laboratory parameters by age group or by mean daily dose in micafungin-treated pediatric patients. Patients with longer treatment duration demonstrated a trend toward higher occurrence of shifts.

Table 69 Incidence of Selected Laboratory Test Abnormalities, Changes from Baseline on Treatment, All Micafungin Treated Pediatric Patients

	Dose Group (mg/kg)				
	< 0.9 mg/kg n = 35 (%)	1 – < 2 n = 198 (%)	2 – < 3 n = 102 (%)	3 – < 4 n = 51 (%)	≥ 4 n = 93 (%)
ALT	N=30	N=165	N=91	N=41	N=82
2.5-<5 x ULN	1 (3.2)	15 (8.5)	6 (6.5)	5 (10)	8 (8.9)
5-<10 x ULN	1 (3.2)	6 (3.4)	4 (4.3)		2 (2.2)
≥10 x ULN		3 (1.7)			
Patients with an increase from baseline (%)	2 (6.7)	23 (13.9)	8 (8.8)	3 (7.3)	7 (8.5)
AST	N=31	N=164	N=91	N=38	N=82
2.5-5 x ULN	4 (12.54)	7 (4)	8 (8.7)	2 (4.4)	4 (4.5)
5-10 x ULN	1 (3.1)	3 (1.7)	7 (7.6)	1 (2.2)	3 (3.4)
≥10 x ULN		2 (1.1)	2 (2.2)		
Patients with an increase from	4 (12.9)	10 (6.1)	15 (16.5)	1 (2.6)	5 (6.1)

	Dose Group (mg/kg)				
	< 0.9 mg/kg n = 35 (%)	**1 – < 2 n = 198 (%)**	**2 – < 3 n = 102 (%)**	**3 – < 4 n = 51 (%)**	**≥ 4 n = 93 (%)**
baseline (%)					
Total Bili	N=30	N=169	N=92	N=41	N=77
2.5-<5 x ULN	3 (9.7)	5 (2.9)	5 (5.4)	1 (2.1)	6 (7.1)
5-<10 x ULN	1 (3.2)	6 (3.3)	4 (4.3)	2 (4.3)	2 (2.4)
≥10 x ULN	1 (3.2)	6 (3.3)	4 (4.3)	1 (2.1)	3 (3.6)
Patients with an increase from baseline (%)	4 (13.3)	11 (6.5)	9 (9.8)	2 (4.9)	3 (3.9)
Alk Phos	N=29	N=165	N=88	N=40	N=83
2.5-<5 x ULN	3 (10)	17 (9.6)	23 (25.9)	5 (10.9)	9 (10.0)
5-<10 x ULN	2 (6.7)	8 (4.5)	8 (9.0)	2 (4.3)	5 (5.6)
≥10 x ULN		1 (0.6)	1 (1.1)	1 (2.2)	
Patients with an increase from baseline (%)	2 (6.9)	18 (10.9)	13 (14.8)	4 (10.0)	4 (4.8)
GGT	N=0	N=21	N=0	N=11	N=22
2.5-<5 x ULN		6 (28.6)		2 (18.2)	4 (18.2)
5-<10 x ULN		2 (9.5)		2 (18.2)	4 (18.2)
≥10 x ULN		2 (9.5)		2 (18.2)	1 (4.5)
Patients with an increase from baseline (%)		8 (38.1)		2 (18.2)	6 (27.3)
Creatinine	N=32	N=186	N=98	N=46	N=85
2-<3 x ULN		5 (2.6)	3 (3)		
3-<4 x ULN		1 (0.5)	1 (1)		
≥4 x ULN					
Patients with an increase from baseline (%)	0	4 (2.2)	3 (3.1)	0	0
Hemoglobin	N=33	N=191	N=98	N=47	N=84
8-<9 g/dL	6 (17.1)	41 (21)	19 (19.2)	6 (11.8)	10 (11)
7-<8 g/dL	3 (8.6)	16 (8.2)	6 (6.1)	9 (17.6)	3 (3.3)
<7 g/dL	1 (2.9)	5 (2.6)	3 (3)		1 (1.1)
Patients with a decrease from baseline (%)	6 (18.2)	39 (20.4)	24 (24.5)	16 (34.0)	13 (15.5)

Modified from ISS Appendix tables 6.1.3 p. 1-23

Table 70 ALT Elevation by Treatment Duration

Treatment Duration (days)	Total	≤ ULN/ No Elevation		> ULN		> 3 x ULN		> 5 x ULN		> 10 x ULN	
		n	%	n	%	n	%	n	%	n	%
1 – 6	104	69	66.3	13	21.2	3	2.9	2	1.9	1	1.0
7 – 10	97	64	66.0	20	48.5	3	3.1	2	2.1	0	0
11 – 14	93	57	61.3	29	45.2	8	8.6	4	4.3	0	0
15 – 28	95	65	68.4	29	53.7	8	8.4	4	4.2	1	1.1
29 – 56	49	25	51.0	24	71.4	5	10.2	3	6.1	0	0
> 56	35	22	62.9	13	74.3	6	17.1	2	5.7	1	2.9
All	473	302	63.8	128	47.1	33	7.0	17	3.6	3	0.6

Adapted from the summary of clinical safety p.53

Table 71 AST Elevation by Treatment Duration

Treatment Duration (days)	Total	≤ ULN/ No Elevation		> ULN		> 3 x ULN		> 5 x ULN		> 10 x ULN	
		n	%	n	%	n	%	n	%	n	%
1 – 6	104	63	60.6	22	21.2	6	5.8	2	1.9	2	1.9
7 – 10	97	48	49.5	47	48.5	5	5.2	3	3.1	1	1.0
11 – 14	93	50	53.8	42	45.2	14	15.1	6	6.5	2	2.2
15 – 28	95	43	45.3	51	53.7	13	13.7	6	6.3	3	3.2
29 – 56	49	13	26.5	35	71.4	13	26.5	9	18.4	1	2.0
> 56	35	8	22.9	26	74.3	13	37.1	7	20.0	3	8.6
All	473	225	47.6	223	47.1	64	13.5	33	7.0	12	2.5

Modified from the ISS Appendix tables 7.1.2, p. 1

Table 72 Total Bilirubin by Treatment Duration

Treatment Duration (days)	Total	≤ ULN/ No Elevation		> ULN		> 1.5 x ULN		> 3 x ULN		> 5 x ULN		> 10 x ULN	
		n	%	n	%	n	%	n	%	n	%	n	%
1 – 6	104	59	56.7	24	23.1	19	19.3	12	11.5	7	6.7	2	1.9
7 – 10	97	69	71.1	11	11.3	7	7.2	4	4.1	4	4.1	3	3.1
11 – 14	93	72	77.4	13	14.0	9	9.7	4	4.3	3	3.2	2	2.2
15 – 28	95	69	72.6	25	26.3	21	22.1	12	12.6	7	7.4	3	3.2
29 – 56	49	39	79.6	10	20.4	8	16.3	5	10.2	4	8.2	2	4.1
> 56	35	27	77.1	8	22.9	7	20.0	4	11.4	4	11.4	2	5.7
All	473	335	70.8	91	19.2	71	15.0	41	8.7	29	6.1	14	3.0

Modified from the ISS Appendix tables 7.4.1, p. 1

Table 73 Creatinine Elevation by Treatment Duration

Percent increase from baseline†	Treatment Duration (days)							
	1 – 14 days n = 292		15 – 28 days n = 92		29 – 56 days n = 47		> 56 days n = 35	
	n	%	n	%	n	%	n	%
≥ 25%	99	33.9	46	50.0	22	46.8	24	68.6
≥ 50%	65	22.3	33	35.9	14	29.8	16	45.7
≥ 100%	24	8.2	19	20.7	7	14.9	10	28.6

Adapted from the clinical summary of safety p. 53

7.4.3 Vital Signs

Not applicable

7.4.4 Electrocardiograms (ECGs)

Not applicable

7.4.5 Special Safety Studies/Clinical Trials

Not applicable

7.4.6 Immunogenicity

Not applicable

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Deaths
The frequency of fatal outcomes did not increase with increasing mean daily dose; the frequency of death was lowest in the highest dose group (≥ 3.6 mg/kg).
Overall, the percentages of pediatric patients who died in each mean daily dose group were as follows: <0.9 mg/kg (11.4%), 1 – < 2 mg/kg (16.2%), 2 – < 3 mg/kg (28.4%), 3 – < 4 mg/kg (7.8%), and ≥ 4 mg/kg (7.5%).

