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/Serial Number:	21-227 SE5-021
Drug Name:	Cancidas™ for injection (caspofungin acetate)
Indication(s):	Pediatric use from 3 months through 17 years of age for the infectious disease indications currently approved in adults.
Applicant:	Merck Research Laboratories
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Keywords: clinical studies, NDA review, pediatrics, anti-fungal, ETFN, aspergillosis, candidemia and invasive candidiasis, esophageal candidiasis

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

Two pediatric safety/efficacy studies provide evidence to support the use of caspofungin in children. The results of one study suggest that the use of caspofungin for the treatment of documented invasive aspergillosis (as salvage therapy), invasive candidiasis, and esophageal candidiasis in patients 6 months to 17 years of age is effective and safe. The results of the second study suggest that the use of caspofungin as empirical therapy in patients with persistent fever and neutropenia aged 2 to 17 years is also safe and effective. The outcomes with caspofungin in the pediatric population are generally consistent with those reported in adults receiving caspofungin for documented *Aspergillus* or *Candida* infections as well as empiric therapy. Both studies were conducted in response to and in accordance with the Final Amended Pediatric Written Request dated July 16, 2007.

1.2 Brief Overview of Clinical Studies

The first clinical safety/efficacy study, Protocol 043, was an open-label, non-comparative study of caspofungin in pediatric patients ages 6 months to 17 years with documented aspergillosis, esophageal candidiasis, or invasive candidiasis. The study was conducted at sites in the United States, Taiwan, Germany, Israel, New Zealand and Belgium. All patients received caspofungin monotherapy 50 mg/m^2 daily after a 70 mg/m^2 loading dose on Day 1. Patients who failed to improve clinically after at least 4 days of caspofungin and in whom the drug had been well-tolerated could receive a dosage increase to 70 mg/m^2 from Day 5 onward. The maximum dose was not to exceed 70 mg/day. The duration of therapy was individualized for each patient and was in accordance with the Infectious Diseases Society of America Treatment Guidelines. In general, the maximum treatment duration was to be 28 days for esophageal and invasive candidiasis and 90 days for invasive aspergillosis. Approximately 40 children with *Candida* infections and a minimum of 10 patients with invasive aspergillosis were planned for the study. The study was conducted primarily to assess the safety of caspofungin in pediatric patients; however, efficacy data was also assessed.

The second clinical safety/efficacy study, Protocol 044, was a double blind, randomized, comparative study to evaluate the safety and efficacy of caspofungin versus AmBisome as empirical therapy for persistent fever and neutropenia. The study was conducted at sites in the United States, Belgium, Germany, and Spain. Patients between 2 and 17 years were randomized in a 2:1 ratio to receive either caspofungin + placebo to AmBisome or AmBisome + placebo to caspofungin. Caspofungin was administered as a loading dose of 70 mg/m^2 on Day 1 followed by maintenance doses of 50 mg/m^2 daily from Day 2. AmBisome was administered as 3 mg/kg/day. If, in the opinion of the investigator, a patient required up-dosing, the dose was increased to either 70 mg/m^2/day caspofungin or 5 mg/kg/day AmBisome. Therapy was to be continued until the resolution of neutropenia or up to 72

hours later; the maximum duration was 28 days. Safety was the primary objective of the study but efficacy data were also collected. Efficacy was assessed based on the 5-part composite endpoint denoted as overall response. The overall response was considered favorable if all of the following criteria were met:

1. successful treatment of baseline invasive fungal infection, if any
2. absence of breakthrough invasive fungal infection up to 7 days post-therapy
3. survival to 7 days post-therapy
4. absence of discontinuation due to lack of efficacy or study drug toxicity
5. resolution of fever for 48 hours during the period of neutropenia.

A failure in any one component resulted in a patient being considered as an unfavorable overall response.

1.3 Statistical Issues and Findings

The primary objective of both studies was the estimation of safety and efficacy of caspofungin in pediatric patients. No formal hypothesis testing was conducted.

Overall, caspofungin treatment was generally safe and well tolerated in pediatric patients with either documented or suspected fungal infections. The most common clinical adverse experiences reported by patients who received caspofungin in the 2 safety/efficacy studies were pyrexia (23.8%), rash (14.3%), diarrhea (9.5%), vomiting (9.5%), and hypertension (9.5%).

In Protocol 043, a 50% favorable response rate [95% exact confidence interval: (18.7%, 81.3%)] was seen in pediatric patients with invasive aspergillosis. For pediatric patients with invasive candidiasis, the overall favorable response rate was 81% [95% exact confidence interval: (64.8%, 92.0%)]. The favorable response rates seen for the pediatric patients with aspergillosis and with invasive candidiasis were similar to those seen in the adult studies conducted for documented *Aspergillus* or *Candida* infections, respectively. Only 1 patient was enrolled with esophageal candidiasis and the patient had a favorable response to treatment with caspofungin.

