U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA 21506
Supplement #:	S-15
Drug Name:	Mycamine (micafungin sodium) for Injection
Indication(s):	Use in pediatric patients ≥ 4 months through 16 years of age for the treatment of candidemia, acute disseminated candidiasis, *Candida* peritonitis and abscesses, esophageal candidiasis, and for the prophylaxis of *Candida* infections in patients under going hematopoietic stem cell transplant
Applicant:	Astellas Pharma Global Development, Inc.
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Keywords: clinical studies, subgroups, anti-fungal, candidemia, invasive candidiasis, esophageal candidiasis, prophylaxis

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1 EXECUTIVE SUMMARY

Mycamine is currently approved in adults for the treatment of candidemia, acute disseminated candidiasis, *Candida* peritonitis and abscesses; esophageal candidiasis; and for the prophylaxis of *Candida* infections in patients undergoing hematopoietic stem cell transplant (HSCT). In this supplemental NDA, the Applicant is requesting pediatric (patients ≥4 months through 16 years of age) approval of these three indications. Since the pathophysiology and risk factors for these indications are similar between adult and pediatric patients, pediatric doses may be derived by determining a pediatric dose regimen that allows for similar exposures that were previously shown to be efficacious in adult patients through the modeling of pharmacokinetic (PK) data of the pediatric population. Based on the modeling of PK data from all studies conducted that included pediatric patients, the Applicant was able to propose pediatric dosing for the three indications.

Supportive pediatric efficacy and safety information from Phase III, randomized, controlled trials is available for two of the three indications: treatment of candidemia, acute disseminated candidiasis, *Candida* peritonitis and abscesses and the prophylaxis of *Candida* infections in patients undergoing HSCT. Study FG463-21-08 studied patients with confirmed candidemia/invasive candidiasis and Study 98-0-050 studied the prophylaxis of invasive fungal infections in patients undergoing HSCT. The trials enrolled both adult and pediatric patients. Patients received doses similar to those proposed by the PK modeling.

The results presented in this review are for the pediatric subgroups that were enrolled under the much larger protocols which included the adult population. The studies were not powered for hypothesis testing in the pediatric subgroup. Therefore, all results presented are descriptive in nature.

Study FG463-21-08 was a Phase III trial that compared the efficacy and safety of micafungin vs. AmBisome in adult and pediatric patients with confirmed candidemia/ invasive candidiasis. Patients were randomized to receive either IV micafungin (initial dose 100 mg/day or 2.0 mg/kg for patients weighing ≤ 40 kg) or AmBisome (initial dose of 3 mg/kg/day). Dose increases up to 200 mg (4 mg/kg patients weighing ≤ 40 kg) for micafungin and 5 mg/kg for AmBisome were allowed after 5 days of treatment if there was persistence of the fungal infection as indicated by continued isolation or histological documentation at the primary site or attributable signs and symptoms in addition to radiographic abnormalities. The primary efficacy analysis population of this trial included 100 patients ≤ 16 years of age, 48 received micafungin and 52 received AmBisome. The primary endpoint was treatment success at end of therapy (EOT). Overall treatment success was defined as a clinical response (complete or partial) and a mycological response (eradication or presumed eradication) at EOT. Patients who died during treatment plus 1 day, missed an evaluation, or used systemic antifungal therapy during or immediately after study therapy were considered failures. At EOT, 67% of micafungin patients had a treatment success compared to 65% of AmBisome treated patients. However, as indicated this trial allowed for a possible increase in the micafungin dose after 5 days of treatment if there was persistence of the fungal infection. Approximately 23% of the micafungin pediatric patients received a dose increase. [redacted] (b) (4) 2 mg/kg or

100 mg for patients weighing > 40 kg. Therefore, a conservative sensitivity analysis was performed by treating those patients who were randomized to micafungin and received a dosage increase as treatment failures. When this criterion is applied, 51% of micafungin treated patients were treatment successes. Overall, the rates for the pediatric population were similar to those seen for the adult population.

Study 98-0-050 was a Phase 3, double-blind, randomized study comparing micafungin to fluconazole for the prophylaxis of fungal infections in adult and pediatric patients scheduled to undergo HSCT. Patients were randomized in a 1:1 ratio to receive either IV micafungin (50 mg/day or 1.0 mg/kg for patients weighing ≤ 50 kg) or fluconazole (400 mg/day or 8 mg/kg/day for patients weighing ≤ 50 kg). The primary efficacy analysis population of this study included 91 patients ≤ 16 years of age, 43 received micafungin and 48 received fluconazole. The primary efficacy variable was treatment success at the end of study. Treatment success was defined as the absence of a proven, probable or suspected fungal infection through the end of the therapy, and absence of a proven or probable fungal infection through the end of the 4 week post-treatment period. The primary endpoint was modified to also include all deaths even if no proven, probable, or suspected fungal infection was identified at the time of death as well as patients lost to follow-up as failures. At the post treatment 4 week follow-up, 72% of micafungin patients had a treatment success compared to 54% of fluconazole treated patients. The results for the pediatric population show similar trends to those seen for the adult population.