MO comment: *No dose dependency in the incidence of death was identified.*

SAE
The table below summarizes the overall frequency of SAEs by micafungin mean daily dose for all pediatric patients. The frequency of SAEs was the lowest in the highest dose group (≥ 4 mg/kg).

Table 74 Frequency of Serious Adverse Events by Dose Group (All Micafungin-treated Pediatric Patients)

	Dose Group (mg/kg)				
	< 0.9 (n = 35)	**1 – < 2 (n = 198)**	**2 – < 3 (n = 102)**	**3 – < 4 (n = 51)**	**≥ 4 (n = 93)**
Any SAE	8 (22.9%)	52 (26.3%)	40 (39.2%)	14 (27.5%)	19 (20.4%)

SAE: serious adverse event.

MO comment: *No dose dependency in the incidence of SAEs was identified.*

TEAE

Table 75 Frequency of Treatment Emergent Adverse Events by Dose Group (All Micafungin-treated Pediatric Patients) >10%

MedDRA (v. 12.0) System Organ Class/Preferred Term	Dose Group (mg/kg)				
	< 0.9 (n = 35)	**1 – < 2 (n = 198)**	**2 – < 3 (n = 102)**	**3 – < 4 (n = 51)**	**≥ 4 (n = 93)**
Any TEAE	**30 (85.7%)**	**191 (96.5%)**	**96 (94.1%)**	**41 (80.4%)**	**81 (87.1%)**
Blood and Lymphatic System Disorders	**15 (42.9%)**	**85 (42.9%)**	**31 (30.4%)**	**12 (23.5%)**	**18 (19.4%)**
Neutropenia	9 (25.7%)	41 (20.7%)	7 (6.9%)	2 (3.9%)	2 (2.2%)
Anemia	8 (22.9%)	32 (16.2%)	11 (10.8%)	3 (5.9%)	9 (9.7%)
Thrombocytopenia	11 (31.4%)	45 (22.7%)	7 (6.9%)	5 (9.8%)	2 (2.2%)
Cardiac Disorders	**7 (20%)**	**41 (20.7%)**	**23 (22.5%)**	**10 (19.6%)**	**16 (17.2%)**
Tachycardia	6 (17.1%)	26 (13.1%)	7 (6.9%)	2 (3.9%)	6 (6.5%)
Gastrointestinal Disorders	**23 (65.7%)**	**157 (79.3%)**	**54 (52.9%)**	**22 (43.1%)**	**29 (31.2%)**
Vomiting	10 (28.6%)	87 (43.9%)	21 (20.6%)	11 (21.6%)	17 (18.3%)
Nausea	8 (22.9%)	63 (31.8 %)	12 (11.8%)	7 (13.7%)	1 (1.1%)
Abdominal pain	4 (11.4%)	50 (25.3%)	9 (8.8%)	8 (15.7%)	5 (5.4%)
Diarrhea	10 (28.6%)	67 (33.8%)	15 (14.7%)	6 (11.8%)	8 (8.6%)
Constipation	3 (8.6%)	20 (10.1%)	6 (5.9%)	1 (2%)	4 (4.3%)
General Disorders and Administration Site Conditions	**21 (60.0%)**	**138 (69.7%)**	**36 (35.3%)**	**22 (43.1%)**	**39 (41.9%)**
Mucosal inflammation	11 (31.4%)	57 (28.8%)	5 (4.9%)	2 (3.9%)	5 (5.4%)
Edema	5 (14.3%)	7 (3.5%)	2 (2%)	1 (2%)	2 (2.2%)
Chills	5 (14.3%)	15 (7.6%)	6 (5.9%)	4 (7.8%)	5 (5.4%)
Pyrexia	7 (20%)	59 (29.8%)	11 (10.8%)	5 (9.8%)	21 (22.6%)
Hepatobiliary Disorders	**7 (20%)**	**37 (18.7%)**	**12 (11.8%)**	**4 (7.8%)**	**7 (7.5%)**
Hyperbilirubinemia	5 (14.3%)	14 (7.1%)	3 (2.9%)	1 (2%)	5 (5.4%)
Investigations	**13 (37.1%)**	**104 (52.5%)**	**32 (31.4%)**	**16 (31.4%)**	**26 (28%)**
Alanine aminotransferase increased	4 (11.4%)	26 (13.1%)	5 (4.9%)	5 (9.8%)	5 (5.4%)
Aspartate aminotransferase increased	2 (5.7%)	24 (12.1%)	7 (6.9%)	5 (9.8%)	5 (5.4%)

MedDRA (v. 12.0) System Organ Class/Preferred Term	Dose Group (mg/kg)				
	< 0.9 (n = 35)	1 – < 2 (n = 198)	2 – < 3 (n = 102)	3 – < 4 (n = 51)	≥ 4 (n = 93)
Metabolism and Nutrition Disorders	**18 (51.4%)**	**121 (61.1%)**	**39 (38.2%)**	**20 (39.2%)**	**33 (35.5%)**
Hypokalemia	8 (22.9%)	39 (19.7%)	14 (13.7%)	10 (19.6%)	16 (17.2%)
Hypocalcaemia	2 (5.7%)	21 (10.6%)	6 (5.9%)	2 (3.9%)	5 (5.4%)
Fluid overload	2 (5.7%)	20 (10.1%)	6 (5.9%)	1 (2%)	5 (5.4%)
Hypomagnesemia	4 (11.4%)	32 (16.2%)	6 (5.9%)	2 (3.9%)	7 (7.5%)
Hypophosphatemia	5 (14.3%)	10 (5.1%)	3 (2.9%)	1 (2%)	7 (7.5%)
Anorexia	4 (11.4%)	22 (11.1%)	2 (2.0%)	1 (2%)	0
Malnutrition	3 (8.6%)	22 (11.1%)	2 (2.0%)	1 (2%)	1 (1.1%)
Hyperglycemia	0	20 (10.1%)	7 (6.9%)	3 (5.9%)	9 (9.7%)
Musculoskeletal and Connective Tissue Disorders	**10 (28.6%)**	**60 (30.3%)**	**13 (12.7%)**	**8 (15.7%)**	**8 (8.6%)**
Pain in extremity	1 (2.9%)	21 (10.6%)	8 (7.8%)	2 (3.9%)	5 (5.4%)
Nervous System Disorders	**13 (37.1%)**	**58 (29.3%)**	**22 (21.6%)**	**13 (25.5%)**	**14 (15.1%)**
Headache	8 (22.9%)	34 (17.2%)	7 (6.9%)	7 (13.7%)	8 (8.6%)
Renal and Urinary Disorders	**10 (28.6%)**	**40 (20.2%)**	**12 (11.8%)**	**6 (11.8%)**	**10 (10.8%)**
Hematuria	4 (11.4%)	10 (5.1%)	2 (2%)	0	2 (2.2%)
Respiratory, Thoracic and Mediastinal Disorders	**16 (45.7%)**	**100 (50.5%)**	**37 (36.3%)**	**12 (23.5%)**	**29 (31.2%)**
Cough	2 (5.7%)	30 (15.2%)	5 (4.9%)	1 (2%)	9 (9.7%)
Epistaxis	5 (14.3%)	21 (10.6%)	9 (8.8%)	3 (5.9%)	7 (7.5%)
Skin and Subcutaneous Tissue Disorders	**15 (42.9%)**	**113 (57.1%)**	**33 (32.4%)**	**13 (25.5%)**	**23 (24.7%)**
Rash	4 (11.4%)	36 (18.2%)	10 (9.8%)	2 (3.9%)	3 (3.2%)
Pruritus	5 (14.3%)	34 (17.2%)	7 (6.9%)	3 (5.9%)	5 (5.4%)
Vascular Disorders	**13 (37.1%)**	**69 (34.8%)**	**28 (27.5%)**	**9 (17.6%)**	**16 (17.2%)**
Hypertension	4 (11.4%)	37 (18.7%)	12 (11.8%)	5 (9.8%)	7 (7.5%)
Hypotension	4 (11.4%)	17 (8.6%)	9 (8.8%)	4 (7.8%)	6 (6.5%)

Modified from the sponsor's clinical summary of safety p 21
Common was defined as greater than 10% in any dose group. Within a MedDRA SOC, patients may have experienced more than 1 adverse event. The sum of the terms may exceed 100%. Analysis is based on the patient's designated mg/kg treatment group rather than calculated mean daily dose.

