CLINICAL REVIEW

Application Type	21-227
Submission Number	S-021
Submission Code	SE-5
Letter Date	January 31, 2008
Stamp Date	January 31, 2008
PDUFA Goal Date	July 31, 2008
Reviewer Name(s)	Yuliya Yasinskaya, M.D. (risk/benefit, efficacy, labeling) Julie-Ann Crewalk, M.D. (clinical trial safety) Eileen Navarro, M.D. (postmarketing safety)
Review Completion Date	July 10, 2008
Established Name	Caspofungin acetate
(Proposed) Trade Name	Cancidas®
Therapeutic Class	Enchinocandin antifungal
Applicant	Merck
Priority Designation	P
Formulation	lyophilized powder for infusion
Dosing Regimen	50, 70mg/m^2
Indications	◦ Empiric therapy of fungal infections in febrile neutropenic patients, ◦ Treatment of candidemia and the following C*andida* infections: intra-abdominal abscesses, peritonitis, and pleural space infections, ◦ Treatment of esophageal candidiasis, ◦ Treatment of refractory invasive aspergillosis
Intended Population	Children 3 months to 17 years

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Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The medical officer recommends approval of the application. This is based on the demonstration of the sufficient similarity in systemic exposure following administration of caspofungin at a loading dose of 70 mg/m^2 and a maintenance dose of 50 mg/m^2 between pediatric patients aged 3 months – 17 years and adults. Also, the safety profile of caspofungin at the proposed regimen in pediatric patients 3 months to 17 years was comparable to that seen in adults at the approved doses.

1.1.1 Confirmation of efficacy

a. Caspofungin was previously approved for use in adults for multiple indications, including treatment of documented fungal infections (invasive candidiasis, esophageal candidiasis, and invasive aspergillosis [as salvage therapy]) and as empirical therapy for suspected IFI in febrile, neutropenic patients. The initial approval of the above indications in adults was based on the results of the adequate and well controlled clinical trials.
b. Although no adequate well controlled clinical trials were conducted in pediatric patients for the above indications, there is a scientific basis to conclude that the epidemiology, pathogenesis, clinical presentation, and mortality of invasive *Candida* and *Aspergillus* infections are sufficiently similar between pediatric patients 3 months to 17 years old and adults (**See Indication section 6.1 of this review**), and that pediatric responses to caspofungin therapy are also similar to those of adults; therefore, the extrapolation of efficacy from adults to children of 3 months to 17 years is possible on the basis of achievement of caspofungin exposure in children at the proposed regimens comparable to that of adults at the approved regimens.
c. In addition, our review of the application finds that the reported efficacy profiles of caspofungin in pediatric patients 3 months to 17 years of age in two safety/efficacy studies are comparable to that seen in adult trials for the approved indications of:
   - Empiric therapy of fungal infections in febrile neutropenic patients,
   - Treatment of candidemia and the following C*andida* infections: intra-abdominal abscesses, peritonitis, and pleural space infections,
   - Treatment of esophageal candidiasis,
   - Treatment of refractory invasive aspergillosis.

   The supportive evidence of caspofungin efficacy in pediatric population from the above mentioned pediatric trials (Protocol 043 and 044) is presented below.
   - Safety/Efficacy Study (Protocol 043): A Multicenter, Open-Label Noncomparative Study to Evaluate the Safety, Tolerability, and Efficacy of Caspofungin in Pediatric Patients [3 Months to 17 Years of Age] With Documented *Candida* or *Aspergillus* Infections.

Table 1 The efficacy data in pediatric patients with documented *Candida* and *Aspergillus* infections from Protocol 043 are compared with the corresponding efficacy data in adult patients.

	Caspofungin Treated Groups					
Treatment Indications	**Pediatrics Study 043 (open label, non-comparative)**			**Adult Studies (compassionate use and comparative)**		
	Protocol/dose	**n/m**	**Therapeutic Response % (95% CI)**	**Protocol/dose**	**n/m**	**Therapeutic Response % (95% CI)**
Invasive Aspergillosis	043 50 mg/m^2 ‖	5/10	50% (18.7, 81.3)	019 50mg[#] 50mg[#] (EP) ‡	46/96 37/83	47.9% (37.6, 47.9) 44.6% (33.7, 55.9)
Invasive Candidiasis	043 50 mg/m^2 ‖	30/37	81.1% (64.8, 92.0)	014 50mg[#]	80/109	73.4% (65.1, 81.7)
Esophageal Candidiasis	043 50 mg/m^2 ‖	1/1	100% N/A	020 50mg	66/81	81.5% (71.3, 89.2)

n/m = Number of patients with a favorable response / Number of patients in the analysis.
‖ Patients received a loading dose of caspofungin 70 mg/m2 (maximum dose for treatment period =70 mg/day) on Day 1.
Patients received a loading dose of caspofungin 70 mg on Day 1.
‡ EP = Expert Panel assessment

AND

- Safety/Efficacy Study (Protocol 044): A Multicenter, Double-Blind, Randomized Comparative Study to Evaluate the Safety, Tolerability, and Efficacy of Caspofungin Versus Liposomal Amphotericin B for Injection as Empirical Therapy in Pediatric Patients 2 to 17 Years of Age With Persistent Fever and Neutropenia

Table 2 The efficacy data in empiric therapy of presumed fungal infections in febrile neutropenic pediatric subjects from Protocol 044 compared with the corresponding efficacy data in adult patients.

	Study 043 (Pediatric subjects 2-17 y)		**Study 026 (Adult subjects)**	
Endpoint	**Caspofungin 70/50 mg/m2 (N = 56) n (%)**	**AmBisome™ 3.0 mg/kg (N = 25) n (%)**	**Caspofungin 70/50 mg (N = 556) n (%)**	**AmBisome™ 3.0 mg/kg (N = 539) n (%)**
Favorable Response (overall)	**25 (44.6)**	**8 (32.0)**	**171 (30.8)**	**171 (31.7)**
Successful treatment of baseline infection	0/4 (0.0)	1/1	32/73 (43.8)	38/85 (44.7)
Absence of breakthrough fungal infection	55 (98.2)	24 (96.0)	491 (88.3)	497 (92.2)
Survival to 7-day follow-up	56 (100)	25 (100)	515 (92.6)	481 (89.2)
Completed therapy or non-endpoint discontinuation	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)

d. Clinical Pharmacology review of this application finds that the systemic exposure following administration of a loading dose of 70 mg/m^2 and a maintenance dose of 50 mg/m^2 was comparable between pediatric patients aged 3 months – 17 years and adults. The steady-state AUC_{24} and C_{24h} were similar between adults and pediatric patients across all the studies conducted in the pediatric WR. The C_{1h} was significantly higher across all pediatric age groups compared to adults. The similarity in systemic exposure (AUC and C_{24}) between pediatric patients and adults observed in 3 PK and 2 safety/efficacy studies in pediatric patients indicated that the effectiveness of caspofungin in the treatment of fungal infections would be similar to that previously observed in adults.

e. The Reviewer was unable to conclude that the indication of neonatal candidiasis is sufficiently similar to the adult indication of candidemia and *Candida* infections of pleural space, peritonitis and intraabdominal abscesses, as higher rates of multiorgan dissemination and up to 40% CNS involvement are seen in neonatal candidiasis as compared to adults. Also, there is no data on caspofungin efficacy in adults with *Candida* meningitis.
   Although, the Sponsor collected limited PK data (only Cmax and Cmin) in 18 neonates (6 in the single dose and 12 in the multiple dose cohorts) the Division is aware that the course of invasive candidiasis in neonates is sufficiently different from adults, and thereby does not permit extrapolation of the approved indication of candidemia and *Candida* infections of pleural space, peritonitis and intraabdominal abscesses in adults to the neonatal population and the pediatric indication of neonatal candidiasis.

f. To comply with FDAAA mandated labeling of all pediatric studies conducted in response to the Pediatric Written Requests, the Reviewer suggests the following addition to the proposed caspofungin label, Section 8.4 Pediatric Use: Although limited PK data were collected in neonates and infants below 3 months of age, these data are insufficient to establish a safe and effective dose of caspofungin in the treatment of neonatal candidiasis. Invasive candidiasis in neonates has a higher rate of CNS and multi-organ involvement than in older patients; the ability of CANCIDAS to penetrate the blood brain barrier and to treat patients with meningitis and endocarditis is unknown. [redacted].

g. To insure [redacted], the Reviewer recommends removal of these data from the label:

[redacted]

h. To ensure balance presentation of the caspofungin efficacy in various risk subgroups in study 044, the Reviewer recommends the following display of the efficacy findings in the Clinical Studies Section 14.5 of the label:

Favorable [redacted] with Persistent Fever and Neutropenia

	CANCIDAS	AmBisome
Number of Patients	56	25*
Overall Favorable Response	26 (46.4%)	8 (32.0%)
High risk	9/15 (60.0%)	0/7 (0.0%)
Low risk	17/41 (41.5%)	8/18 (44.4%)

*One patient excluded from analysis due to no fever at study entry.

1.1.2 Confirmation of safety

a. Overall, the caspofungin dose of 50mg/m^2/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 the pediatric population with the adult population and with the comparator treatment group, we found an overall similar profile of adverse events.
b. None of the 12 caspofungin treated patients, who died, appeared to do so from the study drug itself, nor was there a higher incidence of deaths in this population compared to the comparator (AmBisome) or the adult population. The causes of death consistent with the adult studies, where the major causes of deaths were: AML, respiratory failure, septic shock, and aspergillosis.
c. Discontinuations in the caspofungin treated patients were attributed to: pyrexia, hypotension, and rash. In adults, the main reasons for discontinuation were: respiratory failure, septic shock, and aspergillosis.
d. Serious adverse events such as: pyrexia, hypotension, and hypoxia were higher in the caspofungin treated patients and highest in the pediatric caspofungin treated patients when compared to adult patients.
e. The most common clinical adverse experiences across all pediatric caspofungin studies were pyrexia (29.2%), diarrhea (14.0%), rash (11.7%), chills (11.1%) and hypotension (11.1%). Pyrexia was the most common clinical adverse experience reported at each of the caspofungin dose levels.
f. There were no demographic issues with regards to safety, except for the Asian race. While the numbers enrolled were small and it is difficult to make major conclusions on the effect of caspofungin among pediatric patients of Asian race, it would be helpful to assess for any possible increase in adverse events, including deaths in post-marketing studies.
g. The Reviewer recommends replacing all drug-related adverse reactions with all causality adverse reactions in the Highlights of Prescribing Information and the Adverse Reactions Section 6 of the label as they represent the true incidence of an adverse reaction in a given patient population; they are independent of investigator's selection bias; and they are in agreement with current PLR guidance. In addition, it addresses the need of the medical community for uniform approach to the safety information display in the public domain (Cappelletty, 2007). Therefore, conversion of the safety tables to Treatment Emergent (all causality) adverse reactions for all drugs of the same class will allow practitioners to effectively compare drugs' safety profiles. Moreover, while the incidence of adverse reactions when displayed as treatment emergent is higher than when displayed as drug-related, neither the safety profile of caspofungin has changed nor the difference in the incidence of adverse reactions between the study arms was significantly altered.
h. Based on the OSE review findings the Reviewer recommends adding the following language to the Postmarketing Section of the label: *Hepatobiliary disorders:* ---------- ---------- --- --- ---------- ---------- ---------- ---------- --- hepatic necrosis.
i. Based on the postmarketing review conducted by Eileen Navarro, M.D. the Reviewer recommends adding the following language to the Postmarketing Section of the label:
    - *Gastrointestinal disorders:* pancreatitis
    - ---------- ---------- erythema multiforme, Steven's Johnson

- *Hepatobiliary disorders:* hepatic necrosis

j. Based on CMC and DMEDP review Dosing and Administration Section of the label should include actual amount per vial of caspofungin in mg (54.6 and 75.6mg, instead of 50 and 70mg) and the resulting reconstituted concentration of caspofungin after addition of 10.8ml of diluent (5mg/ml and 70mg/ml, instead of 5.2mg/ml and 7.2mg/ml) to account for the target overfill of ---- in the vial. In addition, 70mg vial should not be recommended for preparation of the dose of ≤50mg in pediatric patients due to difficulties in withdrawal of the appropriate calculated pediatric dose (1mg per 0.14cc of the reconstituted 70mg caspofungin vial) and possibility of medication error. In addition, to prevent potential medication error of administering calculated dose of >70mg to pediatric patients the following statement should be displayed prominently thoughout the highlights and dose and administration section of the label: **The maximum loading dose and the daily maintenance dose should not exceed 70 mg regardless of the patient's calculated dose.**

1.2 Risk Benefit Assessment

Currently, antifungal drug armamentarium for treatment of confirmed and presumed invasive fungal infections in pediatric population is insufficient and is limited to Ambisome (>1month of age), fluconazole (>6months of age), and voriconazole (>12 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. Caspofungin at 70 mg/m^2 loading and 50mg/m^2 dosing regimen was found to achieve exposures similar to 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 the approved indications (treatment of documented fungal infections (invasive candidiasis, esophageal candidiasis, and invasive aspergillosis as salvage therapy) and as empirical therapy for suspected IFI in febrile, neutropenic patients) in adults. Results of 2 safety/efficacy studies in pediatric patients 3 months to 17 years provided the supportive evidence of caspofungin efficacy in invasive fungal infections in pediatric patients. Safety of caspofungin at the proposed regimen in pediatric patients 3 months to 17 years was comparable to that found in adult patients. Therefore, these findings support approval of caspofungin at 70 mg/m^2 loading and 50mg/m^2 maintenance dosing regimen for pediatric patients with invasive fungal infections. Caspofungin approval for pediatric patients is addressing an unmet medical need for the information on dosing, PK, efficacy, and safety of antifungals in pediatric patients.

1.3 Recommendations for Postmarketing Risk Management Activities

No postmarketing risk management activities are necessary.

1.4 Recommendations for other Post Marketing Study Commitments

Under PREA, requirements to study the following indications for pediatric age group 0-3 months:

- **Empirical therapy** for presumed fungal infections in febrile, neutropenic patients.
- **Treatment of Esophageal Candidiasis.**
- **Treatment of Invasive Aspergillosis** in patients who are refractory to or intolerant of other therapies

are waived as the above conditions are extremely rare in this age group and such studies will be highly impractical to conduct.