2 INTRODUCTION

2.1 Overview

This submission is a supplemental NDA for Mycamine. In this supplement, the Applicant is requesting pediatric (patients ≥4 months through 16 years of age) approval of the 3 indications which are currently approved for adults: the treatment of patients with candidemia, acute disseminated candidiasis, *Candida* peritonitis and abscesses; esophageal candidiasis; and for the prophylaxis of *Candida* infections in patients undergoing hematopoietic stem cell transplant (HSCT). The studies for candidemia/invasive candidiasis and prophylaxis which were the basis of the initial approvals in adults of the respective indications included enrollment of pediatric patients. However, there were limitations in the pharmacokinetic (PK) data at the time to allow for pediatric labeling. Therefore, at the time of the approvals of the adult indications, additional PK studies in pediatric patients were required to determine the appropriate pediatric dosing.

Four phase 1 PK and safety studies were conducted to address this requirement. A pediatric population PK model was created using the PK data from three of the 4 pediatric Written Request PK and safety studies (the 4th study was in neonates) as well as the previously conducted legacy studies that included pediatric data. This model provides the information on which to base a dosing recommendation in pediatric patients aged ≥4 months through 16 years for all corresponding adult indications. The proposed pediatric doses provide exposures similar to those achieved in adults for each of the approved adult indications where micafungin efficacy was demonstrated. The pediatric dosing proposed by the Applicant is as follows:

- Candidemia/Invasive Candidiasis: (b) (4)
- Esophageal Candidiasis: (b) (4)
- Prophylaxis of *Candida* infections: (b) (4)

Supportive efficacy information comes from the following studies:

- Study FG463-21-08
  - A Phase III study that compared the efficacy and safety of micafungin vs. liposomal amphotericin B in adults and pediatric patients with confirmed candidemia/ invasive candidiasis. The micafungin daily dose was 100 mg with a dose increase to 200 mg allowed or 2.0 mg/kg with a dose increase to 4.0 mg/kg allowed for patients weighing ≤ 40 kg. This study was reviewed in NDA 21-506 SE1-008. See statistics review written by Cheryl Dixon dated January 11, 2008. (Candidemia/Invasive Candidiasis- 48 patients received micafungin)
- Study 98-0-050
  - A Phase III study that compared micafungin with fluconazole for the prophylaxis of fungal infections in adult and pediatric patients scheduled to undergo HSCT. The micafungin daily dose was 50 mg or 1 mg/kg for patients weighing< 50 kg. This study was reviewed in the original NDA 21-506. See statistics review written by Qian Li dated January 21, 2003. (Prophylaxis- 43 patients received micafungin)
- Study 9463-CL-2101
  - A Phase I PK and safety study that also collected efficacy data and enrolled pediatric patients with proven or probable esophageal candidiasis, invasive candidiasis, or suspected *Candida* infection. Patients < 25 kg received 4.5 mg/kg and patients ≥ 25 kg received 3 mg/kg of micafungin per day. (Candidemia/Invasive Candidiasis- 6 patients received 3 mg/kg and 10 received 4.5 mg/kg, Esophageal Candidiasis-6 patients received 3 mg/kg and 30 received 4.5 mg/kg)
- Study 98-0-047
  - An open label non-comparative Phase II study of micafungin that enrolled adult and pediatric patients with a confirmed diagnosis of candidemia or invasive candidiasis. Patients with esophageal candidiasis were enrolled as a subset of invasive candidiasis. Patients could have been newly diagnosed (de novo) or failed previous anti-fungal therapy for their current infection (efficacy failures). The starting micafungin dose was 50 mg (1 mg/kg for ≤ 40 kg) or 100 mg (2 mg/kg for ≤ 40 kg) for non-*Candida albicans.* Patients who were efficacy failures could receive micafungin alone or in combination with another anti-fungal. (Candidemia/Invasive Candidiasis-16 de novo, 31 efficacy failure in combination with other antifungal and 6 efficacy failure micafungin alone patients received an average daily dose of 1.5 mg/kg with

doses ranging from 0.7 to 4.5 mg/kg, Esophageal Candidiasis- 4 patients received doses ranging from 1.0 to 2.1 mg/kg))