MO comment: *No dose dependency in the incidence of specific TEAEs or TEAEs in a specific SOC was identified.*

7.5.2 Time Dependency for Adverse Events

Death relative to duration of micafungin treatment.
The frequency of death in the pediatric patients was 14.3% (43/300) for the treatment duration of 1 – 14 days, 16.8% (16/95) for the treatment duration of 15 – 28 days, 18.4% (9/49) for the treatment duration of 29 – 56 days, and 22.9% (8/35) for the treatment duration greater than 56 days.

SAEs

The frequency of SAEs in the pediatric patients was 19.4% (93/479) for the treatment duration of 1 – 14 days, 15.6% (28/179) for the treatment duration of 15 – 28 days, 23.8% (20/84) for the treatment duration of 29 – 56 days, and 65.7% (23/35) for the treatment duration greater than 56 days. There is an apparent increase in the frequency of SAEs with increasing treatment duration, which is likely reflective of a more severe underlying disease in those patients requiring a longer duration of antifungal treatment.

MO comment: *A trend of increasing rates of death and SAEs with increasing micafungin treatment duration is likely to be reflective of the severity of the underlying condition and fungal infection, including deep mycoses and invasive aspergillosis that generally require prolonged courses of antifungal treatment and have high rates of unfavorable outcomes including death.*

TEAEs
The frequency of TEAEs did not increase with increasing treatment duration. The overall frequency of TEAEs in the pediatric patients was 91.2% (437/479) for the treatment duration of 1 – 14 days, 80.4% (144/179) for the treatment duration of 15 – 28 days, 79.8% (67/84) for the treatment duration of 29 – 56 days, and 91.4% (32/35) for the treatment duration greater than 56 days.
The most common TEAEs in the pediatric patients by treatment duration were as follows:

- 1 – 14 days: vomiting (26.1%), diarrhea (18.0%), nausea (16.5%), pyrexia (15.7%), mucosal inflammation (13.8%), and hypokalemia (13.4%)
- 15 – 28 days: pyrexia (13.4%), vomiting (9.5%), hypokalemia (9.5%), headache (8.4%), thrombocytopenia (6.7%), abdominal pain (6.7%), and pruritus (6.7%)
- 29 – 56 days: diarrhea (8.3%), pruritus (8.3%), headache (8.3%), vomiting (7.1%), and pyrexia (7.1%)
- Greater than 56 days: pyrexia (34.3%), diarrhea (31.4%), abdominal pain (28.6%), bacteremia (25.7%), and sepsis (22.9%)

Table 76 TEAE by Treatment Duration

MedDRA (v. 12.0) System Organ Class Preferred Term	**1 – 14 days (n = 479)**	**15 – 28 days (n = 179)**	**29 – 56 days (n = 84)**	**> 56 days (n = 35)**
Any TEAE	**437 (91.2%)**	**144 (80.4%)**	**67 (79.8%)**	**32 (91.4%)**
Blood and Lymphatic System Disorders	**135 (28.2%)**	**24 (13.4%)**	**13 (15.5%)**	**16 (45.7%)**
Neutropenia	47 (9.8%)	5 (2.8%)	5 (6.0%)	4 (11.4%)
Febrile neutropenia	16 (3.3%)	1 (0.6%)	3 (3.6%)	5 (14.3%)
Thrombocytopenia	51 (10.6%)	12 (6.7%)	5 (6%)	5 (14.3%)
Anemia	56 (11.7%)	5 (2.8%)	1 (1.2%)	1 (2.9%)
Cardiac Disorders	**73 (15.2%)**	**14 (7.8%)**	**8 (9.5%)**	**12 (34.3%)**
Tachycardia	32 (6.7%)	9 (5%)	4 (4.8%)	4 (11.4%)
Bradycardia	16 (3.3%)	2 (1.1%)	2 (2.4%)	4 (11.4%)
Gastrointestinal Disorders	**268 (55.9%)**	**55 (30.7%)**	**29 (34.5%)**	**24 (68.6%)**
Vomiting	125 (26.1%)	17 (9.5%)	6 (7.1%)	6 (17.1%)

MedDRA (v. 12.0) System Organ Class Preferred Term	**1 – 14 days (n = 479)**	**15 – 28 days (n = 179)**	**29 – 56 days (n = 84)**	**> 56 days (n = 35)**
Nausea	79 (16.5%)	7 (3.9%)	4 (4.8%)	6 (17.1%)
Abdominal pain	54 (11.3%)	12 (6.7%)	2 (2.4%)	10 (28.6%)
Diarrhea	86 (18%)	6 (3.4%)	7 (8.3%)	11 (31.4%)
Constipation	21 (4.4%)	7 (3.9%)	4 (4.8%)	4 (11.4%)
General Disorders and Administration Site Conditions	**222 (46.3%)**	**63 (35.2%)**	**26 (31.0%)**	**19 (54.3%)**
Mucosal inflammation	66 (13.8%)	7 (3.9%)	4 (4.8%)	4 (11.4%)
Pyrexia	75 (15.7%)	24 (13.4%)	6 (7.1%)	12 (34.3%)
Infections and Infestations	**126 (26.3%)**	**41 (22.9%)**	**24 (28.6%)**	**22 (62.9%)**
Bacteremia	20 (4.2%)	3 (1.7%)	4 (4.8%)	9 (25.7%)
Sepsis	17 (3.5%)	3 (1.7%)	2 (2.4%)	8 (22.9%)
Metabolism and Nutrition Disorders	**210 (43.8%)**	**50 (27.9%)**	**17 (20.2%)**	**16 (45.7%)**
Hypokalemia	64 (13.4%)	17 (9.5%)	5 (6.0%)	5 (14.3%)
Fluid overload	23 (4.8%)	5 (2.8%)	3 (3.6%)	4 (11.4%)
Musculoskeletal and Connective Tissue Disorders	**71 (14.8%)**	**23 (12.8%)**	**15 (17.9%)**	**11 (31.4%)**
Pain in extremity	22 (4.6%)	9 (5%)	3 (3.6%)	5 (14.3%)
Musculoskeletal pain	7 (1.5%)	2 (1.1%)	3 (3.6%)	5 (14.3%)
Nervous System Disorders	**89 (18.6%)**	**31 (17.3%)**	**16 (19%)**	**13 (37.1%)**
Headache	45 (9.4%)	15 (8.4%)	7 (8.3%)	6 (17.1%)
Dizziness	11 (2.3%)	3 (1.7%)	2 (2.4%)	4 (11.4%)
Psychiatric Disorders	**60 (12.5%)**	**16 (8.9%)**	**4 (4.8%)**	**6 (17.1%)**
Anxiety	27 (5.6%)	3 (1.7%)	1 (1.2%)	4 (11.4%)
Respiratory, Thoracic and Mediastinal Disorders	**166 (34.7%)**	**47 (26.3%)**	**23 (27.4%)**	**23 (65.7%)**
Respiratory distress	14 (2.9%)	5 (2.8%)	2 (2.4%)	5 (14.3%)
Dyspnea	14 (2.9%)	1 (0.6%)	1 (1.2%)	5 (14.3%)
Cough	36 (7.5%)	7 (3.9%)	2 (2.4%)	5 (14.3%)
Oropharyngeal pain	11 (2.3%)	4 (2.2%)	1 (1.2%)	4 (11.4%)
Rhinorrhea	6 (1.3%)	3 (1.7%)	4 (4.8%)	6 (17.1%)
Respiratory failure	9 (1.9%)	1 (0.6%)	5 (6%)	4 (11.4%)
Epistaxis	32 (6.7%)	8 (4.5%)	2 (2.4%)	4 (11.4%)
Nasal congestion	10 (2.1%)	4 (2.2%)	0	5 (14.3%)
Skin and Subcutaneous Tissue Disorders	**168 (35.1%)**	**45 (25.1%)**	**20 (23.8%)**	**15 (42.9%)**
Urticaria	12 (2.5%)	5 (2.8%)	2 (2.4%)	5 (14.3%)
Vascular Disorders	**103 (21.5%)**	**25 (14.0%)**	**9 (10.7%)**	**8 (22.9%)**
Hypertension	48 (10.0%)	11 (6.1%)	2 (2.4%)	4 (11.4%)
Hypotension	26 (5.4%)	6 (3.4%)	5 (6.0%)	4 (11.4%)

Modified from the summary of clinical safety pp.23-25

7.5.3 Drug-Demographic Interactions

Deaths

The frequency of death was lowest in patients 0 – 4 weeks of age (5.4%). It was similar between patients 121 days – 2 years of age (10.4%) and 2 – 5 years of age (10.2%).