The Division was unable to conclude that neonatal candidiasis is sufficiently similar to the adult indication of candidemia and *Candida* infections of pleural space, peritonitis and intraabdominal abscesses, as higher rates of multiorgan dissemination and up to 40% CNS involvement are seen in neonatal candidiasis as compared to adults. Also, there is no data on caspofungin efficacy in adults with *Candida* meningitis.
Conducting a randomized comparative study in pediatric population with neonatal candidiasis will require a robust dose finding in humans or animal models that ensures penetration of blood/brain barrier. Subjecting neonates with invasive candidiasis to a potentially ineffective dose is posing significant safety concerns (excess of mortality and neurologic impairment). Although, the Sponsor collected limited PK data (only Cmax and Cmin) in 18 neonates (6 in the single dose and 12 in the multiple dose cohorts) the Division is aware that the course of invasive candidiasis in neonates is sufficiently different from adults, and thereby does not permit extrapolation of the approved indication of candidemia and *Candida* infections of pleural space, peritonitis and intraabdominal abscesses in adults to the neonatal population and the pediatric indication of neonatal candidiasis. The concern exists that labeling the limited, as presented above, information on the dose studied and its PK characteristics in neonates may potentially lead practitioners to conclude there is a sufficient evidence that the dose of caspofungin is effective in neonatal candidiasis, whereas a safe and effective dose in neonatal candidiasis has not been established and cannot be extrapolated from adult data.

Therefore, the Division proposes the following language be added to the Pediatric Use section of the labeling:

Although limited PK data were collected in neonates and infants below 3 months of age, these data are insufficient to establish a safe and effective dose of caspofungin in the treatment of neonatal candidiasis. Invasive candidiasis in neonates has a higher rate of CNS and multi-organ involvement than in older patients; the ability of CANCIDAS to penetrate the blood brain barrier and to treat patients with meningitis and endocarditis is unknown. ---------- ---------- - - -----
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Efficacy and safety information is lacking for the currently marketed antifungal drugs in neonatal population. Also, candidemia in neonates is a high burden disease, significantly affecting neonatal morbidity and mortality. Therefore, the Division, supported by PeRC (Pediatric Review Committee), determined that an unmet medical need exists for the indication of neonatal candidiasis and requests the Sponsor to conduct an adequate well controlled study in neonates and young infants <3 months of age for this indication. ----------
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Therefore, the Division defers the above study submission ---

--- tentatively until 2020.

2 Introduction and Regulatory Background

2.1 Product Information

Caspofungin, an intravenous antifungal, is the first approved member of echinocandin class. Caspofungin is an active, semisynthetic inhibitor of B-1,3-D-glucan, an important component of the fungal cell wall of both *Candida* and *Aspergillus* species. By targeting the fungal cell wall (as opposed to the fungal cell membrane), the agents of the echinocandin class exhibit a unique mechanism of action relative to the other currently approved antifungal agents.

2.2 Tables of Currently Available Treatments for Proposed Indications

Cancidas (caspofungin acetate) is approved in adults for the following indications:

- Empirical therapy for presumed fungal infections in febrile, neutropenic patients
- Treatment of Candidemia and the following C*andida* infections: intra-abdominal abscesses, peritonitis and pleural space infections. Cancidas has not been studied in endocarditis, osteomyelitis, and meningitis due to *Candida*
- Treatment of Esophageal Candidiasis
- Treatment of Invasive Aspergillosis in patients who are refractory to or intolerant of other therapies

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

Table 3 US marketed antifungals

Drug name	Indication				Pediatric approval
	Invasive Aspergillosis	Candidemia	Esophageal Candidiasis	Febrile neutropenia	
Fungizone (Amphotericin B deoxycholate)	Yes	Yes	Yes		
Ambisome (Amphotericin B liposomal)	Yes (refractory/intolerant to Amphotericin B)	Yes (refractory/intolerant to Amphotericin B)		Yes	Yes (≥1 month)
Vfend (voriconazole)	Yes	Yes	Yes		Yes (≥12 years)

Mycamine (micafungin)		Yes	Yes		
Eraxis (anidulafungin)		Yes	Yes		
Diflucan (fluconazole)		Yes	Yes		Yes (≥6 months)
Nizoral (Ketoconazole)		Yes	Yes		
Ancobon (flucytosine)		Yes			
Sporanox (itraconazole)	Yes		Yes	Yes	

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 (ELBW) neonates is 3-5 times higher than that of adults.*

2.3 Availability of Proposed Active Ingredient in the United States

Cancidas as caspofungin acetate intravenous is approved and is marketed in the United States since 2001.

2.4 Important Safety Issues With Consideration to Related Drugs

The most extensive data on the safety of the echinocandins is available for caspofungin (clinical trials, postmarketing experience, and medical literature), as it has been approved since 2001, although no comparative studies have been performed across the class some differences in safety have been reported with micafungin and anidulafungin. Histamine-like reactions have occurred with rapid infusion of echinocandins. Anaphylaxis has been reported rarely.
Table below provides a list of the most common adverse drug effects 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 effects and laboratory abnormalities and are considered to be well tolerated.

Table 4 Frequency of Common Adverse Drug Reactions and Laboratory Abnormalities Associated with the Echinocandins in Clinical Trials Reviewed by FDA

Adverse Reaction	Caspofungin N=1747	Micafungin N=3083	Anidulafungin N=204
Phlebitis	4.0	5.6	< 3
Fever	21.1	20	15.2
Abdominal pain	6.2	9.7	5.9
Nausea or Vomiting	8.8, 7.4	22, 21.7	26.1, 16.4
Diarrhea	14.9	23.3	18.1
Headache	10.5	2–17	7.8
Rash or Pruritus	8.6, 4.1	8.7, 6.1	3.9, < 3

Leukopenia	2.6	1.6	< 3
Neutropenia	1.3	14.1	< 3
Thrombocytopenia	3.6	15.1	5.4
Hypokalemia	11.8	18	19.6
Abnormal LFTs	14.1	5.6	3.1

Information is extracted from the NDA under review (information submitted on 04/29/08 upon reviewer's request), 2008 approved Mycamine label, 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 following is the history and background of Pediatric Development Program of NDA -------- (IND 48,484) Cancidas (caspofungin acetate) of Merck (MRL):

Table 5 Presubmission Regulatory History

06/13/2000	MRL submitted a Pediatric Development Program (PDP) proposal to evaluate the safety and efficacy of caspofungin in children with documented *Aspergillus* and *Candida* infections.
11/26/2000	Discussion during a Pre-NDA meeting of Cancidas the timing and rationale for the initiation of clinical studies in pediatric patients.
01/26/2001	Cancidas was approved for invasive aspergillosis in adults who are refractory to or intolerant of other fungal agents
01/26/2001	**FDA issued a Pediatric Written Request (PWR) original** and a deferral of pediatric studies until 1/28/2006 was granted.
04/30/2001	Merck (MRL) submitted a revised proposed PDP.
06/07/2001	FDA's comments (fax) on the revised PDP.
06/11/2001	Telecon to discuss proposed changes to the WR
06/15/2001	MRL submitted a PDP revision (#2).
07/25/2001	MRL's telecon minutes of 6/11/2001.
12/19/2001	MRL requested a deferral of pediatric study requirement for esophageal candidiasis ---------- -- ---- - ---------- in children.
07/02/2002	**FDA re-issued the original PWR** as **Best Pharmaceuticals for Children Act (BPCA)** became a law as of 1/4/2002, **version #1**
09/20/2002	**FDA granted a deferral until 1/28/2006.**
02/15/2003	MRL requested a telecon to discuss PDP and sent a meeting background package.
04/04/2003	MRL sent an E-Mail of a mock-up of MRL's proposed revised WR and stated that MRL agrees to conduct pediatric ETFN study under a new protocol (submitted formally on May 2, 2003).
04/07/2003	Telecon to discuss PDP program MRL sent on 2/15/2003.
09/29/2003	MRL sent Protocol 042 (A Multicenter, Open, Sequential, Dose-Escalation Study to Investigate the Safety, Tolerability, and Pharmacokinetics of 2 Separate Doses of Caspofungin Acetate in Children Between the Age of 3-24 Months).

10/08/2003	FDA concurred that the dose of 50 mg/m^2 is acceptable.
11/05/2003	MRL sent Protocol 043 (A Multicenter, Open-Label, Noncomparative Study to Evaluate the Safety, Tolerability, and Efficacy of Caspofungin Acetate in Children with Documented Candida or Aspergillus Infections).
11/18/2003	MRL sent Protocol 044 (A Multicenter, Double-Blind, Randomized, Comparative Study to Evaluate the Safety, Tolerability, and Efficacy of Caspofungin versus Amphotericin B Liposome for Injection as Empirical Therapy in Pediatric Patients with Persistent Fever and Neutropenia).
05/07/2004	**FDA issued BPCA letter** (BPCA § 18 and § 9).
12/20/2004	**FDA reissued PWR to NDA 21-227, version #2**
02/10/2005	**FDA granted deferral extension** (under PREA) to the final report submission until September 30, 2009, for 3 approved indications (invasive aspergillosis, esophageal candidiasis, and invasive candidiasis). The final report submission for the treatment of presumed fungal infections in febrile, neutropenic patients remains September 30, 2009.
07/20/2005	MRL requested a telecon to discuss PDP (the meeting package date 7/25/2005). The purpose of the meeting was to gain FDA's input and concurrence with: 1. MRL's plans to initiate a study to evaluate the pharmacokinetics and safety of caspofungin in pediatric patients 0-3 months of age 2. Status of MRL's ongoing study evaluating the pharmacokinetics and safety of caspofungin in pediatric patients 3-24 months of age (Protocol 042) 3. Timing for amendment of Protocol 043 (noncomparative study of documented *Candida* and *Aspergillus* infections in pediatric patients) to allow the careful evaluation and enrollment of patients 3-24 months of age in this study.
10/19/2005	Telecon discussing Merck's proposed plans for the evaluation of caspofungin in pediatric patients 0-3 and 3-24 months of age.
11/10/2005	FDA sent facsimile containing information for the ---------- -------- ---------- -------- for evaluating neonatal Candidiasis.
07/12/2006	MRL sent information containing information for the proposed amendments to the Pediatric Written Request (PWR).
10/11/2006	FDA sent facsimile response to the proposed amendments to the PWR submitted of the July 12, 2006 submission.
10/30/2006	FDA sent facsimile comments regarding the PWR (re: --------- ---------- ---------- ---------- --------- and the PWR options).
07/16/2007	**FDA granted PWR amendment #3**
08/15/2007	**FDA granted PWR amendment #4**
01/31/2008	MRL submitted an application for approval for the use of Cancidas® in Pediatric patients from 3 months through 17 years of age for the infectious disease indications currently approved: 1. invasive aspergillosis in adults who are refractory to or intolerant of other fungal agents 2. candidemia and *Candida* infections (intra-abdominal abscesses, peritonitis and pleural space infections) in adults

	3. esophageal candidiasis in adults 4. empirical treatment of suspected fungal infections in febrile, neutropenic adults.

The forth and final amendment of Pediatric Written Request issued on August 15, 2007 included a total of 5 studies: 3 PK studies conducted sequentially: Study 1-- older pediatric population (2-17 year olds), Study 2 – toddlers (3-24 month), and Study 3 -- neonates and young infants (0-3 months), and 2 safety/efficacy studies: Study 4 – comparative study in febrile neutropenic children 2-17 years and Study 5 – non-comparative study in children 3 months to 17 years with invasive fungal infections (invasive aspergillosis, invasive candidiasis, and esophageal candidiasis). The Sponsor conducted the studies consistent with the provisions of the PWR for study types, indications studied, age distribution, minimal number of subjects per indication, per group, per study, and also for the PK and safety endpoints.

Table 6 Post submission regulatory history

03/31/2008	Application filed with additional information requests
04/30/2008	Pediatric 6 months Exclusivity granted
06/25/2008	PeRC review of the pediatric assessment for the NDA 21-227, S-021 • Label 4 approved indications for pediatric patients 3 months to 17 years • Issue a partial waiver for indications of esophageal candidiasis, invasive aspergillosis, and empiric therapy in neonates and young infants <3 months • Defer a study in neonatal candidiasis for neonates and infants <3 months ------- ---------- ---- - ---------- ----------

2.6 Other Relevant Background Information

The Division was in active negotiations with the Sponsor about a neonatal development program that included PK study, - - ---------- - ---------- - --- ------- ---------- ---------- - ---------- ---------- - ------- - - ---------- and completed only neonatal PK study specified in the PWR. Study 058 collected limited PK data (only Cmax and Cmin) in 18 neonates (6 in the single dose and 12 in the multiple dose cohorts). The limitations of such data are summarized below.

Since the initial approval of caspofungin in 2001 the Division had on-going discussions with the Sponsor on the potential plans, utility, and feasibility of the prospective evaluation of caspofungin efficacy in neonates and very young (below 3 month of age) infants with disseminated *Candida* infection (neonatal candidiasis). The discussions included applicability of the Pediatric Rule in such a case. Through consultation with experts in the fields of neonatology and infectious diseases the Division is aware that the course of invasive candidiasis in neonates is sufficiently different from adults, and thereby does not permit extrapolation of the approved indication of candidemia and *Candida* infections of pleural space, peritonitis and intraabdominal abscesses in adults to the neonatal populations for the indication of neonatal candidiasis. Specifically, significant CNS infection occurs in neonates with invasive candidiasis, which is generally not the case with adults. In addition, the pivotal caspofungin study in adults for the

indication of candidemia and infections of pleural space, peritonitis and intraabdominal abscesses due to Candida specifically excluded adult subjects with *Candida* meningitis.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Quality and integrity of the data in the submission were reviewed and deemed to be sufficient. DSI inspections of the bioanalytical and two largest clinical sites were requested. There were no observations that suggest problems with efficacy or safety data from site 005 (enrolled 11/49 subjects in study 043); however, 483 form was issued as there were findings related to collection of PK samples (lack of documentation of adequate storage prior to processing samples at site, conflicting collection times recorded on medical note/computer collection time/CRFs, missed pk samples). Site 003 (enrolled 14/49 subjects in study 043) and bioanalytical laboratory (----- site) were also inspected and found to have complied with the study protocol and their clinical and PK data are considered reliable.

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

Total of 5/158 clinical investigators have disclosed their financial interests.