In Protocol 044, 81 of the 82 patients who received study therapy were included in the MITT population. The rates of favorable overall response were 46.4% [95% exact confidence interval: (33.0%, 60.3%)] for caspofungin and 32.0% [95% exact confidence interval: (15.0%, 53.5%)] for AmBisome. For patients at high-risk of developing a fungal infection, the favorable response rate was numerically higher in the caspofungin group (9/15, 60%) than in the AmBisome group (0/7, 0%). This result must be viewed cautiously due to the small sample size. For patients at low risk of developing a fungal infection, the favorable response rates were similar between the caspofungin group (17/41, 41.5%) and the AmBisome group (8/18, 44.4%). The efficacy results of the pediatric patients were generally similar to that observed in a similarly conducted study in adults.

2. INTRODUCTION

2.1 Overview

This is a supplemental NDA submission for Cancidas™ (caspofungin). Cancidas belongs to the echinocandin class and is intended for the treatment of fungal infections. It has previously been approved in adults for the treatment of invasive aspergillosis in patients refractory to or intolerant of other therapies, the treatment of candidemia and the following *Candida* infections: intra-abdominal abscesses, peritonitis, and pleural space infections, the treatment of esophageal candidiasis, and empirical therapy of suspected fungal infections in febrile, neutropenic patients. This supplemental NDA is in response to the Pediatric Written Request and is to support the use of caspofungin in children 3 months through 17 years of age for the infectious disease indications currently approved in adults. The proposed therapeutic dose and regimen of caspofungin for pediatric patients is based on the patient's body surface area. For all indications, a single 70 mg/m^2 loading dose (not to exceed an actual dose of 70 mg) should be administered on Day 1 followed by 50 mg/m^2 daily thereafter.

The clinical development program for caspofungin in pediatric patients consisted of 3 pediatric pharmacokinetic studies and 2 safety/efficacy clinical studies. The intent of the pharmacokinetic studies was to demonstrate a safe well-tolerated dose with sufficient plasma exposures in pediatric patients, thereby allowing for subsequent use in the pediatric safety/efficacy clinical trials. The first safety/efficacy trial was an open label, non-comparative trial of caspofungin against documented *Candida* and *Aspergillus* infections [esophageal candidiasis, invasive candidiasis, or salvage treatment of invasive aspergillosis] in pediatric patients 2 months through 17 years of age (Protocol 043). The second safety/efficacy study was a controlled study of caspofungin versus liposomal amphotericin B (AmBisome™) to assess the safety and efficacy of caspofungin as empirical therapy for pediatric patients 2 to 17 years of age with persistent fever and neutropenia (Protocol 044). In both studies, the primary objective was to assess the safety of caspofungin; however, efficacy data was also assessed.

2.2 Data Sources

The data analyzed in this review comes from the 2 safety/efficacy trials. The study reports and datasets provided in the electronic submission were reviewed. These can be found in the electronic submission located at: \\Cdsesub1\evsprod\NDA021227\0017. Additional datasets for Protocol 044 are located at \\Cdsesub1\evsprod\NDA021227\0025.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Protocol 043

3.1.1.1 Study Design

Protocol 043 was a prospective, open-label, non-comparative study examining the safety, tolerability, and efficacy of caspofungin in pediatric patients (aged 3 months through 17 years) with documented aspergillosis, esophageal candidiasis, or invasive candidiasis infections. The study was conducted at 21 sites in the United States (11), Taiwan (2), Germany (4), Israel (1), Italy (1), New Zealand (1), and Belgium (1). All patients received caspofungin monotherapy 50 mg/m^2 daily after a 70 mg/m^2 loading dose on Day 1. Patients who failed to improve clinically after at least 4 days of caspofungin and in whom the drug had been well-tolerated could receive a dosage increase to 70 mg/m^2 from Day 5 onward. The maximum dose was not to exceed 70 mg/day. The duration of therapy was individualized for each patient and was in accordance with the Infectious Diseases Society of America Treatment Guidelines. In general, the maximum treatment duration was to be 28 days for esophageal and invasive candidiasis and 90 days for invasive aspergillosis. Approximately 40 children with *Candida* infections and a minimum of 10 patients with invasive aspergillosis were planned for the study.

A patient with invasive aspergillosis could be enrolled in the study if they met the definitions of proven or probable invasive aspergillosis (according to the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections co-Operative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group, EORTC/MSG) and must have been refractory or intolerant of standard antifungal therapy. A patient with invasive *Candida* infections must have had at least 1 positive culture of a *Candida* species from blood or other normally sterile body site, which had been obtained within 4 days of study entry, and have clinical evidence of infection within 48 hours prior to enrollment. A patient with an esophageal *Candida* infection must have had symptoms consistent with esophageal candidiasis, endoscopy grading ≥ 1, a positive stain or wetmount KOH from endoscopy followed by a positive culture for *Candida* spp. or positive histopathology evidence of *Candida* infection, and need IV therapy.