The frequency of death was higher in patients 5 weeks – 120 days of age (22.6%), 6 – 11 years of age (18.6%), and 12 – 16 years of age (21.7%).

The overall frequency of death was 8.9% in black pediatric patients, 16% in white pediatric patients and 29.8% in Asian pediatric patients. The SOC with the highest frequency of TEAEs reported as the primary cause of death was Infections and Infestations for white patients (5%), black patients (5%), and Asian patients (8.5%).

Overall, 14.4% (38/264) of the pediatric males and 17.7% (38/215) of the pediatric females died during the study. The SOC with the highest frequency of TEAEs reported as the primary cause of death for pediatric males was Respiratory, Thoracic and Mediastinal Disorders (5.3%) and the highest frequency SOC for pediatric females was Infections and Infestations (6.5%).

SAEs
The overall frequency of SAEs by age group was lowest in the pediatric patients 0 – 4 weeks of age (13.5%; 5/37). The overall frequencies of SAEs were highest in patients 5 weeks – 120 days of age (35.5%; 11/31) and in patients 12 – 16 years of age 40.0% (46/115).

In the analysis by race, 30.7% (98/319) of white pediatric patients, 17.8% (18/101) of black pediatric patients, and 29.8% (14/47) of Asian pediatric patients experienced an SAE during the study. The most common SAE was sepsis in both white pediatric patients (4.7%) and Asian pediatric patients (6.4%). The most common SAEs in black pediatric patients were pneumonia (2%), acute respiratory distress syndrome (2%), tachycardia (2%), and hypotension (2%).

Gender analysis of SAEs revealed that 29.2% (77/264) of the pediatric males and 26.0% (56/215) of the pediatric females experienced an SAE during the study. The most common SAE for the pediatric males was sepsis (4.9%). The most common SAEs for the pediatric females were respiratory distress (3.3%) and acute respiratory distress syndrome (3.3%).

Table 77 Age Analysis of TEAEs

MedDRA (v. 12.0) System Organ Class Preferred Term	0 – 4 wk (n = 37)	5wk – 120d (n = 31)	121d – <2yr (n = 48)	2 – 5 yr (n = 108)	6 – 11 yr (n = 140)	12 – 16 yr (n = 115)
Any TEAE	**31 (83.8%)**	**27 (87.1%)**	**47 (97.9%)**	**99 (91.7%)**	**126 (90%)**	**109 (94.8%)**
Blood and Lymphatic System Disorders	**7 (18.9%)**	**13 (41.9%)**	**18 (37.5%)**	**38 (35.2%)**	**41 (29.3%)**	**44 (38.3%)**
Neutropenia	0	1 (3.2%)	10 (20.8%)	15 (13.9%)	16 (11.4%)	19 (16.5%)
Febrile neutropenia	0	1 (3.2%)	3 (6.3%)	5 (4.6%)	3 (2.1%)	11 (9.6%)
Thrombocytopenia	1 (2.7%)	3 (9.7%)	7 (14.6%)	16 (14.8%)	20 (14.3%)	23 (20%)
Anemia	4 (10.8%)	3 (9.7%)	7 (14.6%)	21 (19.4%)	16 (11.4%)	12 (10.4%)

MedDRA (v. 12.0) System Organ Class Preferred Term	0 – 4 wk (n = 37)	5wk – 120d (n = 31)	121d – <2yr (n = 48)	2 – 5 yr (n = 108)	6 – 11 yr (n = 140)	12 – 16 yr (n = 115)
Leukocytosis	1 (2.7%)	2 (6.5%)	0	2 (1.9%)	1 (0.7%)	0
Cardiac Disorders	1 (2.7%)	6 (19.4%)	14 (29.2%)	21 (19.4%)	24 (17.1%)	31 (27%)
Tachycardia	0	0	7 (14.6%)	8 (7.4%)	16 (11.4%)	16 (13.9%)
Gastrointestinal Disorders	**8 (21.6%)**	**12 (38.7%)**	**35 (72.9%)**	**63 (58.3%)**	**84 (60%)**	**83 (72.2%)**
Vomiting	4 (10.8%)	5 (16.1%)	22 (45.8%)	36 (33.3%)	43 (30.7%)	36 (31.3%)
Nausea	0	0	9 (18.8%)	15 (13.9%)	28 (20%)	39 (33.9%)
Abdominal pain	0	0	1 (2.1%)	14 (13%)	29 (20.7%)	32 (27.8%)
Diarrhea	0	2 (6.5%)	13 (27.1%)	25 (23.1%)	29 (20.7%)	37 (32.2%)
General Disorders and Administration Site Conditions	**8 (21.6%)**	**9 (29%)**	**27 (56.3%)**	**58 (53.7%)**	**80 (57.1%)**	**74 (64.3%)**
Mucosal inflammation	0	1 (3.2%)	10 (20.8%)	21 (19.4%)	20 (14.3%)	28 (24.3%)
Chest pain	0	0	0	0	6 (4.3%)	16 (13.9%)
Chills	0	1 (3.2%)	2 (4.2%)	8 (7.4%)	12 (8.6%)	12 (10.4%)
Pyrexia	0	2 (6.5%)	13 (27.1%)	28 (25.9%)	34 (24.3%)	26 (22.6%)
Hepatobiliary Disorders	**3 (8.1%)**	**2 (6.5%)**	**6 (12.5%)**	**11 (10.2%)**	**22 (15.7%)**	**23 (20%)**
Hepatomegaly	0	0	5 (10.4%)	4 (3.7%)	8 (5.7%)	9 (7.8%)
Infections and Infestations	**13 (35.1%)**	**13 (41.9%)**	**16 (33.3%)**	**34 (31.5%)**	**52 (37.1%)**	**46 (40%)**
Bacteremia	1 (2.7%)	2 (6.5%)	3 (6.3%)	4 (3.7%)	8 (5.7%)	13 (11.3%)
Investigations	**12 (32.4%)**	**9 (29.0%)**	**32 (66.7%)**	**38 (35.2%)**	**47 (33.6%)**	**53 (46.1%)**
Alanine aminotransferase increased	0	1 (3.2%)	8 (16.7%)	10 (9.3%)	13 (9.3%)	13 (11.3%)
Aspartate aminotransferase increased	1 (2.7%)	0	9 (18.8%)	11 (10.2%)	9 (6.4%)	13 (11.3%)
Gamma-glutamyltransferase increased	0	0	5 (10.4%)	7 (6.5%)	5 (3.6%)	3 (2.6%)
Hemoglobin decreased	0	0	6 (12.5%)	2 (1.9%)	4 (2.9%)	3 (2.6%)
Metabolism and Nutrition Diseases	**13 (35.1%)**	**11 (35.5%)**	**23 (47.9%)**	**43 (39.8%)**	**71 (50.7%)**	**70 (60.9%)**
Hypokalemia	1 (2.7%)	5 (16.1%)	7 (14.6%)	18 (16.7%)	29 (20.7%)	27 (23.5%)
Hypomagnesaemia	0	1 (3.2%)	2 (4.2%)	14 (13%)	18 (12.9%)	16 (13.9%)
Hypocalcaemia	1 (2.7%)	1 (3.2%)	4 (8.3%)	5 (4.6%)	12 (8.6%)	13 (11.3%)
Fluid overload	0	3 (9.7%)	2 (4.2%)	8 (7.4%)	8 (5.7%)	13 (11.3%)
Anorexia	0	0	4 (8.3%)	5 (4.6%)	8 (5.7%)	12 (10.4%)
Hyperglycemia	4 (10.8%)	1 (3.2%)	1 (2.1%)	8 (7.4%)	15 (10.7%)	10 (8.7%)
Musculoskeletal and Connective Tissue Disorders	**2 (5.4%)**	**1 (3.2%)**	**3 (6.3%)**	**20 (18.5%)**	**31 (22.1%)**	**42 (36.5%)**
Pain in extremity	0	0	0	11 (10.2%)	14 (10.0%)	12 (10.4%)
Nervous System Disorders	**4 (10.8%)**	**0**	**8 (16.7%)**	**21 (19.4%)**	**36 (25.7%)**	**51 (44.3%)**
Headache	0	0	0	13 (12.0%)	22 (15.7%)	29 (25.2%)
Psychiatric Disorders	**0**	**0**	**6 (12.5%)**	**11 (10.2%)**	**23 (16.4%)**	**40 (34.8%)**
Anxiety	0	0	0	4 (3.7%)	13 (9.3%)	18 (15.7%)
Agitation	0	0	5 (10.4%)	3 (2.8%)	4 (2.9%)	10 (8.7%)
Insomnia	0	0	0	3 (2.8%)	1 (0.7%)	15 (13%)
Renal and Urinary Disorders	**3 (8.1%)**	**4 (12.9%)**	**4 (8.3%)**	**9 (8.3%)**	**26 (18.6%)**	**32 (27.8%)**
Renal failure	1 (2.7%)	1 (3.2%)	1 (2.1%)	2 (1.9%)	4 (2.9%)	12 (10.4%)
Respiratory, Thoracic and Mediastinal Disorders	**11 (29.7%)**	**5 (16.1%)**	**16 (33.3%)**	**35 (32.4%)**	**62 (44.3%)**	**65 (56.5%)**