Table 7 All Clinical Investigators/Subinvestigators Who Hold Financial Interests or Arrangements Requiring Disclosure

Product/Protocol/ Site	Investigator/ Subinvestigator	Financial Interests or Arrangements	Number of subjects enrolled
---------- -------	- --------- -------	Significant Payments of Other Sorts: $100,113.00	-
---------- -------	--------- ------- -- --- ---	Significant Payments of Other Sorts: $36,871.40	---------- ----- -- -- -- ------ -- -- ----
---------- ------	----- -- -- ---	Significant Payments of Other Sorts: $49,291.00	-
---------- ------	--- -- --- -- --------. (subinvestigator)	Significant Payments of Other Sorts: $91,851.29	- - ------- ------ --- -- ---- -- -- -- - -
---------- ------	- ------ -- --------- - (subinvestigator)	Significant Payments of Other Sorts: $63,452.00	-

MO comment: *Investigators holding financial interest with Merck have enrolled primarily 1-3 subjects each. The only high enrollment investigator, ---------- -- ---------- -------- (17%) subjects) documented overall much lower efficacy rates as compared to the rest of the study sites: site - ---- for caspofungin --- (11%) and Ambisome --- (0%), versus all other study sites ------ (53%) and ----- (40%) for caspofungin and Ambisome, respectively. Although, the study --- ----------, the Reviewer included analyses that excluded the results from the site with high enrollment and the investigator holding financial interests with the study sponsor.*

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

No data regarding CMC were submitted to the NDA under review. The applicant has requested an exemption of an environmental assessment for this submission. The request was acceptable to the CMC Reviewer, Swapan K. De, Ph.D.
No changes to the CMC section of the proposed label were requested. However, the DOSING AND ADMINISTRATION Section of the label for Pediatric Patients as proposed by the Sponsor deemed to be confusing for the practitioners due to undisclosed amount (mg) of overage in the Cancidas vials and redundancy of the Cancidas infusion preparation examples. CMC and DMEDP requested additional information about and clarifications to the DOSING AND ADMINISTRATION Section of the label.

The multidisciplinary team of CMC, DMEDP, and clinical reviewers recommended to the Sponsor properly state the amount of Cancidas contained in the vials prior to reconstitution, i.e. 54.6 and 75.6 mg instead of 50 and 70mg accounting for the target overfill, and also to provide information on the final concentration of the reconstituted Cancidas solution when 10.8 ml of diluent is added to the vial, i.e. 5mg/ml and 7mg/ml. In addition, as only 50 mg vials were used in pediatric clinical trials and the potential for medication errors exists in proper Cancidas dose withdrawal from a 70 mg vial (0.14ml per 1mg dosing increment) the team recommended streamlining the DOSING AND ADMINISTRATION Section of the label. (See labeling Recommendations of this Review, Section 9.2)

4.2 Clinical Microbiology

The Clinical and Laboratory Standards Institute broth microdilution methods for filamentous fungi and yeast were used for determination of the minimum inhibitory concentration (MIC) of caspofungin against *Aspergillus* sp. and *Candida* sp. For *Aspergillus* sp., the range of MIC values was 0.03 to > 32 μg/mL. For *Candida* sp., caspofungin MICs were determined using both a prominent inhibition endpoint at 24 hours incubation (MIC-80) and a complete inhibition endpoint at 48 hours incubation (MIC-100). The MIC-80 ranged from ≤ 0.01 μg/mL to 1 μg/mL and the MIC-100 ranged from 0.05 μg/mL to > 32 μg/mL. All of the MIC-80s and 96 % (70/73) of the MIC-100 had values ≤ 2 μg/mL. Baseline MICs ≤ 2 μg/mL were associated with clinical success in 35/39 (90%) patients with invasive candidiasis. The MIC values of isolates from subjects that failed therapy were similar to the MIC values of isolates from subjects that had a successful clinical and mycological outcome, suggesting that clinical failures occur despite infection with a susceptible isolate. These data support the suggested susceptible breakpoint for caspofungin of ≤ 2 μg/mL for *Candida* sp. No new data are available to set intermediate or resistant interpretive criteria/breakpoints.

4.3 Preclinical Pharmacology/Toxicology

Upon review of the NDA 21-227, S-021 submission Pharmacology Toxicology Reviewer Owen McMaster, Ph.D. concluded that there are no data that preclude the approval of caspofungin in pediatric patients.
He specifically reviewed Study MK-0991, a five-week intravenous toxicity study in infant rhesus macaques *(Macaca mulatta).* There were no drug-related adverse effects observed in this study. The NOAEL was determined to be 5 mg/kg/day, a dose which results in exposures more than 3-fold greater than that expected in the clinic. The findings from the monkey study should be included in the Cancidas® label.
No additional nonclinical studies were recommended.

4.4 Clinical Pharmacology

The systemic exposure following administration of a loading dose of 70 mg/m^2 and a maintenance dose of 50 mg/m^2 was comparable between pediatric patients aged 3 months – 17 years and adults. The steady-state AUC_{24} and C_{24h} were similar between adults and pediatric patients across all the studies conducted in the pediatric WR. The C_{1h} was significantly higher across all pediatric age groups compared to adults. The safety profile in pediatric patients was similar to adults indicating that the increased C_{1h} does not result in elevated safety concerns in pediatric patients. There was no evidence of a relationship between exposure and the safety event of thrombocytopenia (change in platelet counts from baseline) that was selected as a potential concern by the clinical review team.
The similarity in systemic exposure (AUC and C_{24}) between pediatric patients and adults observed in studies 033 and 042 indicated that the effectiveness of caspofungin in the treatment of fungal infections would be similar to that previously observed in adults. This hypothesis is confirmed from the results obtained in studies 043 and 044 which indicated that the caspofungin dose selected from studies 033 and 042 is effective and safe across the age range of 3 months – 17 years and all disease indications. The results of the safety and efficacy trials indicated that caspofungin when administered at a loading dose of 70 mg/m^2 followed by a maintenance dose of 50 mg/m^2 is comparable to adults.
Based on the comparable systemic exposures seen in pediatric patients between the ages of 3 months -17 years and adults and the demonstration of effectiveness and safety of caspofungin in the pediatric patients in the 2 clinical studies, the review team will approve caspofungin in pediatric patients 3 months-17 years at a dosage regimen of 70 mg/m^2 as a loading dose followed by 50 mg/m^2 as the maintenance dose. The sponsor has requested t---------

No outstanding clinical pharmacology issues were identified with caspofungin in this current NDA submission.

5 Sources of Clinical Data

5.1 Tables of Clinical Studies

The following table depicts submitted clinical studies that were conducted by the Sponsor per Pediatric Written Request issued by the Division on August 15, 2007.

Table 8 Pediatric Clinical Studies

Study Type	Protocol Number	Ages Included	Study centers	Number of Subjects	Doses/Duration Evaluated	Endpoints
Pharmacokinetic Studies in Pediatric Patients						
Pharmacokinetic Study in Children and Adolescents with new-onset fever and neutropenia	033	2 to 17 years	8 US	39 evaluable	1 and 1.5mg/kg/day, then 50 mg/m^2 and 70 mg/m^2 for 4-28 days	**PK:** Cmax, Cmin, AUC **Safety**
Pharmacokinetic Study in Young Children with new-onset fever and neutropenia	042	3 to 24 months	5 US	9 evaluable	50 mg/m^2 for 4-28 days	**PK:** Cmax, Cmin, AUC **Safety**
Pharmacokinetic Study in Neonates and Infants with *Candida infections*	058	0 to 3 months	2 US, 1 Mexico 1 Panama, 2 Colombia, 2 India	6 evaluable in SD cohort, 12 in MD cohort	25 mg/m^2	**PK:** Cmax, Cmin **Safety**
Safety/Efficacy Studies in Pediatric Patients						
Open-Label Safety/Efficacy Study in Pediatric Patients with Documented Candida or Aspergillus Infections	043†	3 months to 17 years	6 US, 2 Germany 2 Taiwan, 1 Italy, 1 Israel	49 evaluable: 10 with IA 38 with IC 1 with EC	70/50mg/m^2 2 to 87 days	**Efficacy** **PK:** Cmax, Cmin, AUC **Safety**
Double–Blind, Active Comparator-Controlled Safety/Efficacy Study of Empirical Therapy in Pediatric Patients with Persistent Fever and Neutropenia	044†	2 to 17 years	8 US 4 Germany 4 Spain 1 Belgium	56 evaluable in Caspofungin group 26 in Ambisome	Caspofungin 70/50mg/m^2 Ambisome 3mg/kg Up to 90 cays	**Efficacy** **PK:** Cmax, Cmin, AUC, CSF levels **Safety**

† Pharmacokinetic results from P043 and P044 were assessed in a pooled population PK and PK/PD analysis of P033, P042, P043, and P044 only.

5.2 Review Strategy

The NDA 221-227, S-021 was reviewed by multidisciplinary team. Clinical Pharmacology review of 3 PK studies 033, 042, and 058 and PK data collected in 2 safety/efficacy studies 043 and 044 was conducted by Dakshina Chilukuri, Ph.D. Clinical review of safety for the entire pediatric NDA was performed by Julie-Ann Crewalk, MD. Clinical review of caspofungin postmarketing experience was performed by Eileen Navarro, MD and Christopher Jones, PharmD from OSE. Yuliya Yasinskaya, MD reviewed clinical efficacy of the submission and the proposed label.

6 Review of Efficacy

Efficacy Summary

Our review finds that the reported efficacy profiles of caspofungin in pediatric patients 3 months to 17 years of age and adults are sufficiently comparable for the approved indications of:

- Empiric therapy of fungal infections in febrile neutropenic patients,
- Treatment of candidemia and the following C*andida* infections: intra-abdominal abscesses, peritonitis, and pleural space infections,
- Treatment of esophageal candidiasis,
- Treatment of refractory invasive aspergillosis.

There is also an agreement with the Sponsor on that there is a scientific basis to conclude that the epidemiology, pathogenesis, clinical presentation, and mortality of invasive *Candida* and *Aspergillus* infections are sufficiently similar between children 3 months to 17 years and adults (**See Indication section 6.1 of this review**), and that pediatric responses to caspofungin therapy are also similar to those of adults; therefore, the extrapolation of efficacy from adults to children of 3 months to 17 years is possible on the basis of achievement of caspofungin exposure in children at the proposed regimens comparable to that of adults at the approved regimens.

Reported Caspofungin Efficacy Profiles in Pediatric Studies, NDA 21-227, S-021

The efficacy of caspofungin in pediatric population was assessed in 2 trials (Protocol 043 and 044) as titled below:

- Safety/Efficacy Study (Protocol 043): A Multicenter, Open-Label Noncomparative Study to Evaluate the Safety, Tolerability, and Efficacy of Caspofungin in Pediatric Patients [3 Months to 17 Years of Age] With Documented *Candida* or *Aspergillus* Infections

AND

- Safety/Efficacy Study (Protocol 044): A Multicenter, Double-Blind, Randomized Comparative Study to Evaluate the Safety, Tolerability, and Efficacy of Caspofungin Versus Liposomal Amphotericin B for Injection as Empirical Therapy in Pediatric Patients 2 to 17 Years of Age With Persistent Fever and Neutropenia

The efficacy results for caspofungin in pediatric patients from the above mentioned studies are presented in the following tables.

Table 9 The efficacy data in pediatric patients with documented Candida and Aspergillus infections from Protocol 043 are compared with the corresponding efficacy data in adult patients.

	Caspofungin Treated Groups					
Treatment Indications	**Pediatrics Study 043 (open label, non-comparative)**			**Adult Studies (compassionate use and comparative)**		
	Protocol/dose	**n/m**	**Therapeutic Response % (95% CI)**	**Protocol/dose**	**n/m**	**Therapeutic Response % (95% CI)**
Invasive Aspergillosis	043 50 mg/m^2 ‖	5/10	50% (18.7, 81.3)	019 50mg# 50mg# (EP) ‡	46/96 37/83	47.9% (37.6, 47.9) 44.6% (33.7, 55.9)
Invasive Candidiasis	043 50 mg/m^2 ‖	30/37	81.1% (64.8, 92.0)	014 50mg#	80/109	73.4% (65.1, 81.7)
Esophageal Candidiasis	043 50 mg/m^2 ‖	1/1	100% N/A	020 50mg	66/81	81.5% (71.3, 89.2)

n/m = Number of patients with a favorable response / Number of patients in the analysis.
‖ Patients received a loading dose of caspofungin 70 mg/m2 (maximum dose for treatment period =70 mg/day) on Day 1.
Patients received a loading dose of caspofungin 70 mg on Day 1.
‡ EP = Expert Panel assessment

The above open-label non-comparative study 043 provided information, albeit limited, on efficacy of caspofungin at 70mg/m^2 LD /50mg/m^2 MD regimen in candidemia in non-neutropenic patients and in refractory invasive aspergillosis in 3 months to 17 years old pediatric patients. Although the study was of an open-label non-comparative design, efficacy rates were numerically similar to those historically observed in adult patients with similar indications treated with caspofungin at 70mg LD and 50mg MD regimen.

Table 10 The efficacy data in empiric therapy of presumed fungal infections in febrile neutropenic pediatric subjects from Protocol 044 compared with the corresponding efficacy data in adult patients.

	Study 043 (Pediatric subjects 2-17 y)		**Study 026 (Adult subjects)**	
Endpoint	**Caspofungin 70/50 mg/m2 (N = 56) n (%)**	**AmBisome™ 3.0 mg/kg (N = 25) n (%)**	**Caspofungin 70/50 mg (N = 556) n (%)**	**AmBisome™ 3.0 mg/kg (N = 539) n (%)**
Favorable Response (overall)	**25 (44.6)**	**8 (32.0)**	**171 (30.8)**	**171 (31.7)**
Successful treatment of baseline infection	0/4 (0.0)	1/1	32/73 (43.8)	38/85 (44.7)
Absence of breakthrough fungal infection	55 (98.2)	24 (96.0)	491 (88.3)	497 (92.2)
Survival to 7-day follow-up	56 (100)	25 (100)	515 (92.6)	481 (89.2)
Completed therapy or non-endpoint discontinuation	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)

The above small randomized double blind study of caspofungin at 70 mg/m^2/day LD and 50mg/m^2/day MD in empiric therapy of presumed fungal infections in febrile neutropenic pediatric subjects as compared to Ambisome 3-5mg/kg/day, demonstrated favorable outcomes in caspofungin arm that are comparable and numerically higher than that of historical trials of a similar design in adults. The study was not designed nor powered to show non-inferiority or superiority of caspofungin regimen to that of Ambisome. However, in this study caspofungin response rate was numerically higher than the rate of Ambisome. It held true for the overall composite response, each individual component of the response, and in the majority of the subgroup analyses.

The study provides supportive evidence that caspofungin efficacy in ETFN in pediatric patients is comparable to that seen historically in adults.