- Study 9463-CL-2102
  - A Phase I PK and safety study that also collected efficacy data and enrolled infants and toddlers with esophageal candidiasis or other invasive candidiasis. The micafungin dose was 4.5 mg/kg/day. (Candidemia/Invasive Candidiasis-9 patients)
- Study 9463-CL-2103
  - A Phase I PK and safety study that also collected efficacy data and enrolled pediatric patients undergoing HSCT. The micafungin dose was 1 mg/kg/day ≥ 25 kg or 1.5 mg/kg/day < 25 kg. (Prophylaxis- 15 patients received 1 mg/kg and 25 patients received 1.5 mg/kg)
- Study 98-2-043
  - A Phase I dose escalation, tolerance, and PK study in febrile, neutropenic pediatric patients. The micafungin daily dose was 0.5 mg/kg/day escalation up to 1.0, 1.5, 2.0, 3.0, and 4.0 mg/kg/day. (Prophylaxis- 16, 18, 13, 12, 10, 8 patients received 0.5 mg/kg/day, 1.0, 1.5, 2.0, 3.0, and 4.0 mg/kg/day, respectively)

The focus of this statistics review for supportive efficacy will be the Phase III, randomized, controlled trials: Study FG463-21-08 and Study 98-0-050. The efficacy data provided in the remaining non-comparative Phase I and Phase II studies is limited due to few patients treated with the proposed doses for the respective indications and since efficacy was not the primary objective of most of these studies varying definitions of response were used. For further discussion of the Phase I and Phase II studies and an integrated assessment of all the studies, refer to the Medical Officer's review. As previously stated, both of the Phase III trials were fully reviewed at the time of the submissions for the adult indications. This review will focus on data for the pediatric subgroups from these trials.

2.2 Data Sources

The data analyzed in this review comes from the Phase III trials of the treatment of candidemia and other forms of invasive candidiasis and the prophylaxis of *Candida* infections. The study reports and datasets provided in the electronic submission were reviewed. These can be found in the electronic submission located at: \\Cdsesub1\evsprod\NDA021506\0037.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The datasets submitted are similar to those submitted with the original submissions. Little effort was needed to reproduce the results of the primary efficacy analyses for the pediatric subgroups.

3.2 Evaluation of Efficacy

3.2.1 Study FG463-21-08

3.2.1.1 Study Design and Endpoints

Study FG463-21-08 was a Phase 3, double-blind, randomized, parallel group study comparing intravenous micafungin to intravenous AmBisome in non-neutropenic or neutropenic patients with confirmed invasive candidiasis or candidemia. The study was conducted at 129 centers in Europe (55), North America (20), Brazil (18), India (17), Australia (7), South Africa (7), and Thailand (5). Fifteen of the sites recruited only pediatric patients. Patients were randomized to receive either IV micafungin (initial dose 100 mg/day or 2.0 mg/kg for patients weighing ≤ 40 kg) or AmBisome (initial dose of 3 mg/kg/day). Dose increases up to 200 mg (4 mg/kg patients weighing ≤ 40 kg) for micafungin and 5 mg/kg for AmBisome were allowed after 5 days of treatment if there was persistence of the fungal infection as indicated by continued isolation or histological documentation at the primary site or attributable signs and symptoms in addition to radiographic abnormalities. A dose decrease of 50% for AmBisome was allowed for nephrotoxicity. No dose decrease was allowed for micafungin. The minimum length of therapy was 14 days. The maximum length of antifungal treatment was 4 weeks or 8 weeks for patients with chronic disseminated (hepatosplenic) candidiasis, *Candida* osteomyelitis or *Candida* endopthalmitis.

Adult patients were enrolled in the study if they had candidemia or invasive candidiasis, as documented by typical clinical sign or symptom and confirmed by fungal culture and/or histology. The positive culture was to be documented from a sample obtained no more than 4 days prior to the first dose of study medication. Neonatal and pediatric subjects were also enrolled as part of a sub-study using the same criteria as the adults. Subjects were randomized to micafungin or AmBisome in a 1:1 ratio. Randomization was stratified by site and neutropenic status. For centers that also enrolled pediatric patients, randomization was also stratified by age group.

The primary endpoint was treatment success at end of therapy (EOT). Overall treatment success was defined as a clinical response (complete or partial) and a mycological response (eradication or presumed eradication) at EOT. Patients who died during treatment plus 1 day, missed an evaluation, or used systemic antifungal therapy during or immediately after study therapy were considered a failure.