MedDRA (v. 12.0) System Organ Class Preferred Term	0 – 4 wk (n = 37)	5wk – 120d (n = 31)	121d – <2yr (n = 48)	2 – 5 yr (n = 108)	6 – 11 yr (n = 140)	12 – 16 yr (n = 115)
Cough	0	1 (3.2%)	3 (6.3%)	12 (11.1%)	15 (10.7%)	16 (13.9%)
Rhinorrhea	0	0	5 (10.4%)	3 (2.8%)	4 (2.9%)	6 (5.2%)
Epistaxis	0	0	1 (2.1%)	6 (5.6%)	17 (12.1%)	21 (18.3%)
Skin and Subcutaneous Tissue Disorders	**7 (18.9%)**	**7 (22.6%)**	**22 (45.8%)**	**45 (41.7%)**	**61 (43.6%)**	**55 (47.8%)**
Rash	0	1 (3.2%)	7 (14.6%)	10 (9.3%)	23 (16.4%)	14 (12.2%)
Pruritis	0	0	5 (10.4%)	11 (10.2%)	17 (12.1%)	21 (18.3%)
Dermatitis diaper	3 (8.1%)	2 (6.5%)	8 (16.7%)	4 (3.7%)	0	1 (0.9%)
Petechiae	0	1 (3.2%)	5 (10.4%)	3 (2.8%)	6 (4.3%)	9 (7.8%)
Vascular Disorders	7 (18.9%)	5 (16.1%)	13 (27.1%)	31 (28.7%)	34 (24.3%)	45 (39.1%)
Hypertension	0	0	8 (16.7%)	20 (18.5%)	17 (12.1%)	20 (17.4%)
Hypotension	2 (5.4%)	0	4 (8.3%)	4 (3.7%)	12 (8.6%)	18 (15.7%)
Flushing	0	0	1 (2.1%)	1 (0.9%)	1 (0.7%)	7 (6.1%)

Within a MedDRA SOC, patients may have experienced more than 1 adverse event. Common was defined as at least 10% in any age group. The sum of the terms may exceed 100%.
Modified from the summary of clinical safety pp. 27-31

7.5.4 Additional Safety Analyses

Acceptability of the sponsor's proposed (b) (4) dose for pediatric patients with esophageal candidiasis hinges on the adequacy of the safety information at the proposed dose and higher in pediatric patients. Therefore, the reviewer undertook evaluation of micafungin safety in pediatric patients exposed to micafungin at exposures higher than the 90th percentile of exposure for adults receiving micafungin 150 mg dose.

The review of this supplemental application by the clinical pharmacology team revealed that micafungin exposure at the proposed (b) (4) dose for the indication of esophageal candidiasis in pediatric patients will be higher for 21-46% of pediatric patients weighing 30 kg and greater than that achieved in adults at the approved dose of 150 mg (for EC), the highest approved dose. The table below highlights micafungin exposure differences between adults at 150 mg dose and pediatric patients at the proposed (b) (4) dose with a 150 mg maximum dose.

Table 78 Micafungin Exposures in Adult and Pediatric Patients (b) (4) dose)

Age group	Adults	Children		
		≤30kg N=149	>30-50kg N= 52	>50kg N=28
dose	150 mg	3 mg/kg	3 mg/kg	150 mg
P10 AUC	112.5 (10%)	8%	1.9%	0%
Mean AUC (%)	161 (80%)	164 (76.5%)	209 (51.9%)	186 (78.6%)
P90 AUC	208.5 (10%)	15.4%	46.2%	21.4%

This reviewer attempted to evaluate micafungin safety profile in pediatric subjects who were exposed to micafungin at the levels higher than 90th percentile of adult exposure at

the 150 mg dose. First, the pediatric patients in whom PK data were collected were identified (n=229); this constituted the PK analysis set (PKAS). Then the safety profiles of micafungin in patients in whom micafungin AUC exceeded 211 mcg*h/mL ("Overexposed" – n=56) and those who had AUC in the lower ranges (n=173) were compared. Three tables below present analyses of deaths, SAEs, and TEAEs in these selected populations.

Table 79 Demographic Characteristics PKAS

Characteristic	Pediatric Patients with Exposure at Adult AUC N = 173	Overexposed Pediatric Patients N = 56
Gender:		
Male	99 (57%)	31 (55%)
Race:		
White	114 (66%)	35 (59%)
Underlying Disease:		
HIV	14 (8%)	11(20%)
BMT	40 (23%)	3 (5%)
Hematologic Malignancy	61 (35%)	17 (30%)
Indication:		
Candidemia	28 (16%)	0
Esophageal candidiasis	31 (18%)	41 (73%)
Prophylaxis	11 (58%)	9 (16%)
Deep mycosis	14 (8%)	6 (11%)
Neutropenia	74 (43%)	15 (27%)
Mean Daily Dose	2 mg/kg	4 mg/kg
Mean Duration	12 days	11 days

MO comment: *The "overexposed" and those pediatric patients with exposures in the adult AUC range were different in their make up in regards to the underlying medical conditions, fungal diagnoses, and incidence of neutropenia.*

Table 80 Pediatric Patients with Micafungin Exposures Exceeding 90th Percentile in Adults Given a 150 mg dose (AUC>211 mcg*h/mL), by Dose and Age

Age Group (b) /Daily dose	>=2.0mg/kg	>=3.0mg/kg	>=4.0 mg/kg	Total by age
121 days- < 2 years	0 (0%)	0 (0%)	6 (15%)	6 (11%)
2 years - 5 years	0 (0%)	2 (17%)	21 (51%)	23 (43%)
6 years - 11 years	1 (33%)	9 (75%)	13 (32%)	23 (43%)
12 years - 16 years	2 (67%)	1 (8%)	1 (2%)	4 (7%)
Total by dose	3 (100%)	12 (100%)	41 (100%)	56 (100%)

MO comment: *48% of the patients exposed to the micafungin levels higher than 90th percentile AUC observed in adults at 150 mg dose were 6 years and older.*

Table 81 Safety Summary PKAS

Parameter	Pediatric Patients with Exposure at Adult AUC	Characteristic
Deaths	14 (8.1%)	3 (5.4%)
Deaths on treatment	0	0
Treatment Emergent SAEs	23 (13.3%)	13 (23.2%)
Related STEAE	1 (0.6%)	1 (1.8%)
TEAE	161 (93.1%)	48 (85.7%)
Related TEAE	35 (20.2%)	15 (26.8%)
TEAEs leading to drug discontinuation	5 (2.9%)	3 (5.4%)

MO comment: *No pattern in the overall safety profile of micafungin in overexposed children versus the ones who achieved adult exposure was observed.*