Published Caspofungin Efficacy Profiles in Pediatric Patients

In addition, the Sponsor conducted comprehensive medical literature review on caspofungin efficacy and safety in pediatric patients.
A table summarizing the results of a literature search on the safety and effectiveness of caspofungin therapy in pediatric populations with invasive candidiasis is presented below. Even with variations in dose, duration of treatment, and combinations with other agents, caspofungin was reported to be effective across all studies, regardless of age of population (neonates and infants, children, and adolescents), underlying illness (hematological malignancies, solid tumors, solid organ transplants, various hematological diseases, congenital immunodeficiencies, etc.), or indication (treatment for proven, probable, or possible invasive fungal infection; empirical treatment of febrile neutropenia; or antifungal prophylaxis). Favorable response rates, defined as complete or partial response by published criteria, ranged from 53 – 100% in the patient population. In each study, the authors concluded that caspofungin was an effective drug for the treatment or prophylaxis of IFIs in the pediatric population.
A separate study assessing treatment outcomes in an observational cohort with invasive candidiasis found improved survival in pediatric patients <13 years of age with treatment. In this study, 80% survival occurred in patients <13 years with any antifungal treatment, versus 59% over the age of 13 ($p < 0.001$).

Table 11 Summary of caspofungin (CAS) safety and effectiveness in pediatric population

Authors (reference)	Indication	Number Treated	Age Range (years)	Effectiveness	Safety Results
Cesaro S, Giacchino M, Locatelli F et al.	Invasive aspergillosis	40	1.2 – 17.9	A favorable response (CR or PR) was observed in 21 patients (53%). There was no significant difference in 100-day response rates by treatment regimen. Survival at 100 days was 70% overall (95% CI 55 – 84%). At a median of 0.7 years of follow-up, 20 children (50%) remain alive. In multivariable analysis, no factor was an independent predictor of a favorable response.	Each combination regimen was generally well-tolerated with no Grade III or IV adverse events observed. One patient on CAS developed a transient rash that was controlled with treatment and did not require withdrawal of CAS.There were no clinically meaningful elevations of serum transaminases and no treatment discontinuations due to adverse events.
Franklin JA, McCormick J, and Flynn PM	Treatment of or prophylaxis for IFI	25	0.3 – 26.2	No effectiveness assessment was performed.	3/25 patients (12%) experienced adverse events that were possibly related to CAS: hypokalemia (n=3), elevated bilirubin (n=2); decreased hemoglobin (n=1); elevated ALT (n=1). No events were severe or resulted in discontinuation of caspofungin therapy.
Groll AH, Attarbaschi A, Schuster	Invasive fungal infections	64	0.4 – 17.9	A favorable response was observed for 12/17 (71%), 7/14 (50%), and 13/15 (87%) patients with proven,	34 patients (53%) reported 62 clinical adverse events. None were probably or definitely related to CAS. Of the

FR et al.				probable, and possible IFI. Stable response was observed in 3, 3, and 1 patient(s) per respective group. In those treated empirically, only 6/16 (38%) had breakthrough fungal infection. For all patients in the study, 42/64 (68%) were considered to have a successful response.	eventsthat were possibly related to CAS, 7/62 (11%) were Grade III or higher: 1 report of fever, 5 nausea/vomiting, and 1 skin eruption. Patients with proven IFI were most likely to report adverse events (14/17, 82%). There were mild elevations in ALT and AST at the end of treatment in 14% and 10.9% of patients, respectively. There were no discontinuations of CAS due to adverseevents.
Koo A, Sung L, Allen U et al.	Febrile neutropenia	56	1 – 17	A favorable response (complete or partial response) was observed in 53/67 courses of therapy (79%). Fever resolved in 57 courses (85%) and no patient experienced breakthrough fungal infection. 4/7 patients with proven IFI (57%) had complete response to CAS.	The overall rate of adverse events was low (15%). One case of hypokalemia was probably related to CAS. Adverse events that were possibly related to CAS were rash (3%), hypokalemia, nausea, vomiting, hypomagnesemia, nephrotoxicity, and hepatotoxicity (2% each). One patient discontinued due to rash. 19 patients received cyclosporin A with CAS; one experienced elevated serum transaminases (noted above) but did not require cyclosporin A dose modification.
Merlin E, Galambrun C, Ribaud P et al.	Invasive candidiasis, aspergillosis, and *Rhodolotura*	20	0.1 – 16	17/20 patients (85%) achieved a complete (n=13) or partial (n=4) response. The survival rate was 65% (13/20) at Day 90 and 50% (10/20) overall. Five of 11 patients (45%) with asperillosis survived, 3/7 with candidiasis (43%) and both with *Rhodotorula.* During CAS therapy, there were six deaths, one due to the underlying disease and five due to uncontrolled IFI.	15 patients (75%) reported a total of 45 adverse events; 11 events were possibly drug-related. None led to CASdiscontinuation. Events included livedo(n=1), nausea and vomiting during infusion (n=2), elevated liver enzymes (n=6); moderate hypokalemia (n=2); and peripheral venous thrombosis (n=1). There was no abrogation of renal function. One of 5 patients receiving cyclosporin A had increased transaminase levels.
Natarajan G, Lulic-Botica M, Rongkavilit C et al.	Invasive candidiasis	13	1 – 128 days	Clearance of candidiasis (defined by negative blood cultures) with CAS was achieved in 11/13 infants (85%) vs 5/11 (45%) controls (p=0.04). Median time to clearance was 3 days (range, 1 – 21 days). The 2 patients who did not clear the infection had *C. albicans*. The survival rate was 46% (6/13). Two infants who died had received only two doses of CAS; the other 5 had clearance of candidemia prior to death.	Overall, there were no severe adverse events that were clearly attributable to CAS. Adverse events included thrombophlebitis (n=1) that resolved with a diluted dose; hypokalemia (n=2) that resolved with potassium administration; transaminase elevations (n=4) that resolved in three of the four cases; and isolated direct hyperbilirubinemia in one case. No patient discontinued CAS due to an adverse event.
Odio CM, Araya R, Pinto LE et al.	Invasive candidiasis	10	13 – 105 days	8 patients with persistent candidemia all had resolution of infection after CAS therapy. The patient with renal and CSF infection had sterile blood, urine,	There were no observable adverse events attributable to CAS. All laboratory parameters, including measures of liver injury and electrolytes, remained within normal

				and CSF cultures after one week of treatment but died of septicemia after 19 days. The patient with atrial vegetation had sterile blood cultures after 4 days of CAS and resolution of the atrial vegetation after 9 days of treatment.	ranges during treatment.
Khayat N, Amsellem D, Nerich V et al.	Febrile neutropenia	13	NR	In both groups, 12/13 patients (92%) had treatment success.	One adverse event (hypokalemia) was observed in the CAS group. In contrast, 7/13 patients (54%) in the amphotericin B group had hypokalemia, one (8%) hyponatremia, and 2 (15%) hypocalcemia.
Abboud M, Bizri A, Dbeibo G et al.	Invasive aspergillosis	5	3 – 17	One patient on CAS plus amphotericin had a complete response; the other had a partial response. The child switched from amphotericin to CAS died of other causes while still on treatment. The two patients on CAS monotherapy had complete resolution of infection.	There were no adverse events, including renal and hepatic parameters, attributable to CAS.

As summarized by the Sponsor in response to the Reviewer's request (05/19/08 submission)

MO comments: *Overall caspofungin efficacy in pediatric population as captured by the medical literature is higher than that presented in the NDA under review for most of the approved indications reflecting primarily study design differences, publication and selection biases. Favorable response rates for invasive aspergillosis are much in line with the findings of study 043. Caspofungin experience in neonatal candidiasis is scant (10 cases, 3 different dosing regimens). In vivo models of Candida meningoencephalitis treated with caspofungin have not been described to date. No adult data on caspofungin efficacy in meningitis is available in the public domain. CSF samples for examination of caspofungin CNS distribution were collected from neonates with no underlying CNS infection and demonstrated limited caspofungin penetration into CSF (study 058).*

6.1 Indication(s)

Caspofungin is approved for use in adults for four indications that include: treatment of documented fungal infections (invasive candidiasis, esophageal candidiasis, and as salvage therapy for invasive aspergillosis), and empirical therapy for suspected IFI in febrile, neutropenic patients. As presented in the following table, these indications are based on the results of 4 pivotal clinical trials (014, 019, 020, and 026) in adults, together with data from other supportive studies.

Table 12 Basis for the approval of Caspofungin in Adult Patients for the Indications of Invasive Candidiasis, Esophageal Candidiasis, Invasive Aspergillosis, and Empiric Therapy of suspected Fungal Infections

Adult Patient Indication	Pivotal Study	Supportive Studies	Comment
Invasive Candidiasis (excluded Candida meningitis, osteomyelitis, and endocarditis)	Protocol 014	· Protocol 045 (non-blood candidiasis study) · Protocol 024/025 (compassionate use study)	· Efficacy of caspofungin comparable (non-inferior) to amphotericin B in Protocol 014 (73% vs. 62%) · Efficacy also demonstrated in 2 supportive studies (Protocols 024/025 and 045)
Esophageal Candidiasis	Protocol 020	· Protocol 003 (Phase II dose-ranging study) · Protocol 004 (Phase II efficacy study) · Protocol 024/025 (compassionate use study)	· Efficacy of caspofungin comparable (non-inferior) to fluconazole in Protocol 020 (82% vs. 85%) · Efficacy also demonstrated (similar to amphotericin B) from 2 supportive studies (Protocols 003, 004) and the compassionate use study (Protocol 024/025)
Invasive aspergillosis in patients refractory or intolerant of other antifungal agents	Protocol 019	· Protocol 024/025 (compassionate use study)	· Success of caspofungin monotherapy as salvage therapy in invasive aspergillosis was ~45% in both Protocols 019 and 024/025
Empirical treatment of suspected fungal infections in febrile, neutropenic patients	Protocol 026	· Supported by all studies above for documented IFI due to *Candida* or *Aspergillus spp.*	· Efficacy of caspofungin comparable (non-inferior) to liposomal amphotericin B in Protocol 026 (33% in each treatment group)

MO comments: *Important to note that adults with Candida meningitis, osteomyelitis, and endocarditis were specifically excluded from Invasive Candidiasis study. It is of particular importance when the argument is being made to extrapolate adult efficacy to pediatric population by means of matching of adult to pediatric drug exposures.*

The data presented in the following tables are compiled by the Sponsor and are based on a comprehensive review of the international literature, using mainly population-based studies. They provide evidence of the similarities between the adult and pediatric patient population with regard to the epidemiology and mortality for each of the three indications (candidemia, invasive aspergillosis, and empirical therapy in febrile neutropenic patients). Of note, esophageal candidiasis remains a relatively rare condition in pediatric patients, and there are no population-based epidemiology data available for different pediatric age groups. It should also be noted that a clear distinction between younger children/toddlers (3-24 months of age) and older children/adolescents (2-17 years of age) was not emphasized in the reviewed literature; however, whenever possible, 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 13 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
Candidemia & Other Candida Infections			
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%), followed by *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%), followed by *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, candidiemia 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
Young Children & Toddlers (3-24 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 organism the youngest patients (<1 year) include *C. albicans* (60%), followed by *C. parapsilosis (24%), C. tropicalis (7%), & C. glabrata (3%)*	• Data not readily available for this age group
Neonates and young infants (0-3months)	• 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%), followed by *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) In neonates, 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 age spectrum in children and adults continues to be associated with substantial morbidity and mortality. While it is not possible to determine mortality rates in all age ranges from the literature, several studies have assessed mortality rates due to invasive candidiasis more broadly. In general, 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. It is worth noting that 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 attributable to the patient's comorbid diseases (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, ranging from 13 – 19%.

Modified from the Sponsor's 5/19/08 submission in response to the reviewer's request 04/10/08

MO comment: *In comparative study of micafungin versus Ambisome in candidemia in adults and children the subgroup of 0-3 months old subjects had the following species distribution: C. parapsilosis (36%) followed by C. albicans (30%), C. tropicalis (21%), C. lusitaniae (3%, while in 3-24 month olds the species background was as follows: C. albicans (44%), C. parapsilosis (22%), and C. tropicalis (39%).*

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 14 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 with low CD4 count (~85 to 90%) • Cytotoxic chemotherapy for hematologic malignancy or HSCT • High-dose corticosteroid use or other immunosuppressive therapy Neutropenia	• Most common organism in adults (>15 years) is *C. albicans* (~95%), with approximately 25% as mixed infections of *C. albicans* and other organisms • Non-albicans *Candida* involvements without concurrent *C. albicans* infection is rarely seen (<5%)	• Mean age usually 35-40 years • Concomitant oropharyngeal involvement (thrush) is frequently seen (up to 90% of cases) • Classic symptoms include dysphagia, odynophagia, & retrosternal pain • Esophageal candidiasis in adults is reported to be the second most common AIDS-defining disease after PCP pneumonia • Death seen in ~6% of patients, but this is rarely associated with esophageal candidiasis but is attributed to underlying condition (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 heme malignancy or HSCT • High-dose corticosteroid use or other immunosuppressive therapy (6-8%) • Neutropenia *The strongest associated risk factors are prior oropharyngeal candidiasis low CD4 count, and low CD4*	• 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 oropharyngeal involvement (thrush) is frequently seen (up to 95% of cases) • Classic symptoms include 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

	percentage		• As in adults, death is rarely seen (~10%) but it is rarely associated with esophageal candidiasis but is attributed to the underlying condition (i.e., AIDS)
Young Children & Toddlers (3-24 Months)	• Though data not readily available for this specific age group, similar risk factors are anticipated as above (one case series included patients as young as 2 months, but there was no mention of specific risk factor differences in this younger age group)	• Data not readily available for this specific age group (one case series included patients as young as 2 months, but there was no mention of specific microbiological differences in this younger age group)	• Data not readily available for this specific age group (one case series included patients as young as 2 months, but there was no mention of specific differences in the clinical presentation in this younger age group)

As shown in the table below, the risk factors, microbiology, and clinical presentation in patients with invasive aspergillosis (IA) are relatively similar among adult and pediatric patients. One identifiable risk factor seen predominantly in pediatric patients is the presence of a congenital immunodeficiency. Specifically, chronic granulomatous disease (CGD) is commonly associated with invasive aspergillosis in pediatric patients. In both adult and pediatric patients, *A. fumigatus* and *A. flavus* are the most commonly reported pathogens. The clinical presentation for invasive aspergillosis is also very similar between adult and pediatric patients. A few minor differences in the pediatric patient population include the higher incidence of skin involvement, the less consistent radiographic presentation of pulmonary aspergillosis, and the lack of assay sensitivity of the *Aspergillus* galactomannan sandwich ELISA.