Patients were monitored daily for adverse experiences during caspofungin therapy and for 14 days following the end of therapy. Although the primary intention of the study was to gather information related to safety and tolerability of caspofungin in children with documented fungal infections, efficacy data was also collected. Symptoms of fungal infection were assessed daily while the patient was on therapy, on the last day of therapy, and if the response was favorable at the end of therapy, also at the 14 and 28 day follow-up time points. Radiographic studies, cultures and/or histopathology were performed as clinically indicated while on study therapy or during the follow-up period. The main efficacy evaluation for the study was the proportion of patients with a favorable response, as defined for each infection.

- Invasive aspergillosis: Efficacy was based on the clinical evaluation which incorporated signs/symptoms, radiographic data, and other relevant criteria.
- Invasive candidiasis: Efficacy was based on both the clinical and microbiological response assessments.
- Esophageal candidiasis: Efficacy was based on the assessment of signs/symptoms of infection and the endoscopic findings.

The primary efficacy time point was at the end of therapy. Results are presented and summarized separately for each infection. The proportion and its respective 95% exact confidence interval were calculated for each infection. The primary population for assessing efficacy was the modified Intention-to-Treat (MITT) population. The MITT population included those patients who received at least 1 full dose of caspofungin therapy and had a documented diagnosis of invasive aspergillosis, invasive candidiasis, or esophageal candidiasis. An evaluable-patients population was also defined and was intended to provide supportive evidence to the findings of the MITT population.

The study was conducted for estimation purposes. Therefore, no formal hypothesis testing was performed. The sample size of approximately 50 pediatric patients aged 3 months to 17 years, where at least 10 of these patients were to be enrolled with invasive aspergillosis, was not based on any statistical considerations but logistical considerations.

3.1.1.2 Patient Demographics

A total of 49 patients were enrolled into the study: 10 with invasive aspergillosis, 38 with invasive candidiasis, and 1 with esophageal candidiasis. After study entry, it was found that one of the invasive candidiasis patients had *Trichosporon* not *Candida* infection. This patient was excluded from all efficacy analyses. Therefore, the MITT population consisted of 48 patients. The evaluable-patient population excluded 7 patients (1 with aspergillosis and 6 with invasive candidiasis) who did not receive the minimum duration of caspofungin therapy.

Overall, 29 (59.2%) of the 49 patients completed study therapy. Two aspergillosis patients discontinued therapy due to a clinical adverse experience not related to caspofungin therapy. Three aspergillosis and 6 invasive candidiasis patients discontinued therapy due to lack of efficacy. Nine invasive candidiasis patients discontinued therapy for other reasons (6 due to being discharged from the hospital, 1 due to loss of IV access, 1 switched to oral antifungal therapy after being discharged from the hospital, and 1 protocol deviation due to blood culture with *Trichosporon beigellii*).

Baseline characteristics for the 10 patients with aspergillosis and the 38 patients with invasive candidiasis are presented in Table 1. The one patient with esophageal candidiasis was a 17 year old Caucasian male with recurrent AML and a history of allogeneic bone marrow transplant who received caspofungin as primary treatment.

Of the patients with aspergillosis, the majority were males and white. The mean age was 8 years. All of the patients were refractory and 2 were also intolerant to prior antifungal

therapy. The most common site of aspergillosis was pulmonary. The majority were non-neutropenic at study entry. Four patients had a baseline *Aspergillus* isolate: 1 each of *A. flavus*, *A. fumigatus*, *A. niger*, and *A. terreus.*

Of the patients with invasive candidiasis, slightly more than half were males and the majority was white. The mean age was 8 years and approximately 40% were in the 2 to 6 year age group. Most patients received caspofungin as primary treatment. Candidemia (site of infection blood) accounted for the majority of the invasive candidiasis cases. The majority were non-neutropenic at study entry. Thirty-five patients had a baseline *Candida* isolate: 12 *C. albicans*, 8 *C. parapsilosis*, 4 *C. tropicalis*, 4 *C. glabrata*, 3 *C. lusitaniae*, 2 *C. lambica*, 1 *C. guilliermondii*, and 1 *C. krusei*.

Table 1
Protocol 043- All Patients
Baseline Characteristics

	Infection	
	Invasive Aspergillosis	**Invasive Candidiasis**
# Patients	10	38
Gender		
Male	8 (80.0)	22 (57.9)
Female	2 (20.0)	16 (42.1)
Age mean (SD)	8.3 (3.9)	7.9 (5.4)
median	7.5	6.5
Min, max	3, 16	6 months, 17 years
Race		
White	6 (60.0)	23 (60.5)
Black	-	6 (15.8)
Asian	4 (40.0)	5 (13.2)
Other	-	4 (10.6)
Reason for Study Entry		
Primary therapy	n/a	31 (81.6)
Salvage therapy (refractory)	8 (80.0)	7 (18.4)
Both refractory and intolerant	2 (20.0)	n/a
Site of Infection		
Definite pulmonary	2 (20.0)	n/a
Probable pulmonary	4 (40.0)	n/a
Definite middle ear	1 (10.0)	n/a
Definite intracranial	1 (10.0)	n/a
Multiple sites	2 (20.0)	2 (5.3)
Blood	n/a	35 (92.1)
Psoas muscle abscess	n/a	1 (2.6)
Neutropenia Status at Study Entry		
Non-neutropenic	7 (70.0)	32 (84.2)
Neutropenic	3 (30.0)	6 (15.8)