Table 82 Primary Causes of Death pediatric patients, PKAS

Primary Cause of Death	Exposure at Adult AUC N = 173	Overexposed N = 56
Any Cause of Death	14 (8.1%)	3 (5.4%)
ACUTE LYMPHOBLASTIC LEUKEMIA	1 (0.6%)	
ARRHYTHMIA	1 (0.6%)	
ARTERIO VENOUS RUPTURE	1 (0.6%)	
CARDIORESPIRATORY ARREST	1 (0.6%)	
HEART FAILURE	1 (0.6%)	
INTRACRANIAL HEMORRHAGE	1 (0.6%)	
JUVENILE CHRONIC MYELOMONOCYTIC LEUKAEMIA	1 (0.6%)	
MULTI ORGAN FAILURE	1 (0.6%)	1 (1.8%)
PROBABLE CARDIOPULMONARY	1 (0.6%)	
RESPIRATORY FAILURE	1 (0.6%)	1 (1.8%)
SEPTIC SHOCK	2 (1.2%)	
SUSPECTED PNEUMONIA	1 (0.6%)	1 (1.8%)
WORSENING OF AUTOIMMUNE HEMOLYTIC ANEMIA	1 (0.6%)	

MO comment: *No concerning trends in mortality were observed between overexposed pediatric patients and those who maintained micafungin AUC in the approved adult range.*

Table 83 Serious Treatment Emergent Adverse Events: Pediatric Patients in PKAS

Serious Treatment Emergent Adverse Events/ System Organ Class	Preferred Term	Exposure at Adult AUC N = 173	Overexposed N = 56
All subjects with STEAE	Any STEAE	23 (13.3%)	13 (23.2%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	FEBRILE NEUTROPENIA	0	1 (1.8%)
CARDIAC DISORDERS	CARDIAC FAILURE	2 (1.2%)	2 (3.6%)
	SUPRAVENTRICULAR TACHYCARDIA	0	1 (1.8%)
GASTROINTESTINAL DISORDERS	HAEMATOCHEZIA	0	1 (1.8%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	INFUSION RELATED REACTION	0	1 (1.8%)
	MULTI-ORGAN FAILURE	0	1 (1.8%)
HEPATOBILIARY DISORDERS	CHOLECYSTITIS	0	1 (1.8%)
IMMUNE SYSTEM DISORDERS	GRAFT VERSUS HOST DISEASE	1 (0.6%)	1 (1.8%)
INFECTIONS AND INFESTATIONS	KLEBSIELLA SEPSIS	0	1 (1.8%)
	PNEUMONIA	0	2 (3.6%)
	SEPSIS	5 (2.9%)	1 (1.8%)
	STAPHYLOCOCCAL SEPSIS	0	1 (1.8%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	ENGRAFT FAILURE	0	1 (1.8%)
INVESTIGATIONS	BILIRUBIN CONJUGATED INCREASED	0	1 (1.8%)
	BLOOD ALKALINE PHOSPHATASE INCREASED	0	1 (1.8%)
	BLOOD BILIRUBIN INCREASED	0	1 (1.8%)
	BLOOD BILIRUBIN UNCONJUGATED INCREASED	0	1 (1.8%)
	BLOOD CREATININE INCREASED	0	1 (1.8%)
	BLOOD UREA INCREASED	0	1 (1.8%)
	BLOOD URINE PRESENT	0	1 (1.8%)
	GAMMA-GLUTAMYLTRANSFERASE INCREASED	0	1 (1.8%)
METABOLISM AND NUTRITION DISORDERS	HYPERGLYCAEMIA	0	1 (1.8%)
	HYPOKALAEMIA	1 (0.6%)	1 (1.8%)
RENAL AND URINARY DISORDERS	CYSTITIS HAEMORRHAGIC	0	1 (1.8%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	EPISTAXIS	0	1 (1.8%)
	RESPIRATORY ACIDOSIS	0	1 (1.8%)
	RESPIRATORY FAILURE	0	1 (1.8%)

MO comment: *The percent of pediatric patients with treatment emergent SAEs was higher in the overexposure group. Upon review of the individual patient profiles for the SAEs, the majority of the patients experienced these SAEs as a result of their*

underlying disease progression/decompensation. No individual SAEs listed in the table were of particular safety concern with overexposure to micafungin.

Serious micafungin related adverse events occurred in a single patient in each group. One patient experienced ventricular tachycardia with electrolyte abnormalities in the adult exposure group and an infusion reaction occurred in one patient in the overexposure group.

The preponderance of serious LFT abnormalities in the overexposure group as compared to adult range exposure patients prompted additional investigations. As presented below no difference in increases from baseline in LFT were noted between the groups.

Table 84 Common Treatment Emergent Adverse Events >4.5% for Pediatric Patients in PKAS

Body System or Organ Class	Dictionary-Derived Term	Exposure at Adult AUC N = 173	Overexposed N = 56
Subjects with TEAE	Any TEAE	161 (93.1%)	48 (85.7%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	ANAEMIA	18 (10.4%)	3 (5.4%)
	LEUKOPENIA	0 (0%)	4 (7.2%)
	THROMBOCYTOPENIA	16 (9.3%)	2 (3.6%)
CARDIAC DISORDERS	BRADYCARDIA	4 (2.3%)	4 (7.2%)
	TACHYCARDIA	18 (10.4%)	2 (3.6%)
GASTROINTESTINAL DISORDERS	ABDOMINAL PAIN	24 (13.9%)	5 (8.9%)
	DIARRHOEA	41 (23.7%)	3 (5.4%)
	NAUSEA	28 (16.2%)	2 (3.6%)
	PERIANAL ERYTHEMA	8 (4.6%)	1 (1.8%)
	VOMITING	51 (29.5%)	8 (14.3%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	CHILLS	12 (6.9%)	3 (5.4%)
	INFUSION RELATED REACTION	9 (5.2%)	3 (5.4%)
	INFUSION SITE PAIN	3 (1.7%)	3 (5.4%)
	MUCOSAL INFLAMMATION	27 (15.6%)	5 (8.9%)
	PAIN	15 (8.7%)	2 (3.6%)
	PYREXIA	28 (16.2%)	10 (17.9%)
HEPATOBILIARY DISORDERS	HEPATOMEGALY	8 (4.6%)	0
INFECTIONS AND INFESTATIONS	CENTRAL LINE INFECTION	1 (0.6%)	2 (3.6%)
	PNEUMONIA	1 (0.6%)	3 (5.4%)
INVESTIGATIONS	ALANINE AMINOTRANSFERASE INCREASED	14 (8.1%)	6 (10.7%)
	ASPARTATE AMINOTRANSFERASE INCREASED	16 (9.3%)	6 (10.7%)
	BLOOD ALKALINE PHOSPHATASE INCREASED	4 (2.3%)	3 (5.4%)
	BLOOD CREATININE INCREASED	2 (1.2%)	4 (7.2%)
	BLOOD LACTATE DEHYDROGENASE INCREASED	9 (5.2%)	3 (5.4%)
	BLOOD POTASSIUM DECREASED	6 (3.5%)	3 (5.4%)
	BLOOD TRIGLYCERIDES INCREASED	1 (0.6%)	3 (5.4%)

Body System or Organ Class	Dictionary-Derived Term	Exposure at Adult AUC N = 173	Overexposed N = 56
	BLOOD UREA INCREASED	4 (2.3%)	3 (5.4%)
	BODY TEMPERATURE INCREASED	9 (5.2%)	0
	GAMMA-GLUTAMYLTRANSFERASE INCREASED	9 (5.2%)	8 (14.3%)
	HAEMATOCRIT DECREASED	8 (4.6%)	1 (1.8%)
	HAEMOGLOBIN DECREASED	12 (6.9%)	3 (5.4%)
METABOLISM AND NUTRITION DISORDERS	FLUID RETENTION	10 (5.8%)	2 (3.6%)
	HYPERGLYCAEMIA	9 (5.2%)	4 (7.2%)
	HYPOCALCAEMIA	13 (7.5%)	1 (1.8%)
	HYPOKALAEMIA	21 (12.1%)	9 (16.1%)
	HYPOMAGNESAEMIA	9 (5.2%)	5 (8.9%)
	HYPOPHOSPHATAEMIA	10 (5.8%)	4 (7.1%)
	MALNUTRITION	12 (6.9%)	0 (0%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	PAIN IN EXTREMITY	8 (4.6%)	5 (8.9%)
NERVOUS SYSTEM DISORDERS	HEADACHE	22 (12.7%)	3 (5.4%)
PSYCHIATRIC DISORDERS	ANXIETY	5 (2.9%)	3 (5.4%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	COUGH	12 (6.9%)	5 (8.9%)
	EPISTAXIS	16 (9.3%)	4 (7.1%)
	OROPHARYNGEAL PAIN	8 (4.6%)	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	HYPERHIDROSIS	8 (4.6%)	2 (3.6%)
	PETECHIAE	8 (4.6%)	0
	PRURITUS	15 (8.7%)	1 (1.8%)
	RASH	19 (11%)	3 (5.4%)
	SKIN DISORDER	8 (4.6%)	1 (1.8%)
VASCULAR DISORDERS	HYPERTENSION	17 (9.8%)	3 (5.4%)
	HYPOTENSION	10 (5.8%)	0

MO comment: *Although, overall incidence of TEAEs was higher in the adult range exposure group, no trends in the incidence of individual TEAEs or TEAEs in a specific SOC related to the micafungin exposure were identified.*

As there were numerical differences in the incidence of the LFT abnormalities reported as SAEs and TEAEs, changes of liver function tests on treatment were examined in the PKAS.