Reviewer's Comment: *The definition of the primary endpoint above was the definition used by the Division during the review of the NDA 21-506/S-008 submission.*

3.2.1.2 Statistical Methodologies

The primary focus of the study was the adult population and the primary objective was to assess the non-inferiority of micafungin versus AmBisome with respect to the response rate based on the investigator's assessment of overall treatment success at the end of therapy. The pediatric sub-study was not powered for hypothesis testing. Descriptive statistics only are presented for the analyses of the pediatric subgroup.

Three data sets were used for analysis. The full analysis set (FAS) consisted of all patients who were randomized and received at least 1 dose of study drug. The FAS was the safety population and used as a secondary efficacy population. The modified full analysis set (MFAS) consisted of all randomized patients who received at least one dose of IV study drug and had a confirmed diagnosis of invasive candidiasis or candidemia. The per protocol set (PPS) consisted of all patients who had a confirmed diagnosis of candidemia or invasive candidiasis and did not have a further invasive fungal infection caused by a non-*Candida* fungal pathogen, for who the investigator's assessment of overall treatment success at EOT was available, and who received at least 5 doses of study drug and did not receive a prohibited antifungal medication.

Reviewer's Comment: *The MFAS is considered the primary analysis set for the purposes of this review.*
One of the reasons for exclusion from the PPS was if the patient did not have an investigator's assessment of overall treatment success at EOT. During the review of the NDA 21-506/S-008 submission, it was noted that some patients did not have an assessment because they had died. It was felt by the Medical Reviewer that death should have been considered as an assessment of failure. Therefore, an FDA-PPS was created which adds back into the PPS all subjects who died on treatment and whose reason for exclusion from the PPS was "No investigator assessment of overall treatment success at End Of Therapy".

3.2.1.3 Patient Disposition, Demographic and Baseline Characteristics

A total of 109 pediatric subjects were enrolled and randomized. The pediatric FAS included 108 subjects. Four pediatric subjects in each treatment group did not have a confirmed candidemia or invasive *Candida* infection at baseline and were excluded from the pediatric MFAS. Of the 100 patients in the pediatric MFAS, 15 were excluded from the pediatric PPS: 7 in the micafungin and 8 in the AmBisome group. The reasons for exclusion from the pediatric PPS were received less than 5 days of IV therapy (3 each treatment group), dual infection with a non-*Candida* species (1 each treatment group), and no investigator assessment at EOT (3 micafungin and 4 AmBisome). There was 1 micafungin subject and 2 AmBisome subjects who did not have an investigator assessment at EOT and died while on therapy. These patients were included in the pediatric FDA-PPS. A summary of the pediatric analysis sets is provided in Table 1.

Table 1
Study FG463-21-08
Analysis Sets Pediatric Patients

	micafungin	AmBisome
FAS	52	56
MFAS	48	52
PPS	41	44
FDA-PPS	42	46

Table 2 summarizes the demographic and baseline characteristics of pediatric MFAS. More than half of the study population was male. Most of the patients were white. The median age for

pediatric patients was less than a year old. All age groups were well represented. The majority of the patients were non-neutropenic at baseline. The majority of the subjects enrolled with candidemia only. Sites in Brazil enrolled the largest number of pediatric patients relative to sites in any other region

Table 2
Study FG463-21-08
Demographic and Baseline Characteristics Pediatric Patients (MFAS)

	micafungin	**AmBisome**
# Patients	48	52
Gender		
Male	31 (64.6)	31 (59.6)
Female	17 (35.4)	21 (40.4)
Age (years) mean (SD)	4.3 (5.2)	3.1 (4.5)
median	0.94	0.94
Min, max	0, 15.5	0, 16.8
Age Group		
0-4 weeks	11 (22.9)	9 (17.3)
5 weeks – 120 days	7 (14.6)	8 (15.4)
121 days - < 2 years	8 (16.7)	14 (26.9)
2- 5 years	8 (16.7)	12 (23.1)
6-11 years	7 (14.6)	4 (7.7)
12- 16 years	7 (14.6)	5 (9.6)
Race		
White	27 (56.3)	26 (50.0)
Black	5 (10.4)	9 (17.3)
Other	16 (33.3)	17 (32.7)
Neutropenic at Baseline		
No	42 (87.7)	39 (75.0)
Yes	6 (12.5)	13 (25.0)
Site of Infection		
Candidemia only	44 (91.7)	49 (94.2)
Invasive Candidiasis	4 (8.3)	3 (5.8)
Region		
North America	5 (10.4)	7 (13.5)
Europe	6 (12.5)	8 (15.4)
Brazil	20 (41.7)	19 (36.5)
India	6 (12.5)	5 (9.6)
Australia	1 (2.1)	1 (1.9)
South Africa	5 (10.4)	5 (9.6)
Thailand	5 (10.4)	7 (13.5)

In the MFAS, the median duration of treatment for both treatment groups was 15 days for the pediatric population. The maximum duration of therapy was 42 days for the pediatric population.