3.1.1.3 Efficacy Results

Reviewer's Comment*: Since relatively few patients were excluded from the evaluable patient population within each infection, efficacy results will be presented only for the MITT population.*

All 10 patients with aspergillosis were assessed for efficacy at the end of caspofungin therapy. A favorable outcome to treatment included both a complete and partial clinical response. Five (50.0%) of the 10 patients had a favorable outcome at the end of treatment: 3 complete and 2 partial. The 95% exact confidence interval about the 50% response rate is (18.7, 81.3). None of the 5 patients with a favorable clinical response had a relapse at either the 14-day or 28-day post-therapy follow-up visits. All five of the patients with an unfavorable clinical response at the end of therapy died either during the study or shortly after study completion. Two of the patients with an unfavorable response had invasive aspergillosis involving multiple sites and 3 were neutropenic at study entry.

Thirty-seven of the 38 patients enrolled with invasive candidiasis were included in the MITT population. A favorable overall response to treatment included both a favorable clinical response (complete or partial) and a favorable microbiological response (eradication or presumed eradication). Candidemia patients needed to have a microbiological response of eradication in order to have a favorable overall response. Thirty (81.1%) of the 37 patients had a favorable overall response (all complete response). The 95% exact confidence interval about the 81.1% response rate is (64.8, 92.0). Only 1 patient had a relapse in the *Candida* infection by the 28-day post-therapy follow-up visit. Two patients were not followed through the 28-day post-therapy follow-up visit. Seven patients had an unfavorable response at the end of therapy. Four of the patients had persistent fever (2 with positive blood cultures), 1 had a positive blood culture even though the patient had been asymptomatic, and 2 had suspected fungal infection at a site other than the blood (1 lung, 1 CNS) even though the candidemia had resolved.

A single patient with esophageal candidiasis was enrolled. At the end of caspofungin therapy the patient had a favorable clinical response. The patient had complete resolution of the esophageal and oropharyngeal lesions. The patient did not have a relapse at the 14-day or 28-day post-therapy follow-up visits.

3.1.2 Protocol 044

3.1.2.1 Study Design

Protocol 044 was a double-blind, double-dummy, randomized, comparative study to evaluate the safety, tolerability, and efficacy of caspofungin versus AmBisome in the empiric treatment of pediatric patients with persistent fever and neutropenia. The study was conducted at 17 sites in the United States (8), Belgium (1), Germany (4), and Spain (4). Patients were randomized to receive either caspofungin + placebo to AmBisome or AmBisome + placebo to caspofungin. Caspofungin was administered as a loading dose of 70 mg/m^2 on Day 1 followed by maintenance doses of 50 mg/m^2 daily from Day 2. AmBisome

was administered as 3 mg/kg/day. If, in the opinion of the investigator, a patient required up-dosing, the dose was increased to either 70 mg/m^2/day caspofungin or 5 mg/kg/day AmBisome. The maximum dose of caspofungin allowed was 70 mg daily. Therapy was to be continued until the patient's absolute neutrophil count (ANC) was at least 500/μL and for up to 72 hours later; the maximum duration was 28 days. For patients with a documented fungal infection, the duration of study therapy recommended in the protocol was to continue for at least 14 days and at least 7 days after resolution of neutropenia and of symptoms but for no longer than 90 days.

Pediatric patients 2 to 17 years who had received chemotherapy for leukemia, lymphoma, or other cancers, or had undergone bone marrow or peripheral stem cell transplantation, and were persistently neutropenic and febrile were enrolled in the study. Prior to randomization, eligible patients had to have had at least 96 hours of neutropenia, had received at least 96 hours of systemic antibacterial therapy, and had a fever greater than 38°C. Patients were randomized to treatment in a 2:1 ratio (caspofungin: AmBisome) and stratified according to risk of fungal infection. Patients were defined to be at high risk if they had undergone allogeneic bone marrow or peripheral stem cell transplant and/or received chemotherapy for a relapse of acute leukemia. All others were defined to be at low risk.

Patients were monitored for safety daily while on study therapy and for 14 days after the end of study therapy. Physical examinations, vital signs, and laboratory tests were also collected during the study therapy and follow-up period. An independent Adjudication Committee reviewed the cases of suspected fungal infections and determined whether or not the patient had a baseline or breakthrough fungal infection. For patients with a baseline fungal infection, the Adjudication Committee determined if the treatment of the infection was a success.

The study was conducted for estimation purposes. Therefore, no formal hypothesis testing was performed. Approximately 100 pediatric patients were planned for enrollment. Based on the 2:1 randomization, it was expected that approximately 67 patients would receive caspofungin and 33 would receive AmBisome. The study, however, closed with a final enrollment of 82 patients due to difficulty finding eligible patients.