Table 85 Lab Abnormalities on Treatment for Pediatric Patients in PKAS

Parameter lab value maximum on treatment	Pediatric Patients with Adult-Matching Micafungin Exposure N= 173 (%)	Overexposed Pediatric Patients AUC >211 mcg/dL*h N = 56 (%)	All micafungin treated Pediatric Patients N = 479 (%)
ALT	**N= 173**	**N = 56**	**N=478**
Normal	115 (66.5)	39 (69.6)	284 (59.3)
2 - <5 x ULN	37 (21.4)	13 (23.2)	129 (26.9)
5 - <10 x ULN	13 (7.5)	2 (3.6)	50 (10.4)
≥ 10 x ULN	3 (1.7)	2 (3.6)	15 (3.4)
AST	**N= 169**	**N = 56**	**N = 478**
Normal	121 (71.6)	41 (73.0)	290 (60.5)
2 - <5 x ULN	37 (21.9)	8 (14.3)	138 (28.8)
5 - <10 x ULN	8 (4.7)	3 (5.4)	30 (6.3)
≥ 10 x ULN	3 (1.8)	4 (7.1)	19 (4.0)
Total Bili	**N = 167**	**N = 52**	**N = 476**
Normal	147 (88.0)	47 (90.4)	351 (73.3)
2 - <5 x ULN	14 (8.4)	3 (5.8)	69 (14.4)
5 - <10 x ULN	4 (2.4)	0	30 (6.3)
≥ 10 x ULN	2 (1.2)	2 (3.4)	26 (5.4)

MO comment: *ALT, AST and bilirubin values on treatment were similar between the two populations of pediatric patients in the PKAS and were generally better than those observed in the whole pediatric population.*

Table 86 Change from Baseline ALT on Treatment for pediatric patients in PKAS

ALT baseline/ on treatment	Exposure at Adult AUC					Overexposure				
	Normal	2 - <5 x ULN	5 - <10 x ULN	≥ 10 x ULN	Increase from baseline	Normal	2 - <5 x ULN	5 - <10 x ULN	≥ 10 x ULN	Increase from baseline
Normal	107 (61.9%)	22 (12.7%)	10 (5.8%)	2 (1.2%)	34 (19.7%)	34 (60.7%)	9 (16.1%)	1 (1.8%)	2 (3.6%)	12 (21.8%)
2 - <5 x ULN	0	19 (11.0%)	1 (0.6%)	1 (0.6%)	2 (1.2%)	0	7 (12.5%)	1 (1.8%)	0	1 (1.8%)
5 - <10 x ULN	0	0	4 (2.3%)	0	0	0	0	1 (1.8%)	0	0
≥ 10 x ULN	0	0	0	1 (0%)	0	0	0	0	0	0
Increase from baseline all					**36 (20.8%)**					**13 (23.6%)**
Subjects	107 (61.9%)	41 (23.7%)	15 (8.7%)	4 (2.3%)	**173 (100%)**	34 (60.7%)	16 (28.6%)	3 (5.4%)	2 (3.6%)	**55 (100%)**

Table 87 Change from Baseline AST on Treatment for pediatric patients in PKAS

AST baseline/ on treatment	Exposure at Adult AUC					Overexposure				
	Normal	2 - <5 x ULN	5 - <10 x ULN	≥ 10 x ULN	Increase from baseline	Normal	2 - <5 x ULN	5 - <10 x ULN	≥ 10 x ULN	Increase from baseline
Normal	115 (66.5%)	27 (15.6%)	3 (1.7%)	2 (1.2%)	32 (18.4%)	36 (64.3%)	5 (8.9%)	2 (3.6%)	2 (3.6%)	9 (16.1%)
2 - <5 x ULN	0	16 (9.3%)	3 (1.7%)	1 (0.6%)	4 (2.4%)	0	5 (8.9%)	1 (1.8%)	2 (3.6%)	3 (5.3%)
5 - <10 x ULN	0	0	1 (0.6%)	0	0	0	0	1 (1.8%)	0	0
≥ 10 x ULN	0	0	0	1 (0.6%)	0	0	0	0	0	0
Increase from baseline					**36 (20.8%)**					**12 (21.4%)**
Subjects	115 (66.5%)	43 (24.9%)	7 (4.1%)	4 (2.3%)	**173 (100%)**	36 (64.3%)	10 (17.9%)	4 (7.1%)	4 (7.1%)	**56 (100%)**

Table 88 Change from Baseline Total Bilirubin on Treatment: Pediatric Patients in PKAS

Total Bili baseline/ on treatment	Exposure at Adult AUC					Overexposure				
	Normal	2 - <5 x ULN	5 - <10 x ULN	≥ 10 x ULN	Increase from baseline	Normal	2 - <5 x ULN	5 - <10 x ULN	≥ 10 x ULN	Increase from baseline
Normal	146 (84.4%)	9 (5.2%)	2 (1.2%)	1 (0.6%)	12 (6.9%)	47 (83.9%)	1 (1.8%)	0	0	1 (1.8%)
2 - <5 x ULN	0	5 (2.9%)	1 (0.6%)	0	1 (0.6%)	0	3 (5.4%)	0	1 (1.8%)	1 (1.8%)
5 - <10 x ULN	0	0	0	1 (0.6%)	1 (0.6%)	0	0	0	1 (1.8%)	1 (1.8%)
Increase from baseline					**14 (8.1%)**					**3 (5.4%)**
Subjects	146 (84.4%)	14 (8.1%)	3 (1.7%)	2 (1.2%)	**173 (100%)**	47 (83.9%)	4 (7.1%)	0	2 (3.6%)	**56 (100%)**

MO comment: *No clear tendency in the increases of LFT values from baseline were identified in the two exposure groups of pediatric patients.*

Summary and Conclusions: Safety analyses were conducted to evaluate the incidence of adverse events and laboratory abnormalities (especially LFTs) in the pediatric patients with known micafungin exposures higher than the 90th percentile of adult exposures achieved at the highest approved adult dose of 150 mg. This group of "overexposed" pediatric patients was compared to pediatric patients with micafungin exposures matching adult exposures at a 150 mg dose. The following were observed:

- No patients in the "overexposed" group died while on treatment with micafungin. Posttreatment mortality, although numerically higher in the adult exposure group, was related to the patients' underlying conditions.
- The incidence of serious adverse events was 10% higher in the overexposure group; however, no pattern of the observed adverse events was evident. Individual patients had up to 9 SAEs deemed to be related to the underlying conditions of these patients. Serious micafungin-related adverse events occurred in a single patient in each group.
- Incidence of treatment emergent adverse events was overall lower in the overexposure group as compared to patients in the adult exposure group. However, treatment emergent adverse events that were deemed to be related to micafungin by the investigator, were numerically (5%) higher in the overexposed patients. No concerning pattern in the adverse event profile was identified.
- Liver function test abnormalities were evaluated in detail. No differences in the incidence of the LFT increases from baseline were observed between the two groups.