Table 15 Comparative overview of the indication of Invasive Aspergillosis in adults and children of different ages

Age Group	Risk Factors	Microbiology	Clinical Presentation & Pathogenesis
Invasive Aspergillosis			
Adults	Risk factors include the following: • Severe, prolonged neutropenia/ granulocytopenia • Hematologic malignancy • HSCT • Solid organ transplantation • High-dose corticosteroid use or other immunosuppressive therapy • Persons with HIV infection • Lung cavitation	• Most common organisms in adults include *A. fumigatus* (67%) followed by *A flavus* (16%)	• Represents the most common cause of filamentous fungal infection in adults • Most common sites of infection include lung (70-80%) and sinus (10-15%). Dissemination to CNS can also occur. • Adults with pulmonary aspergillosis traditionally demonstrate evidence of cavitation (50%) and/or air crescent formation (40%) on chest radiography
Children & Adolescents (2-17 Years)	including the following: • Severe, prolonged neutropenia/granulocytopenia (59%) • Hematologic malignancy (38%) • HSCT (37%) • Solid organ transplantation (11%) • High-dose corticosteroid use (69%) or other immunosuppressive therapy	• In one series, most common organisms in pediatric patients included *A. fumigatus* (62%), followed by *A. flavus* (14%) and *A. nidulans* (7%) In second series, most common organisms in pediatric patients included *A. fumigatus* (48%), followed by *A*	• As in adults, it represents the most common cause of filamentous fungal infection in pediatric patients • Most common sites of infection include lung (60%), with less common involvement of sinus (10%) and skin (10%). Dissemination to CNS can also occur. In pediatric patients, central cavitation is seen but felt to be less frequent (22-43%) and air-crescent formation is not routinely seen • Biggest difference relative to adults is in diagnosis: the false positive rate of the *Aspergillus* galactomannan ELISA assay is at least 4-fold

	(43%) • GVHD (12%) • Congenital immunodeficiency (CGD, 12%)	*flavus* (26%), *A. niger* (4%), and unspecified *Aspergillus species* (22%)	higher in pediatric patients than in adult patients. The overall specificity of the test was 48%, as compared with an overall specificity of 98% in adult patients
Young Children & Toddlers (3-24 Months)	• risk factors data not readily available for this specific age group	• microbiological data not readily available for this specific age group	• Only notable difference is that pulmonary cavitation and air crescent formation is even less common as the age of patient decreases below 2 years
Mortality: High mortality rates (18-76%) are reported in uncontrolled invasive aspergillosis, regardless of age. The wide variation in mortality rates reported is mostly due to the studied patients' comorbid diseases characteristics. For example, in one study of immunocompromised children ages 2-14, the overall death rate was 18% (Zaoutis et al, 2006). The rate varied from 0% in children with bone malignancy to 69% in those with CNS malignancy. The majority of the patients had leukemia with death rate approximating 21%. In addition, when children with IA were matched to children with the same underlying disease without IA, in nearly all cases there were significantly higher mortality rates with IA than without. Age appears to be less of a factor for mortality than underlying disease.			

Empirical therapy indication for patients with persistent fever and neutropenia in adults and children is similar between both groups as the major risk factor (i.e., neutropenia in the setting of recent cytotoxic chemotherapy for hematological malignancy or hematopoietic stem cell transplantation [HSCT]) is the same across the adult and pediatric patient populations. Furthermore, the clinical presentation for this indication (i.e., fever in the setting of neutropenia despite 4 days of broad spectrum antibacterial therapy) is also the same across the adult and pediatric populations. Additionally, there are no associated microbiology data in patients who receive empirical therapy for persistent fever and neutropenia as all patients who receive empirical antifungal therapy have, by definition, only suspected infections at study entry (without confirmed microbiological involvement). If these patients were to go on to develop a breakthrough infection with *Candida* or *Aspergillus* species while on empirical antifungal therapy, their clinical presentation would be as described above in the included tables for the other 3 indications.

6.1.1 Methods

Clinical data from 2 safety/efficacy pediatric studies: 043, 044 were used in the efficacy review to support the proposed pediatric dosing regimen for the following indications:

- Empirical therapy for presumed fungal infections in febrile, neutropenic patients
- Treatment of Candidemia and the following C*andida* infections: intra-abdominal abscesses, peritonitis and pleural space infections. Cancidas has not been studied in endocarditis, osteomyelitis, and meningitis due to *Candida*
- Treatment of Esophageal Candidiasis
- Treatment of Invasive Aspergillosis in patients who are refractory to or intolerant of other therapies.

In addition, three pediatric PK studies were also reviewed by the Clinical Pharmacology Reviewer, Dakshina Chilukuri, to examine caspofungin exposure in pediatric patients of different ages 3months -17 years at the proposed dosing regimen of 70/50mg/m2 and compare it to caspofungin exposure at the approved regimen of 70/50mg in adults.

6.1.2 Demographics

Overall, the majority ofthe patients who received caspofungin in the pediatric studies were of White race (67.8%) and of male gender (60.8%). Most patients were also of non-Hispanic ethnicity (77.8%). The mean age of patients was 6.6 years, and the majority (60.2%) were in the 2–11 year age group.

Table 16 Demographic and Baseline Characteristics (All Treated Pediatric Caspofungin Subjects)

	Study 043			Study 044	PK studies (033, 042, 058)	Total
Indications studied	Invasive Aspergillosis	Invasive Candidiasis	Esophageal Candidiasis	Febrile neutropenia	Febrile neutropenia	All
Characteristic	**N = 10**	**N = 38**	**N = 1**	**N = 56**	**N = 66**	**N = 171**
Gender: n (%)						
Female	2 (20)	16 (42.1)		21 (37.5)	28 (42.4)	67 (39.2)
Male	8 (80)	22 (57.9)	1	35 (62.5)	38 (57.6)	104 (60.8)
Race: n (%)						
White	6 (60)	23 (60.5)	1	48 (85.7)	38 (57.6)	116 (67.8)
Black		6 (15.8)		4 (7.1)	3 (4.5)	13 (7.6)
American Indian/ Alaskan Native		2 (5.3)		2 (3.6)	8 (12.1)	12 (7.0)
Asian/Pacific Islander	4 (40)	5 (13.2)			5 (7.6)	14 (8.2)
Multi-racial		2 (5.3)		2 (3.6)	12 (18.2)	16 (9.4)
Ethnicity						
Hispanic or Latino		7 (18.4)		5 (8.9)	26 (39.4)	38 (22.2)
Not Hispanic or Latino	10(100)	31 (81.6)	1	51 (91.1)	40 (60.6)	133 (77.8)
Age: years						
<3mos					18 (27.3)	18 (10.5)
3 to 23 months		3 (7.8)			9 (13.6)	12 (7.0)
2 to 6 years	3 (30)	16 (42.1)		29 (51.8)	18 (27.3)	66 (38.6)
7 to 11 years	5 (50)	6 (15.8)		15 (26.8)	12 (18.2)	38 (22.2)
12 to 17 years	2(20)	13 (34.2)	1	12 (21.4)	10 (15.2)	38 (22.2)
Mean	8.3±3.9	7.9±5.4	17	7.4±4.5	4.8±4.9	6.6±5.0
Median	7.5	6.5	17	6.0	2.5	6.0
Min - Max	3 to 16	6 mos to 17y		2 to 16	0-16	0-17

MO comment: *Pediatric population in the NDA under review was sufficiently diverse with respect to age, race, gender, and ethnicity.*

6.1.3 Patient Disposition

The following table provides a summary of subject's disposition across all pediatric studies.

Table 17 Subject's Disposition. Pediatric NDA21-227, S-021

	Study 043			Study 044	PK studies (033, 042, 058)	Total
Indications studied	Invasive Aspergillosis	Invasive Candidiasis	Esophageal Candidiasis	Febrile neutropenia	Suspected Invasive Candidiasis (033), Febrile neutropenia	All
Patient disposition	**N = 10**	**N = 38**	**N = 1**	**N = 56**	**N = 66**	**N = 171**
Screened		53		57	43+9+21	183
Randomized	10	38	1	57	40+9+18	173
Received Study Therapy	10	38	1	56	39+9+18	171
Completed Study Therapy	5	23	1	46	21+8+17	121
Discontinued Prematurely	5	15	-	10	18+1+1	50 (29)
Lack of efficacy	3	6	-	3	-+-+-	12 (7)
Adverse Experience	2	-	-	3	6+-+1	12 (7)
Other		9	-	4	12+1+-	26 (15)
Completed Study Follow-up	6	36	1	56	39+8+15	161 (94)
Discontinued study prematurely	4	2	-	-	-+1+3	10
Adverse Experience	4	-	-	-	-+1+3	8
Other	-	2	-	-	-	2

Among the subjects that discontinued study drug prematurely "other" reasons for discontinuation were examined closely and the Reviewer was unable to identify any additional cases of discontinuations due to adverse experiences or lack of efficacy. The subjects that discontinued prematurely for other reasons were discharged home, withdrew consent, or transferred from the study hospital to another facility in efficacy studies and primarily persistent fever and neutropenia for study 033. Thirteen (7.6%) patients discontinued prematurely from caspofungin study therapy as a result of a clinical adverse experience. The incidence of discontinuations due to a clinical adverse experience was highest for the caspofungin 1 mg/kg group with 2 (22%) patients discontinuing due to a clinical adverse experience. The incidence of discontinuations due to a clinical adverse experience was otherwise similar for the remaining caspofungin dose groups (25 mg/m2, 50 mg/m2, and 70 mg/m2), at 6%, 7% and 8%, respectively. The incidence of discontinuations due to a clinical adverse experience in the patients receiving caspofungin in the pharmacokinetic studies and in the patients receiving caspofungin in the safety/efficacy studies was 12% (8/66) and 5% (5/105), respectively.

***MO comment**: Approximately 50% of subjects who discontinued the study therapy prematurely did so for the reasons other than adverse experience or lack of efficacy. Particularly in studies 043 and 044 these discontinuations were due to transfers of the study subjects to outpatient care per parental request. In PK studies these discontinuations included persistent fever and neutropenia*

6.2 Discussion of Individual Studies

6.2.1 Study 043

Study Report 043: A Multicenter, Open-Label, Noncomparative Study to Evaluate the Safety, Tolerability, and Efficacy of Caspofungin Acetate in Children With Documented Candida or Aspergillus Infections

6.2.1.1 Methods

INVESTIGATORS: 21 investigators, 12 of whom enrolled subjects

STUDY CENTERS: 21 centers 12/21 centers (6 U.S., 2 Germany, 2 Taiwan, 1 Italy, 1 Israel) enrolled patients.

STUDY PERIOD: 21-May-2004 to 05-July-2007

OBJECTIVES: The **primary** objective was to report the proportion of pediatric patients (3 months through 17 years of age) with invasive aspergillosis (IA) who are refractory to or intolerant of standard therapy or those with invasive or esophageal Candida infections treated with caspofungin at 50 mg/m2 IV once daily (maximum 70 mg/day) following a loading dose of 70 mg/m2 (maximum 70 mg/day) on Day 1 with one or more drug-related clinical or laboratory adverse experience(s).

Secondary objectives were:
1. To report the proportion of patients who discontinue study therapy due to a drug-related adverse experience or who have a serious drug-related adverse experience.
2. To report the proportion of patients with a favorable efficacy response to caspofungin therapy in each of the different infection types.

METHODOLOGY: Open-label, multicenter, non-comparative study

NUMBER OF SUBJECTS: Total enrollment was 49 subjects.

STUDY DRUG: IV caspofungin acetate given as a loading dose of 70mg/m² on Day 1 and 50 mg/m² on Day 2 onward.
MO comment: *During labeling review it became apparent that the direction of infusion constitution are not clear and transparent: if constituted as directed in the label the resulting infusion solution might contain an improper dose of caspofungin as calculated based on the BSA. This is due to the*

When the actual dose administered to individual subjects was checked for in the efficacy studies, the dose administered in mg ranged widely from 17.05mg to 70mg. It, thus, appeared impossible to withdraw an exact dose of 17.05mg from a reconstituted 50mg vial (5.2mg/ml) and then reconstitute a final infusion solution containing this dose. DMETS was consulted and Sponsor was asked to provide explanations and alternative labeling. The Reviewer later in the review learned that the

study investigators were provided with a table of precalculated volumes of the reconstituted solution per mg dose (range 11mg-70mg). individual calculated doses were rounded to the nearest full mg.

The batch numbers for the caspofungin acetate are depicted in the following table.

Table 18 The Appearance, Formulation, and Dosage Strength of the Study Drug used in the Study 043

Study Drugs	Appearance	Formulation	Dose Unit	Batch numbers
Caspofungin acetate	white cake	Lyophilized Powder for injection	50mg/vial	0991HLS016B003, 0991HLS016B004, 0991HLS017B004, 0991HLS017B005, 0991HLS016B005, 0991HLS017B002, 0991HLS017B006, 0091HLS017B001, WL00008764, WL00020744, WL00017427, WL00024008

DURATION OF TREATMENT: The duration of therapy was individualized for each patient and was in accordance with the Infectious Diseases Society of America (IDSA) Treatment Guidelines. In general, therapy duration was dictated by (1) the rapidity of the patient's clinical and microbiological response to study therapy, (2) recovery from immunosuppression (if the patient was persistently immunosuppressed), and (3) the type of fungal infection and the site of infection.

TREATMENT COMPLIANCE: Study drug infusion information, including dosage and volume prescribed, and volume administered was collected daily.

STUDY DESIGN: This study was designed as a non-comparative, open-label study to evaluate the safety, tolerability, and efficacy of caspofungin therapy in children with documented esophageal candidiasis, invasive candidiasis, or invasive aspergillosis. Eligible subjects were to be children or adolescents ages 3 months to 17 years with proven esophageal or invasive candidiasis (primary or salvage therapy) , or proven or probable invasive aspergillosis according to the EORTC/MSG criteria (unresponsive or intolerant to standard antifungal therapy).
MO comment: *This study was conducted in response to the pediatric written request should include at least 10 pediatric subjects with invasive aspergillosis.*
A dose of caspofungin 50 mg/m2 daily (maximum 70 mg/day) was chosen for this study based on results from pharmacokinetic studies in children showing this dose produced similar plasma concentrations as those seen in adult patients who received 50 mg/day. A loading dose of 70 mg/m^2 (maximum 70 mg/day) was also used on Day 1 in order to achieve trough concentrations in children that were similar to those achieved in adults with a 70-mg loading dose.
In patients who failed to improve clinically after 4 days and in whom the study drug had been well tolerated, the caspofungin dosage could be increased to 70-mg/m^2/day (not to exceed the maximum daily dose of 70 mg) on Day 5 onward.
If toxicity occurred after the patient had been updosed (70 mg/m^2/day), the investigator was able to reduce the dose of study drug to standard dose (50 mg/m^2/day) instead of interrupting or discontinuing study treatment. If the toxicity did not resolve with dose reduction, consideration should have been given to discontinue study therapy.
Subject safety assessments were scheduled to occur daily for the duration of caspofungin therapy, and 14 days follow-up. Proportion of subjects with favorable response was determined at the end of

caspofungin therapy. The subjects with favorable response at the end of therapy were also assessed for relapse at the 14 and 28-day follow-up visits. Symptoms of fungal infection were assessed daily while on study therapy, on the last day of therapy and on Day 14 and 28 follow-up time points. Radiographic studies, cultures and histopathology were performed as clinically indicated during the study.