3.2.1.4 Results and Conclusions

The results of treatment success at the end of therapy for the pediatric population are summarized in Table 3. Although the confidence intervals are wide due to the small sample

sizes, micafungin was comparable to AmBisome. The overall rates for the pediatric population are similar to those seen for the adult population (refer to Supplemental Table S-1).

Table 3
Study FG463-21-08
Treatment Success at End of Therapy
Pediatric Population

	micafungin	AmBisome	Difference and 95% CI
MFAS	32/48 (66.7)	34/52 (65.4)	1.3 (-19.3, 21.9)
PPS	32/41 (78.1)	33/44 (75.0)	3.1 (-17.3, 23.5)
FDA-PPS	32/42 (76.2)	33/46 (71.7)	4.5 (-16.1, 25.1)

The study allowed for dose increases after 5 days of treatment if there was persistence of the fungal infection. The AmBisome label is currently labeled to allow doses of 3 mg/kg/day to 5 mg/kg/day. However, the Applicant is requesting labeling (b) (4) . Approximately 23% (11 of 48) of the micafungin patients and 25% (13 of 52) of the AmBisome patients in the MFAS received a dose increase during treatment. Therefore, a sensitivity analysis was performed by treating subjects who were randomized to micafungin and received a dosage increase as failures. This is considered highly conservative since it is unknown if these subjects would have gone on to improve with further dosing of the initial dose. When this criterion is applied, 51% of micafungin treated patients are considered treatment successes. If only those patients who received the to-be labeled dose are considered, 68% of micafungin treated patients were treatment successes.

During the post-treatment phase of the study, 3 micafungin treated pediatric subjects experienced a recurrence and no AmBisome treated pediatric subjects had a recurrence. Of the 3 recurrent fungal infections, 2 were candidemia and 1 was invasive candidiasis affecting the CNS/brain.

3.2.2 Study 98-0-050

3.2.2.1 Study Design and Endpoints

Study 98-0-050 was a Phase 3, double-blind, randomized study comparing micafungin to fluconazole for the prophylaxis of fungal infections in adult and pediatric patients scheduled to undergo autologous or syngeneic (for hematologic malignancies) or allogeneic hematopoietic stem cell transplant (HSCT). The study was conducted at 70 sites in the United States and Canada. Patients were randomized in a 1:1 ratio to receive either IV micafungin (50 mg/day or 1.0 mg/kg for patients weighing ≤ 50 kg) or fluconazole (400 mg/day or 8 mg/kg/day for patients weighing ≤ 50 kg). Study drug was initiated at the time when the transplant conditioning regimen was initiated or within 48 hours of initiating the transplant conditioning regimen. Study drug was administered until patients had neutrophil recovery to a post nadir ANC of ≥500 cells/mm^3 for three consecutive days. At the investigator's discretion, study drug could be continued for up to 5 days following recovery from neutropenia. The maximum length of therapy was up to 42 days after transplant. Randomization was stratified by study center, age (6

months to 12 years of age or 13 years of age and older), and type of transplant (autologous, matched-sibling allogeneic or any other allogeneic transplant) and risk for transplant related mortality (low risk or high risk).

Fungal infection assessments were made twice weekly during the treatment period, at end of therapy, and at 4 weeks post-treatment. The primary efficacy variable was treatment success at the end of study. Treatment success was defined as the absence of a proven, probable or suspected fungal infection through the end of the therapy, and absence of a proven or probable fungal infection through the end of the 4 week post-treatment period. The primary endpoint was also modified, based on Division recommendations during the review of the primary NDA, to include as failures, all deaths even if no proven, probable, or suspected fungal infection was identified at the time of death as well as patients lost to follow-up.

3.2.2.2 Statistical Methodologies

The primary objective of the study was to assess the non-inferiority of micafungin versus fluconazole with respect to the treatment success rate for the overall study population (including both adults and pediatrics). However, since fluconazole does not have the indication of prophylaxis of fungal infections in patients undergoing HSCT, the Medical Division required a superior difference of micafungin over fluconazole to be shown. Presentation of the data by age group was part of descriptive subgroup analyses only.

Two analysis populations were used for analysis. The full analysis set (also known as safety analysis set) and per protocol set. The full analysis set included those patients who received at least 1 dose of study drug. The primary efficacy analysis was performed on the full analysis set. The per protocol set included all randomized patients who received at least one dose of study drug and who were deemed evaluable following patient classification criteria. Patient classification criteria were determined by the sponsor prior to unblinding the study. The per protocol set was a confirmatory analysis.