Efficacy assessments were based on the 5-part composite endpoint denoted as overall response. The overall response was considered favorable if all of the following criteria were met:

1. successful treatment of baseline invasive fungal infection, if any
2. absence of breakthrough invasive fungal infection up to 7 days post-therapy
3. survival to 7 days post-therapy
4. absence of discontinuation due to lack of efficacy or study drug toxicity
5. resolution of fever for 48 hours during the period of neutropenia.

A failure in any one component resulted in a patient being considered as an unfavorable overall response. The main efficacy evaluation was the proportion of patients with a favorable overall response. For both treatment groups, the estimated proportion of patients with a favorable overall response were calculated using Cochran-Mantel-Haenszel weights to adjust for strata and their respective 95% confidence intervals were computed using the

normal approximation to the binomial distribution and Cochran-Mantel-Haenszel weights to adjust for strata. Observed proportions and their respective exact confidence interval were also calculated for the overall response and each of the 5 individual components of the composite endpoint.

Two patient populations were defined for the efficacy evaluation: the modified intention-to-treat (MITT) and evaluable-patient population. The MITT population included all patients who received at least 1 dose of therapy, received chemotherapy for malignancy or a HSCT, and met the protocol defined inclusion criteria for fever and neutropenia at study entry. The evaluable patient analysis was performed to provide supportive data to the MITT analysis for only the overall response and its 5 individual components. The evaluable population consisted of patients who met the criteria for inclusion in the MITT analysis; had not received a prohibited prior or concomitant systemic antifungal therapy during the period of IV study therapy; received at least 4 days of study therapy, unless a protocol endpoint of premature discontinuation due to drug-related toxicity had already been met; had an end of study evaluation at 7 days post-therapy or survival through 7 days post-therapy was demonstrated, unless a protocol failure endpoint had already been met; and did not have any protocol violations that would interfere with the assessment of efficacy.

3.1.2.2 Patient Demographics

A total of 82 patients were randomized and received study treatment, 56 patients were randomized to receive caspofungin and 26 to receive AmBisome. All patients with the exception of one patient in the AmBisome group completed the study. Ten (17.9%) caspofungin patients and 7 (26.9%) AmBisome patients discontinued early from study therapy. The MITT population included 81 patients (56 in the caspofungin group and 25 in the AmBisome group). The one AmBisome patient was excluded from the MITT population because the patient did not have a fever at the time of study entry. The evaluable population consisted of 45 caspofungin patients and 20 AmBisome patients. The most common reasons for exclusion from the evaluable population were protocol violation that confounded assessment (17.1%) and less than 4 days of study therapy received (6.1%).

Table 2 summarizes the demographic and baseline characteristics of the patients who received treatment. There were no significant differences across treatment groups. The majority of the patients was male and was white. The mean age of the patients was 7.4 years with a range of 2 to 16 years. The most common primary underlying disease was acute leukemia. Approximately 25% of patients were categorized as being at higher risk for developing a fungal infection. Slightly more than half of the patients received antifungal prophylaxis prior to study entry.

Table 2
Protocol 044- All Patients
Demographic and Baseline Characteristics

	Treatment Group	
	Caspofungin	**AmBisome**
# Patients	56	26
Gender		
Male	35 (62.5)	20 (76.9)
Female	21 (37.5)	6 (23.1)
Age mean (SD)	7.4 (4.5)	7.4 (4.9)
median	6.0	5.5
Min, max	2 to 16	2 to 16
Race		
White	48 (85.7)	21 (80.8)
Black	4 (7.1)	2 (7.7)
Other	4 (7.1)	3 (11.5)
Underlying Disease		
Acute Leukemia	34 (60.7)	17 (65.4)
Lymphoma	6 (10.7)	4 (15.4)
Solid tumor	16 (28.6)	4 (15.4)
Other	0	1 (3.8)
Risk of Fungal Infection		
High	15 (26.8)	7 (26.9)
Low	41 (73.2)	19 (73.1)
Prior Prophylaxis		
Yes	28 (50.0)	14 (53.8)
No	28 (50.0)	12 (46.2)

3.1.2.3 Efficacy Results

Table 3 summarizes the results of overall response for the MITT population. The favorable overall response rate was numerically higher in the caspofungin group (46.4%) than in the AmBisome group (32.0%). The corresponding 95% exact confidence intervals are (33.0, 60.3) for caspofungin and (15.0, 53.5) for AmBisome. In addition to the MITT analysis, a supportive analysis was performed using the evaluable patient population. The favorable overall response rate in the evaluable patient population was 40% (18/45) in the caspofungin group and 30% (6/20) in the AmBisome group. The corresponding 95% exact confidence intervals are (25.7, 55.7) for caspofungin and (11.9, 54.3) for AmBisome.