SAMPLE SIZE

In previous adult studies, the rates of clinical and laboratory drug-related adverse experiences, respectively, were: 12.7% and 13.7% in invasive aspergillosis (Study 019); 28.9% and 23.7% in invasive candidiasis (Study 014); and, 41.0% and 28.9% in esophageal candidiasis (Study 020).Assuming the experience in children would be similar to that observed in the adult studies, one would expect, with 50 patients, rates of 29.9±12.7% (95% confidence) for clinical and 23.5±11.8% (95% confidence) for laboratory drug-related adverse experiences.

INCLUSION CRITERIA:

General

- Age 3 month to 17 years
- Negative urine/serum pregnancy test if adolescent female
- Understanding of study procedures by the patient or guardian

1. Have Invasive aspergillosis (criteria developed by the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Co-Operative Group (EORTC/IFICG) and the National Institute of Allergy and Infectious Diseases - Mycoses Study Group (NIAID-MSG**):**

a) Proven:

- Histopathology/cytopathology showing hyphae from a needle aspiration or biopsy with evidence of associated tissue damage (either microscopically or unequivocally by imaging).

OR

- Positive culture from a normally sterile site, obtained by a sterile procedure, and clinical or radiological findings consistent with infection.

b) Probable: Defined as at least one of the following host criteria:

- Neutropenia: Polymorphonuclear neutrophils (PMN) of $<500/mm^3$ for more than 10 days.
- Persistent fever for >96 hours refractory to appropriate broad spectrum antibacterial treatment.
- Body temperature either >38°C (oral) or <36°C (oral) AND any of the following predisposing conditions:
- prolonged neutropenia (>10 days) in the previous 60 days; recent or current use of significant immunosuppressive agents in the previous 30 days; proven or probable invasive fungal infection in a previous episode of neutropenia; or coexistence of acquired immune deficiency syndrome (AIDS).
- Signs and symptoms indicating Graft versus Host Disease (GVHD).
- Prolonged use of corticosteroids (>3 weeks) in the previous 60 days.

AND one microbiological criterion from the following

- Positive culture for an *Aspergillus* species from sputum or bronchoalveolar lavage (BAL).
- Positive culture or cytology/direct microscopy for an *Aspergillus* species from a sinus aspirate.
- Positive evidence of *Aspergillus* infection documented by galactomannan ELISA in BAL, cerebrospinal fluid (CSF), or >2 blood samples.

AND one major (or 2 minor) clinical criteria related to findings at a site, consistent with infection. Clinical criteria must have been related to the same site as the microbiological criteria and temporally related to the current episode. Clinical criteria, shown by site of infection, are as follows:

Lower Respiratory Tract Infection

Major criteria: Any of the following new infiltrates on CT imaging: halo sign, air-crescent sign, or cavity within an area of consolidation.

Minor criteria included:

a) Symptoms of lower respiratory tract infection (cough, chest pain, hemoptysis, dyspnea);
b) Physical finding of pleural rub;
c) Any new infiltrate not fulfilling major criterion;
d) Pleural effusion.

Sino-nasal Infection

Major criteria: Suggestive radiological evidence of invasive infection in the sinuses (i.e., erosion of sinus walls or extension of infection to neighboring structures, extensive skull base destruction).

Minor criteria included:

a) Upper respiratory symptoms (nasal discharge, stuffiness);
b) Nose ulceration or eschar of nasal mucosa or epistaxis;
c) Periorbital swelling;
d) Maxillary tenderness;
e) Black necrotic lesions or perforation of the hard-palate.

Central Nervous System Infection

Major Criteria: Radiological evidence of central nervous system (CNS) infection (e.g., mastoiditis or other parameningeal foci, extradural empyema, intraparenchymal brain or spinal cord mass lesion).

Minor Criteria: For minor criteria to be included the CSF must have been negative for other pathogens by culture, microscopy and negative for malignant cells. Minor criteria included:

a) Focal neurological symptoms and signs (including focal seizures, hemiparesis and cranial nerve palsies);
b) Mental changes;
c) Meningeal irritation findings;
d) Abnormalities in CSF biochemistry and cell count.

Disseminated Infection

Major Criteria: Papular or nodular skin lesions without any other explanation, or intraocular findings suggestive of hematogenous fungal chorioretinitis or endophthalmitis.

Minor Criteria: Did not apply.

2) Patients must have been refractory to or intolerant of standard antifungal therapy.
   a) Refractory: Progression of disease or failure to improve clinically despite therapy with at least 7 days of therapeutic doses of the following standard therapy:
      - Amphotericin B (IV), at the maximum tolerated dose (ε0.75 mg/kg/day);
      - AMPHOTEC™ (Intermune, Inc.), at least 3.0 mg/kg/day;
      - ABELCET™ (Enzon Pharmaceuticals, Inc.), at least 5 mg/kg/day;
      - AMBISOME™ (Gilead Sciences, Inc.), at least 3.0 mg/kg/day;
      - Itraconazole, at least 100 mg/day.
      - Voriconazole, at least 3 mg/kg q12.

- Other antifungal agents with known clinical activity against *Aspergillus spp.* at age-appropriate doses for the treatment of invasive aspergillosis;

Patients refractory to combination regimens were eligible unless an echinocandin was part of the combination regimen.

Patients who did not improve after receiving prophylactic doses of antifungals were not eligible for the study. For this study, prophylactic doses included any doses less than the therapeutic doses outlined above.

b) Intolerant: A 50% increase in serum creatinine or, for a creatinine value that was above the normal limit for age at baseline, an increase of 0.5 mg/dL; any creatinine value ε2.5 mg/dL; or other significant intolerance (e.g., acute, infusion-related toxicity).

Invasive *Candida* infection

1) Patient must have had at least 1 obtained by a sterile procedure positive culture of a *Candida* species from blood or other normally sterile body site within 4 days of study entry. Culture must have been obtained by a sterile procedure. Cultures obtained through an indwelling drain (such as peritoneal or pleural drain) were not sufficient for diagnosis unless obtained at the time of sterile placement of the catheter or drain.
2) The following clinical evidence of infection must have been present at some time within 48 hours prior to enrollment:
   a) Temperature (oral, or oral equivalent) >100°F (37.8°C) on 2 occasions at least 4 hours apart, or 1 determination >101°F (38.3°C), or clinically significant hypothermia <96.8°F (36.0°C);
   b) Systolic blood pressure below the lower limit of normal for age;
   c) Signs of inflammation (swelling, heat, erythema, pain/tenderness, purulent drainage) at a site infected with *Candida* (e.g., joint, skin, eye).
3) Patients with the above not responding to or intolerant of prior nonechinocandin antifungal therapy were also eligible for enrollment.

Esophageal *Candida* infection

1) Patients with a diagnosis of esophageal candidiasis based on symptoms, endoscopy and microbiology or histopathology for whom IV therapy was appropriate, as documented by:
   a) Symptoms consistent with esophageal candidiasis (dysphagia, odynophagia, etc.). (Note: Patients not responding to or intolerant of prior non-echinocandin antifungal therapy or who relapsed following such therapy were also eligible for enrollment provided they have recent endoscopic evidence of disease.)

   AND

   b) Endoscopy grading (within 48 hours prior to enrollment) of >1 using criteria in the Grading System of Disease specified in the protocol.

   AND

   c) Positive stain or positive wetmount KOH of brushing or biopsy from endoscopy followed by either a positive culture (from brushing or biopsy) for *Candida* spp., or positive histopathologic evidence of *Candida* infection.

   Note: At study entry only the positive stain or positive wetmount KOH for *Candida* spp. was required.

EXCLUSION CRITERIA:

1) Patient was <3 months or >18 years of age (at time of the first dose of study drug administration).
2) Patient had any of the following abnormal laboratory values:
    a) International normalization ratio (INR) >1.6 or, if patient was receiving anticoagulants, INR >4.0.
    b) Bilirubin >3 times the upper limit of normal for age.
    c) AST (SGOT) or ALT (SGPT) >5 times the upper limit of normal for age.
    d) Platelet count <5000/μL.
3) Patient was not expected to survive for at least 5 days.
4) Patient was pregnant or breast-feeding.
5) Patient had a diagnosis of acute or chronic hepatic disease or cirrhosis due to any cause.
6) Patient had or was participating in any other clinical study involving the administration of an investigational antibiotic, or antifungal, within 14 days prior to study entry or during the course of the study. (Note: Phase I trials of investigational cancer agents were prohibited only during the course of study therapy. Patient was allowed to continue any routine antineoplastic agent or medication for supportive care of underlying cancer.)
7) Patient had previously participated in this study.
8) Patient had taken caspofungin or other echinocandin within 10 days prior to study entry.
9) Patient had any condition or concomitant illness, which in the opinion of the investigator, might confuse the results of the study or pose additional risk in administering the study drugs to the patient.
10) Patient was taking rifampin, cyclosporin A, or concomitant systemic antifungal therapy.
11) Patient had a history of allergy, hypersensitivity, or any serious reaction to echinocandin antifungals.

Exclusion Criteria for Patients With Invasive *Aspergillus* Infections

1) Patients with disease limited to allergic sinus or bronchopulmonary aspergillosis, aspergilloma, or ocular disease.
2) Patients who did not meet criteria for refractory or intolerance as defined.

Exclusion Criteria for Patients With Invasive *Candida* Infections

1) Patients with evidence of infection limited to a positive culture for *Candida* from urine, sputum or broncho-alveolar lavage, catheter tip, catheter drainage or intraocular fluid. (Note: Patients with a positive urine culture who had signs and symptoms of upper urinary tract disease were able to be enrolled.)
2) Patients with suspected *Candida* endocarditis, osteomyelitis, or meningitis.
3) Patients with prosthetic devices at a suspected site of infection were excluded unless the device was removed at study entry or within 72 hours following study entry. Patients with an indwelling vascular catheter were not excluded but the catheter should have been removed, if feasible.

Exclusion Criteria for Patients With Esophageal *Candida* Infections

1) Patients with *Candida* disease limited to the oropharynx only. (Note: Patients with both oropharyngeal and esophageal candidiasis were able to be enrolled.)
2) Patients with another cause of esophagitis (i.e., CMV, HSV, bacterial, gastroesophageal reflux, pill related) or who had clearly defined ulcers on endoscopy in which the likelihood of another non-*Candida* pathogen was high.
3) Patients who had other esophageal pathology (e.g., stenosis, mass lesions) on endoscopy which was unrelated to acute esophageal candidiasis.

STUDY PROCEDURES: The schedule of clinical and laboratory measurements for Invasive Aspergillosis, Invasive Candidiasis, and Esophageal Candidiasis are depicted in the Tables below. The study included a screening period (Visit 1), the study therapy period (Visits 2, and 3), a 14 day posttherapy follow-up period (Visit 4), and a 28 day posttherapy follow-up period (Visit 5). Visit 5 was required only for patients who had a favorable response at the end of study therapy (V3) since it was only for relapse assessment.

Table 19 Study 043 Flowchart for subjects with Invasive Aspergillosis

	Preliminary Screening	Random-ization	Treatment Days								Follow-Up Assessment	
Clinic Visit ID:	Prestudy Visit	Treatment Day 1	2	3	4	5	6	7	Continuing IV Antifungal Tx Past Day 7	Last Day of Caspofungin Therapy†	14 days After Discontinuation of Caspofungin Tx	28 days After Discontinuation of Caspofungin Tx¶¶
Informed consent	X											
Medical history	X											
Physical examination	X	X			X			X	Twice wkly	X	X	X
Assessment of signs and symptoms	X	X	X	X	X	X	X	X	Daily	X	X	X
CD4 count & viral load (in HIV+ patients)	X§											
ECG	X‖											
Chest x-ray/chest CT	X‖											
Pregnancy test (hCG)	X¶								X¶			
Body temperature	X	X	X	X	X	X	X	X	Daily	X		
Blood for safety	X#				X			X	Twice wkly	X	X	
Urine for safety	X#									X		
Noninvasive cultures or ELISA/PCR††	X								Weekly	X	X	X
Radiographic studies‡‡	X								X	X	X	X
Monitor for adverse experiences	X	X	X	X	X	X	X	X	Daily	X	X§§	
Assessment of outcome‡										X	X	X
Plasma for drug levels∠	X∠				X∠			X∠	X∠			

† Duration of IV treatment should have been according to criteria specified in text of protocol.
‡ Assessment of outcome may have included radiographic studies/biopsies/cultures as clinically indicated
§ Performed only if patient is HIV positive and it had not been performed within the 4 months prior to screening.
ECG was to be completed with in 4 weeks prior to study entry. Chest radiograph (x-ray or CT) needed to be completed within 48 hours prior to study entry however, a radiograph did not need to be repeated if a chest radiograph was performed within 5 days prior to study entry, and a repeat radiograph at the time of study entry was not clinically indicated. Note, a chest CT should have been done for patients with pulmonary invasive aspergillosis.
¶ Female adolescents of childbearing potential must have had a negative serum or urine pregnancy test (sensitive to 25 IU hCG) within 7 days prior to IV study therapy and every 4 weeks thereafter while on study therapy.
# To have been obtained within 48 hours prior to study entry.
†† As specified in the inclusion criteria, patients with probable invasive aspergillosis must have had microbiological evidence of invasive aspergillosis (non-invasive culture) or positive *Aspergillus* infection detected by PCR or galactomannan ELISA. PCR/ELISA should have been performed once a week while the patient is on study therapy if it was used in making the diagnosis.
‡‡ Radiographic studies of site(s) of infection (CT/MRI preferred over CXR) were to be completed every 1 month and as clinically indicated during study therapy. Radiographic studies of the site(s) of infection should have also been completed within 7 days prior to the end of study therapy.
§§ Adverse experiences were collected through 14 days after the end of study therapy.
∠ A plasma blank for caspofungin drug levels should have been drawn at screening at all study sites. Pharmacokinetic samples were to be collected at all study sites preinfusion and within 5 minutes after the end of caspofungin infusion on Days 4, 7, 14. At all study sites for patients aged 3 months to <24 months and at a subset of study sites for patients aged 24 months to 17 years, 5-point plasma sampling for pharmacokinetics (predose, 1 hour, 2 hour, 4 hour, and 24 hour) were to also be done on Day 4.
¶¶ Only required for patients who have had a non-relapse response at the 14-day posttreatment follow-up visit.