Reviewer's Comment: *It should be noted that in the original submission of NDA 21-506, the cutoff for pediatrics was <16 years rather than ≤16 years which is used in this review.*

3.2.2.3 Patient Disposition, Demographic and Baseline Characteristics

A total of 91 pediatric subjects received at least one dose of study drug and are included in the pediatric FAS. Of the 91 patients in the pediatric FAS, 5 were excluded from the pediatric PPS: 2 in the micafungin and 3 in the fluconazole group. A summary of the pediatric analysis sets is provided in Table 4.

Table 4
Study 98-0-050
Analysis Sets Pediatric Patients

	micafungin	fluconazole
FAS	43	48
PPS	41	45

Reviewer's Comment: *Since few pediatric patients were excluded from the PPS, the FAS will be the focus of the remainder of this review.*

Table 5 summarizes the demographic and baseline characteristics of the pediatric FAS. More than half of the pediatric population was male. Most of the pediatric patients were white. The median age for pediatric patients was approximately 8.5 years old. The majority of the pediatric patients received an allogeneic transplant.

Table 5
Study 98-0-050
Demographic and Baseline Characteristics Pediatric Patients (FAS)

		micafungin	fluconazole
# Patients		43	48
Gender			
Male		23 (53.5)	29 (60.4)
Female		20 (46.5)	19 (39.6)
Age(years)	mean (SD)	8.7 (4.9)	8.2 (5.1)
	median	8.2	9.0
	Min, max	0.6, 19.9	0.6, 16.7
Age Group			
121 days - < 2 years		5 (11.6)	7 (14.6)
2- 5 years		9 (20.9	10 (20.8)
6-11 years		15 (34.9)	22 (45.8)
12- 16 years		14 (32.6)	9 (18.8)
Race			
White		37 (86.1)	43 (89.6)
Black		4 (9.3)	4 (8.3)
Asian		2 (4.7)	1 (2.1)
Transplant Type			
Allogeneic		41 (95.3)	46 (95.8)
Autologous or Syngenic		2 (4.7)	2 (4.2)

In the pediatric FAS, the median duration of therapy was 22 days with micafungin and 21 days with fluconazole. The maximum duration of therapy for both treatment groups was 51 days in the pediatric population.

3.2.2.4 Results and Conclusions

The results of treatment success at the post-treatment 4-week follow-up period for the pediatric FAS population are summarized in Table 6. Micafungin was numerically better than fluconazole. However, statistical claims for superiority are not able to be made due to the small sample sizes for the pediatric population. The overall rates for the pediatric population show similar trends to those seen for the overall and adult populations (refer to Supplemental Tables S-2 and S-3). There were 4 pediatric patients with a proven fungal infection during the study. One micafungin patient had proven zygomycosis. The other 3 were in fluconazole patients: 2 proven aspergillosis and 1 proven *C. parapsilosis* candidemia. The single micafungin patient with

proven fungal infection died. None of the 3 fluconazole patients with proven fungal infection died.

Table 6
Study 98-0-050
Treatment Success at Post-Treatment 4-week Follow-up Period
FAS Pediatric Population

	micafungin (n=43)	**fluconaozle** (n=48)	**Difference and 95% CI**
Success	31 (72.1)	26 (54.2)	17.9 (-3.8, 39.6)
Failure	12 (27.9)	22 (45.8)	
All Death	5 (11.6)	6 (12.5)	
Proven/Probable Fungal Infection Prior to Death	1 (2 3)	0	
Proven/Probable Fungal Infection	0	3 (6.3)	
Suspected Fungal Infection	7 (16.3)	13 (27.1)	
Lost to Follow-up	0	0	

3.3 Evaluation of Safety

Micafungin is currently approved for adults for 3 indications: the treatment of patients with candidemia, acute disseminated candidiasis, *Candida* peritonitis and abscesses; esophageal candidiasis; and for the prophylaxis of *Candida* infections in patients undergoing hematopoietic stem cell transplant (HSCT). The safety profile of micafungin in pediatric patients was similar to that of the adult population. As the pediatric data from Studies FG 463-21-08 and 98-0-050 were reviewed at the time of the adult approvals, there are no new safety findings based on these studies. Table 7 and Table 8 include a brief summary of treatment emergent adverse events (TEAE) and deaths from Studies FG463-21-08 and 98-0-050, respectively. The high rate of TEAEs is consistent with the patients' underlying disease states for the two populations studied. Rates of any or serious TEAEs and mortality for micafungin treated pediatric patients were similar to AmBisome treated and fluconazole treated pediatric patients in these two comparative trials. For a detailed review of the pediatric safety data, please see the Medical Officer's review.