Table 3
Protocol 044- MITT Population
Overall Response and Response by Component

	caspofungin (n=56)	**AmBisome** (n=25)
Overall Response*	26 (46.4)	8 (32.0)
95% exact confidence interval	(33.0, 60.3)	(15.0, 53.5)
No breakthrough fungal infection within 7 days of EOT	56 (100.0)	24 (96.0)
Survival through 7 days of EOT	56 (100.0)	26 (100.0)
No discontinuation due to lack of efficacy or toxicity	51 (91.1)	21 (84.0)
Resolution of fever during neutropenia	27 (48.2)	9 (36.0)
Successful treatment of baseline infection	0/1	n/a

*The 95% confidence interval about the difference in overall response (caspofungin –AmBisome) calculated using the normal approximation to the binomial adjusted for risk strata is (-10.1, 38.9).

All patients in both treatment groups survived for at least 7 days after the completion of therapy. A single AmBisome patient had a documented breakthrough invasive fungal infection. Only one patient in the study had a documented baseline fungal infection. This patient was randomized to caspofungin and was considered to have failed treatment of the baseline infection.

Although not part of the primary analysis of overall response, data on documented infections occurring after the 7 day post-therapy visit and possible fungal infections were also provided. There was one caspofungin patient who had a probable fungal infection after the 7-day follow-up visit. There were 4 patients in the caspofungin group with possible infections (3 baseline and 1 breakthrough) and 1 patient in the AmBisome group with a possible baseline infection. All 3 of the caspofungin patients with a possible baseline infection were considered to be unsuccessfully treated for the baseline infection. The AmBisome patient with a possible baseline infection was considered to have been successfully treated for the baseline infection. In the caspofungin group, 2 of the 3 patients with a possible baseline infection and the patient with the possible breakthrough infection were already considered an unfavorable overall response for other reasons. Therefore, if possible infections are included, the favorable overall response rate for caspofungin would be 44.6% [25/56, 95% exact confidence interval (31.3, 58.5)] and the AmBisome rate would be unchanged (32.0%).

Overall, 5 patients in the caspofungin groups and 4 patients in the AmBisome group discontinued prematurely from study therapy due to lack of efficacy or toxicity and considered failures in this endpoint. Three of the 5 caspofungin patients and 1 of the 4 AmBisome patients discontinued due to lack of efficacy. The remaining 2 caspofungin patients and 3 AmBisome patients discontinued due to a drug-related adverse event.

Overall response is primarily driven by the resolution of fever during neutropenia component. As previously discussed in the review of the adult study (see Statistical Review dated June 28, 2004), resolution of fever as part of the composite endpoint has been the subject of considerable discussion and the definition of the fever resolution component has an impact on the response rate seen. Therefore, 3 additional variations of the resolution of fever endpoint were also explored: 1) resolution of fever for 24 hours prior to the recovery of

neutropenia, 2) resolution of fever at the 7-day post-therapy follow-up visit, and 3) excluding fever resolution from the composite endpoint. These results are presented in Table 4. For both treatment groups, favorable overall response rates show a progressive increase as the definition of fever resolution becomes less conservative.

Table 4
Protocol 044- MITT Population
Overall Response with Alternative Definitions of Fever Resolution

	caspofungin (n=56)	**AmBisome** (n=25)
Resolution of fever for 48 hours prior to resolution of neutropenia (protocol defined)	26 (46.4)	8 (32.0)
Resolution of fever for 24 hours prior to resolution of neutropenia	34 (60.7)	13 (52.0)
Resolution of fever at 7 day post-therapy follow-up	43 (76.8)	15 (60.0)
Excluding fever resolution	50 (89.3)	21 (84.0)

3.2 Evaluation of Safety

The primary objective of both Protocol 043 and Protocol 044 was to estimate the proportion of pediatric patients treated with caspofungin reporting one or more clinical and/or laboratory drug-related adverse experiences. Secondary objectives included estimating the proportion of caspofungin treated patients who discontinued caspofungin therapy due to a drug-related adverse experience or who had a serious drug-related adverse experience. For a detailed review of the safety data, please see the medical officer's review.

***Reviewer's Comment**: In general, assessment of an adverse experience as drug-related is considered highly subjective. Therefore, rates of all treatment emergent adverse events will also be presented in this review.*

3.2.1 Protocol 043

All 49 patients enrolled in the study received at least 1 dose of caspofungin therapy and were included in the safety evaluations. Of the 49 patients, 43 (87.8%) reported at least 1 clinical adverse experience. The most frequently reported clinical adverse experiences included pyrexia (16.3%), diarrhea (12.2%), and hypertension (10.2%). One or more serious clinical adverse experience was reported in 8 (16.3%) patients (5 with aspergillosis and 3 with invasive candidiasis) while on caspofungin therapy or in the 14 day post-therapy period. Five (10.2%) patients, all with aspergillosis, died during the study. Two (4.1%) patients discontinued caspofungin therapy due to a clinical adverse experience. Both patients had aspergillosis and both discontinuations were due to serious clinical adverse experiences.