Table 20 Study 043 Flowchart for Subjects with Invasive Candidiasis

	Preliminary Screening	Random-ization	Treatment Days							Follow-Up Assessment	
Clinic Visit ID:	Prestudy Visit	Treatment Day 1	2	3	4	5	6	7	Continuing IV Antifungal Tx Past Day 7	Last Day of Caspofungin Therapy†	14 days After Discontinuation of Caspofungin Tx	28 days After Discontinuation of Caspofungin Tx§§
Informed consent	X											
Medical history	X											
Physical examination	X	X			X			X	Twice wkly	X	X	X
Assessment of signs and symptoms	X	X	X	X	X	X	X	X	Daily	X	X	X
CD4 count & viral load (in HIV+ patients)	X§											
ECG	Xl											
Chest x-ray	Xl											
Pregnancy test (hCG)	X¶								X¶			
Body temperature	X	X	X	X	X	X	X	X	Daily	X		
Blood for safety	X#				X			X	Twice wkly	X	X	
Urine for safety	X#									X		
Blood cultures and/or other cultures††	X	X	X	X	X	X	X	X	Daily	X	X	X
Monitor for adverse experiences	X	X	X	X	X	X	X	X	Daily	X	X	
Assessment of outcome‡										X	X	X
Plasma for drug levels‡‡	X‡‡				X‡‡			X‡‡	X‡‡			

† Duration of IV treatment should have been according to criteria specified in text of protocol.
‡ Assessment of outcome may have included radiographic studies/biopsies/cultures as clinically indicated.
§ Performed only if patient is HIV positive and it had not been performed within the 4 months prior to screening.
l ECG was to be completed within 4 weeks prior to study entry. Chest radiograph (x-ray or CT) needed to be completed within 48 hours prior to study entry; however, a radiograph did not need to be repeated if a chest radiograph was performed within 5 days prior to study entry, and a repeat radiograph at the time of study entry was not clinically indicated.
¶ Female adolescents of childbearing potential must have had a negative serum or urine pregnancy test (sensitive to 25 IU hCG) within 7 days prior to IV study therapy and every
4 weeks thereafter while on study therapy.
To have been obtained within 48 hours prior to study entry.
†† To have been obtained within 4 days prior to study entry. For patients with candidemia, blood cultures should have been collected daily while on study drug until the cultures are negative for *Candida* for at least 48 hours. For non-blood stream infections, cultures from the site of infection should have been obtained while on study drug as clinically indicated. Follow-up cultures for all invasive candidiasis should have been obtained as clinically indicated.
‡‡ A plasma blank for caspofungin drug levels was to be drawn at screening at all study sites. Pharmacokinetic samples were to be collected at all study sites preinfusion and within 5 minutes after the end of caspofungin infusion on Days 4, 7, 14. At all study sites for patients aged 3 months to <24 months and at a subset of study sites for patients aged 24 months to 17 years, 5-point plasma sampling for pharmacokinetics (predose, 1 hour, 2 hour, 4 hour, and 24 hour) were also to be done on Day 4.
§§ Only required for patients who have had a non-relapse response at the 14-day posttreatment follow-up visit.

Table 21 Study 043 Flowchart for Subjects with Esophageal Candidiasis

	Preliminary Screening	Random-ization	Treatment Days							Follow-Up Assessment	
Clinic Visit ID:	Prestudy Visit	Treatment Day 1	2	3	4	5	6	7	Continuing IV Antifungal Tx Past Day 7	Last Day of Caspofungin Therapy†	14 days After Discontinuation of Caspofungin Tx	28 days After Discontinuation of Caspofungin Tx§§
Informed consent	X											
Medical history	X											
Physical examination	X	X			X			X	Twice wkly	X	X	X
Assessment of signs and symptoms‡	X	X	X	X	X	X	X	X	Daily	X	X	X
CD4 count & viral load (in HIV+ patients)	X§											
ECG	Xl											
Chest x-ray	Xl											
Endoscopy	X¶									X¶		
Pregnancy test (hCG)	X#								X#			
Body temperature	X	X	X	X	X	X	X	X	Daily	X		
Blood for safety	X††				X			X	Twice wkly	X	X	
Urine for safety	X††									X		
Monitor for adverse experiences	X	X	X	X	X	X	X	X	Daily	X	X	
Assessment of outcome										X	X	X
Plasma for drug levels‡‡	X‡‡				X‡‡			X‡‡	X‡‡			

† Duration of IV treatment should have been according to criteria specified in text of protocol.
‡ Assessment of signs and symptoms relating to esophagitis. Patients should have also been assessed for symptoms of oropharyngeal candidiasis.
§ Performed only if patient is HIV positive and it had not been performed within the 4 months prior to screening.

l ECG was to have been completed within 4 weeks prior to study entry. Chest radiograph (x-ray or CT) needed to be completed within 48 hours prior to study entry; however, a radiograph did not need to be repeated if a chest radiograph was performed within 5 days prior to study entry, and a repeat radiograph at the time of study entry was not clinically indicated.
¶ An endoscopy should have been performed within 48 hours prior to enrollment and within 2 days of the last day of study therapy.
# Female adolescents of childbearing potential must have had a negative serum or urine pregnancy test (sensitive to 25 IU hCG) within 7 days prior to IV study therapy and every 4 weeks thereafter while on study therapy.
†† To have been obtained within 48 hours of study entry.
‡‡ A pretherapy (blank) blood sample for caspofungin drug level was to be drawn at screening at all study sites. Pharmacokinetic blood samples were to be collected at all study sites preinfusion (trough) and within 5 minutes after the end of caspofungin infusion (peak) on Days 4, 7, 14. At all study sites for patients aged 3 months to <24 months and at a subset of study sites for patients aged 24 months to 17 years, 5-point plasma sampling for pharmacokinetics (predose, 1 hour, 2 hour, 4 hour, and 24 hour) were to be done on Day 4.
§§ Only required for patients who have had a non-relapse response at the 14-day posttreatment follow-up visit.

EVALUATION OF EFFICACY

Efficacy assessments in this study were made at the end of caspofungin study therapy and, if applicable, at the 14- and 28-day posttherapy follow-up visits. The primary endpoint for efficacy was the end of caspofungin therapy assessment. A favorable clinical response could either be a "complete response" or a "partial response", as defined below for each of the fungal infections. A favorable microbiologic response could either be "eradication" or "presumed eradication". Relapse was assessed at the 2 posttherapy follow-up visits (Visits 4 and 5) in patients with a favorable response at the end of caspofungin therapy.
Efficacy assessments were made by the primary investigator. Evaluation guidelines were defined in the protocol for each of the 3 fungal diagnoses, and these details are outlined below.

Invasive Aspergillosis

For invasive aspergillosis, efficacy ("Clinical Response") was based on a clinical evaluation that incorporated data on symptoms and signs, radiography, and other relevant criteria. Because of the difficulties inherent in microbiological diagnosis of *Aspergillus* infection, primary outcome of treatment focused on clinical response. In an attempt to provide supportive microbiological data, non-invasive cultures were obtained as clinically indicated.
Definition of Clinical Response:

- Complete Response: Resolution of symptoms attributed to invasive aspergillosis, and resolution of all radiographic and other relevant investigative (e.g., bronchoscopy) abnormalities due to *Aspergillus* infection.
- Partial Response**:** Clinically significant improvement of symptoms attributed to the invasive aspergillosis infection, and clinically significant improvement of radiographic and other relevant investigative (e.g., bronchoscopy) abnormalities due to *Aspergillus* infection.
- Unfavorable Response: Lack of improvement or deterioration in attributable clinical or radiographic abnormalities, necessitating alternative antifungal therapy or resulting in death.

Definition of Microbiologic Response:

- Eradication: Negative cultures at the end of therapy.
- Presumed eradication: If no culture data were available at the end of study therapy, culture data obtained within 7 days of therapy discontinuation was used. If a patient had complete clinical and radiological response to therapy and no cultures were obtained, the patient was considered to have presumed eradication.
- Persistence: Cultures remained positive during therapy and at the end of study therapy.
- Presumed persistence: If no culture data were available at the end of study therapy, culture data obtained within 7 days of therapy discontinuation were used. If a patient had clinical and radiological failure to therapy and no cultures were obtained, the patient was considered to have presumed persistence.

- Indeterminate**:** Cultures not available at the end of therapy and no data available on which to base assessment. If a patient had partial clinical and radiological improvement or stable disease and no cultures were obtained, the patient was considered to be microbiologically indeterminate.

Definitions of Relapse:

- Clinical Relapse: Reemergence of clinical, radiographic or other relevant abnormalities indicating invasive aspergillosis after discontinuation of study therapy.
- Microbiological Relapse: At the posttherapy follow-up visit(s), follow-up cultures had become positive for *Aspergillus* after being negative during study therapy.

Invasive Candidiasis

Definitions of Clinical Response

- Complete Response: Resolution (or return to pre-infection baseline) of all signs and symptoms attributed to the invasive *Candida* infection and resolution of all relevant radiographic findings (if previously present).
- Partial Response: Improvement of most signs and symptoms of the invasive *Candida* infection and improvement in relevant radiographic findings.
- Unfavorable: Persistence of signs and symptoms of the invasive *Candida* infection or of relevant radiographic findings.

Definitions of Microbiological Response

- Eradication: Follow-up cultures from site of infection (sterile collection) negative for *Candida.*
- NOTE: For patients with candidemia, eradication must be documented by demonstration of negative blood cultures for at least 48 hours. Presumed eradication is not an appropriate favorable microbiological response assessment for patients with candidemia.
- Presumed Eradication: Infections which would require an invasive procedure for documentation of a follow-up negative culture were considered to have an evaluation of "presumed eradication" if there was no apparent evidence of residual infection from symptoms, physical examination, and appropriate non-invasive studies (laboratory test, CT, MRI, etc.). Because radiographic changes lag behind clinical findings, residual radiographic abnormalities consistent with resolving infection did not require culture confirmation.
- Persistence: Follow-up cultures remained positive for *Candida* at the original site (sterile collection) of infection or at other normally sterile body sites.
- Indeterminate: Follow-up cultures not obtained at the end of study therapy and patient did not meet the definition of presumed eradication (i.e., patient had a partial or unfavorable clinical response).

Definition of Overall Response

In order for the overall assessment to be considered a favorable response, a clinical response of complete or partial and a microbiological response of eradication or presumed eradication was necessary.

Definitions of Relapse:

- Clinical Relapse: Recurrence of symptoms/signs of *Candida* infection necessitating additional systemic antifungal therapy for a presumed or proven invasive fungal infection. (NOTE: Those patients at high risk for recurrent fungal infections who were maintained on prophylactic systemic antifungal therapy and those patients who received antifungal therapy

for non-invasive *Candida* infections [e.g., oral thrush, *Candida* urinary tract infection, or vaginal candidiasis] were not considered "clinical" relapses.)

- Microbiological Relapse: Recurrence of a positive culture for *Candida* spp. from a normally sterile, invasive body site at anytime during the post antifungal follow-up period.

Esophageal Candidiasis

Efficacy assessment ("Clinical Response") was based on symptomatic and endoscopic criteria. There was no separate microbiological response assessment.

Definitions of Clinical Response:

- Complete Response: No remaining lesions seen on endoscopy or a reduction of endoscopic lesions by at least 2 stepwise grades AND all previously noted esophageal signs/symptoms had resolved.
- Partial Response: No endoscopy performed or reduction of endoscopic lesions by one stepwise grade. AND improvement of esophageal signs/symptoms from baseline findings. Unfavorable Response: Not meeting the definitions of complete or partial response at the end of caspofungin therapy.

Assessment of Oropharyngeal Response: If oropharyngeal lesions were present at baseline, the response of these lesions to caspofungin was also assessed.

Relapse Assessment:

Relapse in esophageal (or oropharyngeal) candidiasis in patients with a favorable response at the end of caspofungin therapy at the 14- or 28-day posttherapy follow-up visits was defined as recurrence of symptoms of esophageal candidiasis or evidence of recurrent candidiasis on follow-up endoscopy (if performed). Relapse of oropharyngeal candidiasis at the 14- and 28-day posttherapy follow-up visits was defined as recurrence of oropharyngeal symptoms and/or evidence of *Candida* lesions on follow-up oropharyngeal examination.

REASONS FOR WITHDRAWAL:

1. The patient develops a serious clinical or and laboratory adverse experience related to study medication.
2. The patient or guardian refuses further treatment or follow-up and withdraws consent.
3. The patient requires treatment with investigational drugs other than the patient's antineoplastic or supportive care regimen.
4. Progression of the patient's fungal infection on high dose study medication.
5. Any other reason, which may significantly affect the quality of the data.

STATISTICS:

This study was analyzed as an estimation study. In this study, each investigator independently evaluated the diagnosis of invasive aspergillosis, invasive candidiasis, and esophageal candidiasis based on the criteria provided in the protocol and assessed the efficacy based on definitions of response outlined in the protocol.

Primary Endpoint

The primary efficacy endpoint was the proportion of patients with a favorable treatment outcome at the end of caspofungin therapy.

- Invasive aspergillosis – clinical response
- Invasive candidiasis – clinical and microbiological responses
- Esophageal candidiasis – clinical and endoscopic response

Secondary Endpoints

- Invasive aspergillosis:
    - Favorable microbiological response at the end of caspofungin therapy.
- Invasive candidiasis:
    - Favorable clinical response at the end of caspofungin therapy;
    - Favorable microbiological response at the end of caspofungin therapy.
- Esophageal candidiasis:
    - Favorable symptom response at the end of caspofungin therapy;
    - Favorable endoscopic response at the end of caspofungin therapy.
- In those patients successfully treated with caspofungin, evidence of relapse of the fungal infection was also assessed during the 14- and 28-day post therapy follow-up periods.