In addition, the micafungin study safety database contains data on 514 adult and 109 pediatric patients exposed to micafungin mean daily doses of ≥ 3 mg/kg for ≥7 days. Safety evaluation of micafungin in pediatric and adult patients did not reveal dose dependent increases in:

- The incidence of death of any cause or cause specific mortality
- Overall incidence of serious adverse events or incidence of serious adverse events of the particular class or grouping
- Overall incidence of treatment emergent adverse events or events of a particular class or special interest
- Overall incidence or individual incidence of adverse events resulting in study drug discontinuation
- Treatment emergent elevation of laboratory parameters above baseline values (LFTs, Cr, Hb)

The above findings allow the reviewer to conclude that the sponsor's proposed (b) (4) dose for esophageal candidiasis is unlikely to result in a safety profile that is different from that of pediatric patients and adults treated with doses up to 2 mg/kg and 150 mg, respectively.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

There is limited data on the carcinogenic nature of micafungin in humans. Pharmacology/toxicology reviewer Dr. Owen McMaster reviewed non-clinical data for the micafungin NDA for the original and subsequent approvals. At high doses (5-10

times the clinical dose) prolonged duration of micafungin administration produced irreversible changes in the liver. Two-year studies in rats were performed to evaluate the reversibility of altered hepatocellular foci observed. In these studies, the rats were treated for three or six months with doses 5 to 8 times the recommended human dose based on exposure comparisons and sacrificed after varying recovery periods. An increased rate of adenomas and carcinomas in the livers were recorded in the rats during the 18- and 21-month follow-up period. Juvenile animal studies were also preformed by the sponsor to evaluate whether immaturity affects the rates of the liver tumors in the animals after prolonged exposure. No difference in the rates of the liver tumors was found between juvenile and adult animals that were exposed to micafungin at 5-8 times the human exposure at the approved micafungin doses.

7.6.2 Human Reproduction and Pregnancy Data

No new reproductive studies were performed in the micafungin pediatric clinical development program. Use in pregnancy and lactation is addressed in the product label.

7.6.3 Pediatrics and Assessment of Effects on Growth

There is no data regarding the effects on growth in the pediatric population.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Micafungin is highly protein bound; it is not dialyzable. No cases of overdose have been reported with micafungin. Repeated daily doses up to 8 mg/kg (maximum total daily dose of 896 mg) in adult patients, up to 6 mg/kg in pediatric patients ≥ 4 months of age, and up to 10 mg/kg in pediatric patients <4 months of age have been administered in clinical studies with no reported dose-limiting toxicity. The minimum lethal dose of micafungin is 125 mg/kg in rats, equivalent to 8 times the highest recommended adult human clinical dose (150 mg) and approximately 7 times the highest pediatric clinical dose (3 mg/kg), based on body surface area comparisons.

7.7 Additional Submissions / Safety Issues

None.

8 Postmarket Experience

The sponsor submitted a review using the Astellas safety database. A total of 220 pediatric cases were retrieved from the safety database up to 23 April 2012. Of the 220 cases, 33 reported a patient outcome of death [Table 3]. The percentage of death cases reported was similar across age categories. Among the 220 cases, there were 197 serious adverse events.

Table 89 Postmarketing Cases and Adverse Events in Pediatric Patients Reported in the Astellas Safety Database

Age Category	Cases	Death	Serious Adverse Events	Non-serious Adverse Events
≥ 4 months to < 2 years	25	4	29	26
≥ 2 years to < 6 years	60	9	51	80
≥ 6 years to < 12 years	66	6	51	81
≥ 12 years to < 16 years	69	14	66	79
TOTAL	220	33	197	264

Modified from Postmarketing Review Report 5.3.6 p.6

Table 90 Postmarketing Cases and Adverse Events in Pediatric by Age and SOC

System Organ Class	≥ 4 months to < 2 years	≥ 2 years to < 6 years	≥ 6 years to < 12 years	≥ 12 years to < 16 years
Blood and lymphatic system disorders	4	8	16	8
Cardiac disorders	0	0	0	2
Congenital, familial and genetic disorders	0	0	1	0
Endocrine disorders	0	0	0	1
Eye disorders	0	0	1	0
Gastrointestinal disorders	4	13	15	12
General disorders and administration site conditions	7	19	7	11
Hepatobiliary disorders	8	14	20	19
Immune system disorders	0	3	5	6
Infections and infestations	6	23	15	22
Injury, poisoning and procedural complications	0	2	1	3
Investigations	15	26	31	27
Metabolism and nutrition disorders	1	5	4	6
Musculoskeletal and connective tissue disorders	0	1	0	0
Neoplasms benign, malignant and unspecified (includes cysts and polyps)	2	4	3	5
Nervous system disorders	1	0	2	5
Renal and urinary disorders	1	4	1	6
Respiratory, thoracic and mediastinal disorders	1	0	1	2
Skin and subcutaneous tissue disorders	3	6	5	4
Surgical and medical procedures	0	0	1	1
Vascular disorders	2	1	3	5
Total	**55**	**129**	**132**	**145**

Adapted from Postmarketing Review Report 5.3.6 p.7

Deaths
Among pediatric postmarketing safety reports 33 had fatal outcome (33/220, 15.0%). These deaths were attributed to underlying disease and thought to be unrelated to micafungin administration. All reported cases are confounded by serious underlying medical conditions such as cancer or transplantation as well as by numerous concomitant medications whose role in the adverse reaction and fatal outcome cannot be excluded.

Hepatic Events
There were 132 reports of hepatic postmarketing adverse events in pediatric patients (132/220, 60.0%) ranging from liver function test abnormalities to 2 cases of hepatic failure. The majority of these cases, 95/132 (72%) resolved or were resolving at the end of case follow up. In some cases temporal association with micafungin administration was present; however, most of the cases had confounding factors: severe co-morbidities and concomitant medications that might have contributed to the adverse event. Micafungin labeling includes the following language in Section 5.3 Warnings and Precautions: Hepatic Effects: Abnormalities in liver function tests; isolated cases of hepatic impairment, hepatitis, and hepatic failure have been observed.
Modification of the current PI for the hepatic events is not warranted at this time.

Renal Events and Electrolyte Abnormalities
Review of pediatric postmarketing adverse events yielded 6 renal cases (6/220, 2.7%) and 6 additional cases of electrolyte abnormalities (hypokalemia). Four events in each category were reported as resolved, while for two events in each category outcome was unknown. Confounding factors were present in all cases.
Micafungin labeling includes the following language in Section 5.4 Warnings and Precautions: Renal Effects: Elevations in BUN and creatinine; isolated cases of renal impairment or acute renal failure have been reported. Modification of the current PI with regards to renal adverse reactions is not warranted at this time.

Disseminated Intravascular Coagulation (DIC)
Review of pediatric postmarketing adverse events yielded 5 cases of disseminated intravascular coagulation (5/220, 2.3%). All cases had confounding factors contributing to the event. DIC is a labeled adverse event in the micafungin US PI in the Section 6.3 Postmarketing Adverse Reactions.

Neoplasms
There were a total of 13 cases of neoplasms (13/220, 5.9%) in the pediatric postmarketing reports. Twelve of them were listed as pre-existing conditions. A single case of acquired neoplasm (209US000179) was a case of hepatoblastoma in a 16 month old male with VACTERL syndrome. This case was previously reviewed by the clinical reviewer Yuliya Yasinskaya, M.D., and deemed to be unrelated to micafungin primarily because hepatoblastoma is a tumor of embryonal origin. Presence of other

congenital abnormalities in this case speaks to the problems during embryonal period of gestation.

In the 120–day safety update the sponsor provided information on the completed and ongoing clinical studies and referenced PSUR 16 submitted on December 6, 2012 covering the period between April 9, 2012 and October 8, 2012. Between October 9, 2012 and December 31, 2012 there were:

- No additional countries approved for micafungin
- No actions were taken for safety reasons by either a regulatory authority or by Astellas concerning withdrawal, rejection, suspension, or failure to obtain a renewal of a marketing authorization
- No distribution restrictions, dosage modifications, or changes made to the target population, formulation, or indications
- No revisions to the approved Company Core Data Sheet or US prescribing information

A line-listing of postmarketing reports received between April 9, 2012 and December 31, 2012 was reviewed. No new signals affecting the previously reported safety profile or benefit/risk for Mycamine were identified.

9 Appendices

9.1 Literature Review/References

No publications were referenced in the review.

9.2 Labeling Recommendations

To be finalized upon reaching agreement with the sponsor during labeling negotiations.

9.3 Advisory Committee Meeting

Not applicable.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

YULIYA I YASINSKAYA
03/08/2013

JOHN J ALEXANDER
03/08/2013