Table 7
Study FG463-21-08
Overall Adverse Events
Pediatric FAS Population

	micafungin (n=52)	**AmBisome** (n=56)
Any TEAE	48 (92.3)	52 (92.9)
Serious TEAE	16 (30.8)	21 (37.5)
Deaths	15 (28.8)	14 (25.0)

Table 8
Study 98-0-050
Overall Adverse Events
Pediatric FAS Population

	micafungin (n=43)	fluconazole (n=48)
Any TEAE	43 (100)	48 (100)
Serious TEAE	9 (20.9)	7 (14.6)
Deaths	5 (11.6)	6 (12.5)

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

Table 9 summarizes the number of pediatric patients who had treatment success at the end of therapy for gender, age, and race for Study FG463-21-08. These results should be interpreted with caution due to small sample sizes. Subgroup analyses by region are not presented since the study was primarily conducted outside North America.

Table 9
Study FG463-21-08 Subgroup Analyses
Treatment Success at End of Therapy
Pediatric MFAS Population

	micafungin	AmBisome
Gender		
Male	21//31 (67.7)	22/31 (71.0)
Female	11/17 (64.7)	12/21 (57.1)
Age		
0-4 weeks	9/11 (81.8)	5/9 (55.6)
5 weeks – 120 days	5/7 (71.4)	5/8 (62.5)
121 days - < 2 years	5/8 (62.5)	9/14 (64.3)
2- 5 years	7/8 (87.5)	8/12 (66.7)
6-11 years	3/7 (42.9)	3/4 (75.0)
12- 16 years	3/7 (42.9)	4/5 (80.0)
Race		
White	19/27 (70.4)	16/26 (61.5)
Black	4/5 (80.0)	6/9 (66.7)
Others	9/16 (56.3)	12/17 (70.6)

Table 10 summarizes the number of pediatric patients who had treatment success at the post-treatment 4-week follow-up period for gender, age, and race for Study 98-0-050. These results should be interpreted with caution due to small sample sizes. Subgroup analyses by region are not presented since the study was conducted only in North America.

Table 10
Study 98-0-050 Subgroup Analyses
Treatment Success at Post-Treatment 4-week Follow-up Period
Pediatric FAS Population

	micafungin	fluconazole
Gender		
Male	19/23 (82.6)	17/29 (58.6)
Female	12/20 (60.0)	9/19 (47.4)
Age		
121 days - < 2 years	4/5 (80.0)	5/7 (71.4)
2- 5 years	6/9 (66.7)	3/10 (30.0)
6-11 years	12/15 (80.0)	13/22 (59.1)
12- 16 years	9/14 (64.3)	5/9 (55.6)
Race		
White	27/37 (73.0)	23/43 (53.5)
Black	2/4 (50.0)	2/4 (50.0)
Asian	2/2 (100.0)	1/1 (100.0)

4.2 Other Special/Subgroup Populations

Study FG463-21-08 was stratified at randomization by baseline neutropenic status. Most of the subjects were not neutropenic at baseline so results by baseline neutropenic status should be interpreted with caution.

Table 11
Study FG463-21-08
Treatment Success at End of Therapy by Baseline Neutropenic Status
Pediatric MFAS Population

	micafungin	AmBisome
Baseline Neutropenic Status		
Neutropenic	5/6 (83.3)	8/13 (61.5)
Non-neutropenic	27/42 (64.3)	26/39 (66.7)

Study 98-0-050 was stratified at randomization by transplant type. Most of the subjects received an allogenic transplant so results by baseline neutropenic status should be interpreted with caution.

Table 12
Study 98-0-050
Treatment Success at Post-Treatment 4-week Follow-up Period by Transplant Type
Pediatric FAS Population

	micafungin	fluconazole
Transplant Type		
Allogenic	29/41 (70.7)	24/46 (52.2)
Autologous or Syngeneic	2/2 (100.0)	2/2 (100.0)

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

The results presented in this review are for pediatric subgroups that were enrolled under the much larger protocols which included the adult population. The studies were not powered for hypothesis testing in the pediatric subgroup. All results presented are descriptive in nature.

5.2 Collective Evidence

For the indication of treatment of candidemia and/or invasive candidiasis, a single randomized controlled trial provides supportive efficacy and safety data for pediatric patients, Study FG463-21-08. The primary efficacy analysis population of this study included 100 patients ≤ 16 years of age, 48 received micafungin and 52 received AmBisome. At the end of therapy, 67% of micafungin patients had a treatment success compared to 65% of AmBisome treated patients. However, this study did not study only a fixed dose of micafungin. It allowed for an increase in the micafungin dose after 5 days of treatment if there was persistence of the fungal infection. Approximately 23% of the micafungin pediatric patients received a dose increase. (b) (4) , a conservative analysis of the data was performed by treating those subjects who received an increase in their micafungin dose as treatment failures. Based on this, 51% of micafungin treated patients were treatment successes. The rates for the pediatric population were similar to those seen for the adult population.