Overall, 13 (26.5%) patients reported one or more drug-related clinical adverse experience in the study. None of the 49 patients developed a serious drug-related adverse experience or were discontinued from caspofungin study therapy as a result of a drug-related adverse experience.

3.2.2 Protocol 044

A total of 56 patients received at least one dose of caspofungin therapy and 26 patients received at least one dose of AmBisome therapy. Fifty-three (94.6%) caspofungin patients and 19 (73.1%) AmBisome patients reported at least 1 clinical adverse experience. The most commonly reported adverse experiences in the caspofungin group were pyrexia (30.4%), rash (23.2%), and chills (12.5%). The most commonly reported adverse experiences in the AmBisome group were pyrexia (23.1%), tachycardia (19.2%), and diarrhea (15.4%). Eleven (19.6%) patients in the caspofungin group and 6 (23.1%) in the AmBisome group reported at least one serious clinical adverse experience. One patient in each treatment group died during the 14 day follow-up period. One additional caspofungin patient died post study. Overall, 8 patients were discontinued from study therapy due to a clinical adverse experience: 3 (5.4%) caspofungin patients and 5 (19.2%) AmBisome patients.

Drug-related adverse experiences were reported in 27 (48.2%) caspofungin patients and 12 (46.2%) AmBisome patients. One (1.8%) of the caspofungin and 3 (11.5%) of the AmBisome drug-related adverse experiences were considered serious. Two (3.6%) caspofungin patients and 3 (11.5%) AmBisome patients discontinued therapy due to a drug-related adverse experience.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

The following table summarizes the number of patients who had a favorable response at end of caspofungin therapy for gender, race, and age for Protocol 043 by infection. For aspergillosis, the small number of patients in each subgroup limits the interpretation of the results. For invasive candidiasis, a favorable overall response at the end of caspofungin of at least 75% was seen across all gender and race groups and all age categories except patients between 12 and 14 years.

Table 5
Protocol 043
Subgroup Analyses Favorable Response

	Infection	
	Invasive Aspergillosis	**Invasive Candidiasis**
Gender		
Male	4/8 (50.0)	17/21 (81.0)
Female	1/2 (50.0)	13/16 (81.3)
Age		
3 to 6 months	-	1/1
13 to 18 months	-	1/1
19 to 23 months	-	1/1
2 years to 6 years	2/3 (66.7)	12/15 (80.0)
7 to 11 years	2/5 (40.0)	6/6 (100.0)
12 to 14 years	0/1	4/7 (57.1)
15 to 17 years	1/1	5/6 (83.3)
Race		
White	4/6 (66/7)	18/23 (78.3)
Black	-	5/6 (83.3)
Asian	1/4 (25.0)	3/4 (75.0)
Others	-	4/4 (100.0)

The following table summarizes the number of patients who had a favorable overall response for gender, race, and age for Protocol 044. The small numbers in each of the subgroups limits the interpretation of the results especially for the AmBisome treatment group. For the caspofungin group, there appears to be a trend for increasing favorable response rate with increasing age. Based on the discussions with the Medical Reviewer, there does not appear to be a clinical explanation for this trend (i.e. no apparent differences in patient characteristics, adverse events, or drug exposure level for the various age groups).

Table 6
Protocol 044- MITT Population
Subgroup Analyses Favorable Overall Response

	Infection	
	caspofungin	**AmBisome**
Gender		
Male	15/35 (42.9)	5/19 (26.3)
Female	11/21 (52.4)	3/6 (50.0)
Age		
2 years to 6 years	10/29 (34.5)	7/14 (50.0)
7 to 11 years	6/15 (40.0)	0/4
12 to 14 years	3/5 (60.0)	1/4 (25.0)
15 to 17 years	7/7 (100.0)	0/3
Race		
White	20/48 (41.7)	7/20 (35.0)
Black	3/4 (75.0)	0/2
Others	3/4 (75.0)	1/3 (33.3)

4.2 Other Special/Subgroup Populations

For Protocol 043, there are no other special/subgroup populations of interest.

For Protocol 044, overall response is also presented by risk for fungal infection, the stratification factor, and prior antifungal prophylaxis. Table 7 summarizes the results of overall response for these subgroups. The overall response rates are somewhat higher in the high risk category than the low risk category for the caspofungin group. For patients at high-risk of developing a fungal infection, the favorable response rate was numerically higher in the caspofungin group than in the AmBisome group. This result must be viewed cautiously due to the small sample size. Caspofungin patients who did not receive prior antifungal prophylaxis have a slightly higher overall response rate when compared to caspofungin patients who received prior antifungal prophylaxis.

Table 7
Protocol 044- MITT Population
Overall Response by Risk Category and Antifungal Prophylaxis Status

	Treatment Group	
	Caspofungin	**AmBisome**
Risk Category		
High	9/15 (60.0)	0/7
Low	17/41 (41.5)	8/18 (44.4)
Antifungal Prophylaxis		
Prior prophylaxis	11/28 (39.3)	4/13 (30.8)
No prophylaxis	15/28 (53.6)	4/12 (33.3)

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The primary objective of both pediatric studies was to estimate the safety, tolerability, and efficacy of caspofungin. The study design of Protocol 044 was not powered to demonstrate statistically significant difference in safety and efficacy parameters between the caspofungin and AmBisome treatment groups. As a result, no formal comparisons between the 2 treatment groups were made. The sample size in both studies was selected based on logistical considerations rather than statistical considerations.

The pediatric study, Protocol 043, in documented fungal infections was designed as close as possible to the corresponding studies in adults (Protocol 014 for Invasive Candidiasis, and Protocol 019 for Invasive Aspergillosis, Protocol 020 for Esophageal Candidiasis) in an effort to allow for comparison and extrapolation of the data from adults to pediatrics. The diagnostic criteria for documented infections in Protocol 043 are similar to those criteria used in the various adult studies. Additionally, the efficacy time points and endpoints in Protocol 043 are the same as those used in the corresponding adult studies. The following table is a side by side presentation of the pediatric and adult efficacy results by infection. The proportion of patients in the MITT population with a favorable response and the

corresponding 95% confidence interval are presented in the table. For each of the 3 indications, the efficacy results were generally similar between adults and pediatric patients. For a complete discussion of the adult studies, please refer to the Joint Clinical and Statistical Review dated May 23, 2003 for Protocol 014, and the Statistical Reviews dated January 18, 2001 for Protocol 019 and March 6, 2002 for Protocol 020.

Table 8
Pediatric Study (Protocol 043) versus Adult Studies (Protocol 019, 014, 020)
Favorable Response
MITT Population

Treatment Indication	**Pediatric Study**	**Adult Studies**
Invasive Aspergillosis[1]	50% (5/10) (18.7, 81.3)*	41.3% (26/63) (29.0, 54.4)
Invasive Candidiasis[2]	81.1% (30/37) (64.8, 92.0)	73.4% (80/109) (64.1, 81.4)
Esophageal Candidiasis[3]	100% (1/1) (n/a)	81.5% (66/81) (71.3, 89.2)

[1]Adult Study - Protocol 019
[2]Adult Study - Protocol 014
[3]Adult Study - Protocol 020
* Exact 95% confidence interval

As with Protocol 043, the design of the pediatric study, Protocol 044, was similar to that of the study of adult patients with persistent fever and neutropenia, Protocol 026. This was in an effort to maximize the ability to extrapolate the data from adults to pediatric patients. Similar entry criteria, endpoints, time points, and the same comparator were used in both the adult and pediatric studies. Table 9 presents the results of the adult and pediatric studies side by side. Overall, the results of the pediatric study are consistent with those observed in adults. For a complete discussion of Protocol 026, please refer to the Statistical Review dated June 28, 2004.

Table 9
Pediatric Study (Protocol 044) versus Adult Study (Protocol 026)
Favorable Overall Response
MITT Population

	Pediatric Study (Protocol 044)		**Adult Study (Protocol 026)**	
	Caspofungin (n=56)	AmBisome (n=25)	Caspofungin (n=556)	AmBisome (n=539)
Overall Response 95% exact confidence interval	26 (46.4) (33.0, 60.3)	8 (32.0) (15.0, 53.5)	190 (34.2) (30.2, 38.3)	181 (33.6) (29.6, 37.7)
No breakthrough fungal infection within 7 days of EOT	56 (100.0)	24 (96.0)	527 (94.8)	516 (95.7)
Survival through 7 days of EOT	56 (100.0)	26 (100.0)	515 (92.6)	481 (89.2)
No discontinuation due to lack of efficacy or toxicity	51 (91.1)	21 (84.0)	499 (89.8)	461 (85.5)
Resolution of fever during neutropenia	27 (48.2)	9 (36.0)	229 (41.2)	223 (41.4)
Successful treatment of baseline infection	0/1	n/a	14/27 (51.9)	7/27 (25.9)

5.2 Conclusions and Recommendations

The results of Protocol 043 suggest that caspofungin administered as 50 mg/m^2/day after a loading dose of 70 mg/m^2 (maximum 70 mg/day) is effective in the treatment of documented invasive aspergillosis, invasive candidiasis, and esophageal candidiasis in patients 6 months to 17 years of age. Outcomes in this pediatric population are generally consistent with those reported in adults receiving caspofungin for documented *Aspergillus* or *Candida* infections. In addition, this dosing regimen was shown to be generally safe and well-tolerated in the pediatric patients.

The results of Protocol 044 suggest that caspofungin administered as 50 mg/m^2/day after a loading dose of 70 mg/m^2 (maximum 70 mg/day) is effective as empirical therapy in pediatric patients 2 to 17 years of age. Outcomes in this pediatric population are generally consistent with those reported in adults receiving caspofungin as empirical therapy for persistent fever and neutropenia. In addition, this dosing regimen was shown to be generally safe and well-tolerated in the pediatric patients.

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