For the indication of prophylaxis of *Candida* infections, a single randomized controlled trial provides supportive efficacy and safety data for pediatric patients, Study 98-0-050. The primary efficacy analysis population of this study included 91 patients ≤ 16 years of age in, 43 received micafungin and 48 received fluconazole. At the post treatment 4 week follow-up, 72% of micafungin patients had a treatment success compared to 54% of fluconazole treated patients. The results for the pediatric population show similar trends to those seen for the adult population.

5.3 Conclusions and Recommendations

It was determined by the Medical Division and the Applicant that since there are similarities between the pediatric and adult population for candidemia/invasive candidiasis and prophylaxis of *Candida* infections in patients undergoing HSCT, it is possible to base the selection of the dose regimen for the pediatric population on that which achieves an exposure in the pediatric population which is similar to the exposure in adults which has previously been shown to be effective. Therefore, doses for pediatric patients were proposed by modeling the pharmacokinetic data of the pediatric population. These doses are:

- Candidemia/Invasive Candidiasis: (b) (4)
- Esophageal Candidiasis: (b) (4)
- Prophylaxis of *Candida* infections: (b) (4)

This review was of the supportive evidence of efficacy and safety for the pediatric population which comes from two randomized controlled Phase III trials. One trial studied the treatment of patients with candidemia and/or invasive candidiasis and studied micafungin at a dose of 2 mg/kg or 100 mg for patients weighing > 40 kg. The other trial studied the prophylaxis of *Candida* infections in patients undergoing HSCT and studied micafungin at a dose of 1 mg/kg or 50 mg for patients weighing > 50 kg. (b) (4) In both of these trials the efficacy and safety data for the pediatric patients was similar to that of the adult patients.

5.4 Labeling Recommendations

The Applicant proposes to revise the Clinical Studies section with the following:

- Indicate that the current subsections are for the adult treatment of candidemia and other *Candida* infections, the adult treatment of esophageal candidiasis. (b) (4)
- (b) (4)

Denoting the current sections, 14.1 Treatment of Candidemia and other *Candida* Infections and 14.2 Treatment of Esophageal Candidiasis, as Adult is acceptable since the trials discussed in these sections included only adults. (b) (4)

(b) (4)

(b) (4)

Supplemental Tables

Table S-1
Study FG463-21-08
Treatment Success at End of Therapy
Adult Population

	micafungin	AmBisome	Difference and 95% CI
MFAS	156/247 (63.2)	147/245 (60.0)	3.7 (-4.9, 12.2)
PPS	153/202 (75.7)	146/188 (77.7)	-1.3 (-9.6, 7.1)
FDA-PPS	153/215 (71.2)	146/205 (71.2)	0.4 (-8.2, 9.1)

*Difference (micafungin – AmBisome) and confidence interval are stratified by neutropenic status at baseline.

Table S-2
Study 98-0-050
Treatment Success at Post-Treatment 4-week Follow-up Period
FAS Overall Population

	Micafungin (n=425)	fluconazole (n=457)	Difference and 95% CI
Success	343 (80.7)	337 (73.7)	7.0 (1.5, 12.5)
Failure	82 (19.3)	120 (26.3)	
All Death	18 (4.2)	26 (5.7)	
Proven/Probable Fungal Infection Prior to Death	1 (0 2)	3 (0.7)	
Proven/Probable Fungal Infection	6 (1.4)	8 (1.8)	
Suspected Fungal Infection	53 (12.5)	83 (18.2)	
Lost to Follow-up	5 (1.2)	3 (0.7)	

Table S-3
Study 98-0-050
Treatment Success at Post-Treatment 4-week Follow-up Period
FAS Adult Population

	Micafungin (n=382)	fluconaozle (n=409)	Difference and 95% CI
Success	312 (81.7)	311 (76.0)	5.7 (-0.2, 11.6)
Failure	70 (18.3)	98 (24.0)	
All Death	13 (3.4)	20 (4.9)	
Proven/Probable Fungal Infection Prior to Death	0	3 (0.7)	
Proven/Probable Fungal Infection	6 (1.6)	5 (1.2)	
Suspected Fungal Infection	46 (12.0)	70 (17.1)	
Lost to Follow-up	5 (1.3)	3 (0.7)	

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/s/

CHERYL A DIXON
02/25/2013

KAREN M HIGGINS
02/25/2013
I concur.