Analysis populations:

Modified Intention-to-Treat (MITT) Patient Population included those patients who received at least 1 full dose of caspofungin study therapy and had a documented diagnosis of invasive aspergillosis, invasive candidiasis, or esophageal candidiasis as defined in the protocol. The MITT patient population was the primary population for assessing efficacy

Evaluable-Patient Population included those patients who met the following prespecified criteria as outlined in the Data Analysis Plan:

1. The patient must have met the protocol-defined definition for documented invasive aspergillosis, invasive candidiasis, or esophageal candidiasis.
2. The patient must not have received >1 day of concomitant systemic antifungal therapy while receiving caspofungin study therapy if the total duration of caspofungin therapy was 3 weeks or less. For durations of caspofungin therapy exceeding 3 weeks, the patient must not have received concomitant systemic antifungal therapy that amounted to more than 5% of the total duration of caspofungin therapy.
3. The patient had an end of treatment assessment appropriate for the patient's specific infection:
    - symptoms and endoscopy for esophageal candidiasis;
    - symptoms, radiographic studies appropriate for the site of infection, if applicable, and/or cultures for invasive candidiasis;
    - symptoms, physical findings, and appropriate radiographic studies for invasive aspergillosis.
4. A patient with either invasive or esophageal candidiasis must have received at least 5 days of caspofungin study therapy. A patient with invasive aspergillosis must have received >7 days of caspofungin study therapy.
5. The patient must not have committed any protocol violations that interfered with the assessment of efficacy.

The evaluable-patient population was intended to provide supportive evidence to the findings of the MITT patient population.

Sample size: Approximately 50 male or female pediatric patients 3 months to 17 years of age with invasive aspergillosis, invasive candidiasis, or esophageal candidiasis were planned for this study. At least 10 patients with invasive aspergillosis were expected to be enrolled with the majority of the remaining patients having invasive candidiasis.

EVALUATION OF SAFETY:

Primary Endpoint: Clinical or laboratory drug-related adverse experience during caspofungin therapy and the 14-day posttherapy period.

Secondary Endpoints:

- Clinical or laboratory serious drug-related adverse experience during caspofungin therapy and the 14-day posttherapy period;
- Clinical or laboratory drug-related adverse experience leading to discontinuation of study therapy;
- Systemic or local infusion-related adverse event;
- Deaths occurring during the study.

PROTOCOL CHANGES:
1 protocol amendment dated December 7, 2005 accompanied the protocol for this study and included the following protocol modifications:

- Personnel contact information was updated to reflect current telephone numbers, fax numbers, email addresses, and mailing addresses.
- The Background section was shortened to provide only new and the most relevant information. The reader is referred to the Product Package Insert and the Confidential Investigator's Brochure (CIB) for detailed background information.
- The included age range was expanded from patients aged 2 to 17 years to patients aged 3 months to 17 years and a rationale for this change was added.
- Instructions for collection of blood samples for pharmacokinetic (PK) analysis were modified. Five-point PK sampling on Day 4 is required for all patients aged 3 months to <24 months while for patients aged 24 months to 17 years only a subset of sites will perform 5-point sampling on Day 4.
- The wording under Section I. E. 2. 3 Infusion of Caspofungin has been updated
- The estimated overall duration of the study was increased to 36 months and an interim report is now planned.
- The List of References was updated
- Several appendices were restructured to clarify the procedures for processing and shipping of fungal isolates and PK samples

RESULTS

6.2.1.2 Patient Disposition

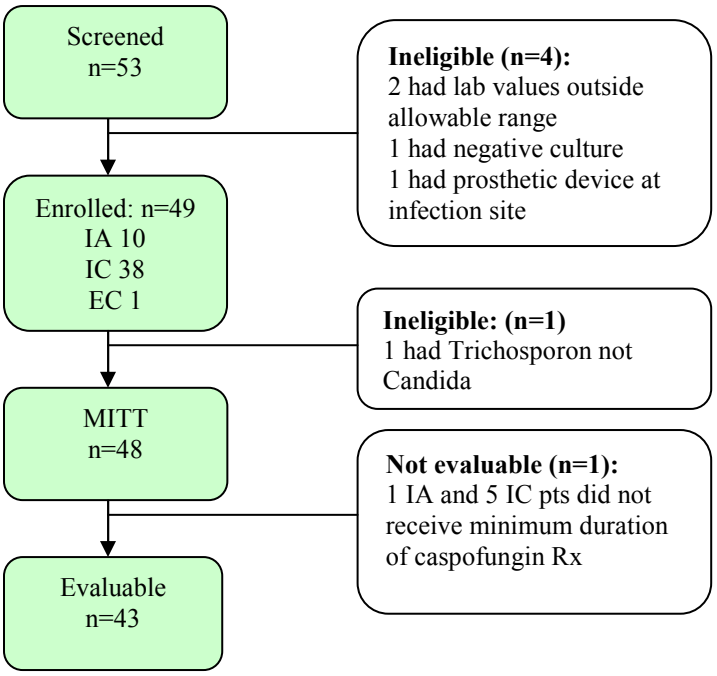
Study centers: 21 study centers; subjects were enrolled at 12/21 centers (6 U.S., 2 Germany, 2 Taiwan, 1 Italy, and 1 Israel).

Total patients enrolled: 49

The subjects were from diverse geographical areas, represented by the following countries: 33 subjects (67%) from USA, 7 subjects (14%) from Taiwan, 3 subjects each (6%) from Germany, Italy, and Israel. Each of the following 3 study sites randomized more than 10% of the subjects: 3, 5, and 21. Sites 3 and 5, clinical investigators ---------- and ---------- enrolled 25 (11 and 14 respectively) subjects, >50% of the study population.

The following flowchart and the tables summarize the composition of the applicant's populations for analysis, the primary reasons for exclusion and the demographics of the study population.

Figure 1 Subject's Disposition



6.2.1.3 Demographics and Baseline Characteristics

Table 22 Demographic and Baseline Characteristics, All Treated Subjects (043)

Characteristic	Invasive Aspergillosis N = 10	Invasive Candidiasis N-= 38	Esophageal Candidiasis N-= 1
Gender: n (%)			
Female	2 (20)	16 (42.1)	
Male	8 (80)	22 (57.9)	1
Race: n (%)			
White	6 (60)	23 (60.5)	1
Black		6 (15.8)	
American Indian/ Alaskan Native		2 (5.3)	
Asian/Pacific Islander	4 (40)	5 (13.2)	
Multi-racial		2 (5.3)	
Ethnicity			
Hispanic or Latino		7 (18.4)	
Not Hispanic or Latino	10(100)	31 (81.6)	1
Age: years			
3 to 23 months		3 (7.8)	
2 to 6 years	3 (30)	16 (42.1)	
7 to 11 years	5 (50)	6 (15.8)	
12 to 17 years	2(20)	13 (34.2)	1
Mean	8.3±3.9	7.9±5.4	17
Median	7.5	6.5	17
Min - Max	3 to 16	6 months to 17	

Reason for Study entry			
Primary Therapy		31(81.6)	1
Salvage Therapy	10 (100)	7 (18.4)	
Risk factors			
Active malignancy	8 (80)	12 (31.6)	1
Broad Spectrum antibiotics		28 (73.7)	
Diabetes mellitus		1 (2.6)	
Immunosuppression	9 (90)	21 (55.3)	1
Major surgery		8 (21.1)	
Neutropenia	3 (30)	7 (18.4)	
Total parenteral nutrition		24 (63.2)	
Transplant	6 (60)	9 (23.7)	1
Vascular catheter		30 (78.9)	
Other§		2 (5.3)	

† Patients with multiple sites of infection are displayed only under multiple sites. Multiple sites include 1 patient (AN 6105) with blood and peritoneal fluid candidiasis and 1 patient (AN 6154) with nasal cavity (with histopathologic confirmation) and hepatosplenic candidiasis.
‡ Patients may appear in more than one risk category.
§ Other includes 1 patient (AN 6022) listed for a heart transplant and 1 patient (AN 6083) on chemotherapy.

MO comment: *Children enrolled in this study were primarily immunosuppressed white non-Hispanic males under 12 years across all three diagnostic categories: invasive aspergillosis, candidemia, and esophageal candidiasis.*

Table 23 Baseline Disease Characteristics (IA), Study 043

Characteristic	Invasive Aspergillosis N = 10
Site of infection: n (%)	
Definite pulmonary	2 (20.0)
Probable pulmonary	4 (40.0)
Definite Middle ear, right	1 (10.0)
Definite intracranial	1 (10.0)
Multiple sites†	2 (20.0)

† 1 subject with probable pulmonary and definite skin; 1 patient with probable pulmonary, CNS, and skin

MO comment: *The reviewer examined each case of invasive aspergillosis for fulfillment of the diagnostic criteria. All 5 definite cases had positive tissue biopsy for fungal forms consistent with Aspergillus upon cytological examination/fungal culture results. In all probable cases risk factors for invasive aspergillosis were present; microbiological criterion was fulfilled either by positive serum gallactomannan ELISA x2, or positive culture of the sputum/BAL; at least 2 minor criteria were present in each of the probable cases (fever and cough as clinical signs and new infiltrates on chest CT/X-ray).*

Table 24 Baseline Disease Characteristics (IC), Study 043

	Invasive

Characteristic	Candidiasis N = 38
Site of infection: n (%)	
Blood	35 (92.1)
Psoas muscle abscess	1 (2.6)
Multiple sites†	2 (5.3)

† Patients with multiple sites of infection are displayed only under multiple sites. Multiple sites include 1 patient (AN 6105) with blood and peritoneal fluid candidiasis and 1 patient (AN 6154) with nasal cavity (with histopathologic confirmation) and hepatosplenic candidiasis.

MO comment: *Invasive candidiasis study population was comprised primarily of candidemic patients majority of them non-neutropenic. Among sites other than candidemia one subject appears unlikely to have had invasive candidiasis. Subject AN 6106 17 year old black female with Crohn's disease and history of bacterial psoas abscess on ciprofloxacin prophylaxis developed RLQ tenderness and CT documented interim abscess size increase. Abscess was drained on Day -4 and the culture revealed C. albicans. This non-candidemic subject, however, was on piperacillin-tazobactam since D -9 through the course of the study therapy, limiting investigator's and Reviewer's ability to judge if primary etiology of the abscess was C. albicans alone or mixed bacterial/fungal infection or mixed bacterial etiology with Candida colonization. The subject underwent laparotomy and further debridement of the abscess, cecectomy, and intestinal re-anastomosis on Day 4 of the study. She received both caspofungin and piperacillin-tazobactam through Day 10 of the study and was documented to have complete clinical response.*

Mycological characteristics of the study population

A total of 4 unique baseline *Aspergillus* isolates, one per patient, were available for central laboratory testing from 4 of the 10 invasive aspergillosis patients.

Table 25 Invasive Aspergillosis, Fungal Isolates, Susceptibility Profile (043)

Organism (Number of Isolates)	Antifungal	Range
Aspergillus flavus (1)	Amphotericin B	4
	Caspofungin Acetate	0.03
	Itraconazole	0.25
	Voriconazole	0.5
Aspergillus fumigatus (1)	Amphotericin B	2
	Caspofungin Acetate	0.06
	Itraconazole	0.5
	Voriconazole	0.5
Aspergillus niger (1)	Amphotericin B	0.5
	Caspofungin Acetate	0.06
	Itraconazole	0.12
	Voriconazole	0.12
Aspergillus terreus (1)	Amphotericin B	4
	Caspofungin Acetate	0.03
	Itraconazole	0.5
	Voriconazole	0.12

MO comment: *Susceptibility profiles of the Aspergillus isolates are of unknown clinical significance. ¾ subjects with positive Aspergillus culture had outcome of failure despite of relatively low MICs to caspofungin.*

Table 26 Invasive Candidiasis, Species Distribution among Candida isolates (local laboratory), MITT (043)

Candida Isolates	Number of isolates N (%)
C. albicans	**13 (35)**
C. glabrata	**4 (11)**
C. parapsilosis	**8 (22)**
C. tropicalis	**5 (14)**
C. krusei	**1(3)**
C. guilliermondii	**1 (3)**
C. lusitaniae	**3 (8)**
C. lambica	**2 (5)**
Total	**37 (100)**

MO comment: *Species distribution of Candida isolates in the study under review is reflecting pattern described in medical literature in recent years: Candida albicans remains a predominant pathogen across all age groups; however C. parapsilosis in children is the second most common Candida species followed by C. tropicalis, while in adults species distribution is the pattern is slightly different: C. albicans > C. glabrata > C. parapsilosis ≥ C. tropicalis1,2,3.*

Table 27 Invasive Candidiasis, Fungal Isolates, Susceptibility Profile (central laboratory), MITT (043)

Organism (Number of Isolates)	Antibiotic	Range	MIC_{50} §	MIC_{90} ‡	Geometric Mean
Candida albicans (12)	Amphotericin B	0.5 - 4	1	2	1.26
	Caspofungin acetate Prominent	0.03 – 0.12	0.06	0.06	0.05
	Caspofungin acetate Complete	0.06 – 0.5	0.12	0.25	0.13
	Fluconazole	0.12 – 256	0.5	256	2.81
	Voriconazole	≤0.015 - >32	0.06	64	0.62
Candida glabrata (4)	Amphotericin B	1 – 4	1		1.41
	Caspofungin acetate Prominent	0.03 – 0.12	0.06		0.06
	Caspofungin acetate Complete	0.06 – 0.12	0.06		0.08
	Fluconazole	8 – 64	16		19.03
	Voriconazole	0.25 – 2	0.5		0.71
Candida guillermondii (1)	Amphotericin B	0.5			
	Caspofungin acetate Prominent	0.25			
	Caspofungin acetate Complete	>32			
	Fluconazole	4			
	Voriconazole	0.03			
Candida krusei (1)	Amphotericin B	2			
	Caspofungin acetate Prominent	0.12			
	Caspofungin acetate Complete	0.25			
	Fluconazole	64			
	Voriconazole	0.5			
Candida lambica (2)	Amphotericin B	1 – 4	1		2.00
	Caspofungin acetate Prominent	0.03 – 0.12	0.12		0.17
	Caspofungin acetate Complete	0.06 – 0.12	0.25		0.50
	Fluconazole	8 – 64	0.5		0.71
	Voriconazole	≤0.015 – 0.03	0.015		0.02
Candida lusitaniae (3)	Amphotericin B	0.5 – 2	2		1.26
	Caspofungin acetate Prominent	0.25 – 1	0.5		0.50
	Caspofungin acetate Complete	0.5 – 1	1		0.79
	Fluconazole	0.25 – 0.5	0.25		0.31
	Voriconazole	≤0.015	0.015		0.02
Candida parapsilosis (8)	Amphotericin B	0.5 – 4	2		2.00
	Caspofungin acetate Prominent	≤0.015 – 0.5	0.25		0.21
	Caspofungin acetate Complete	0.25 - >32	1		1.30
	Fluconazole	0.12 – 2	0.5		0.54
	Voriconazole	≤0.015 – 0.12	0.03		0.03
Candida tropicalis (4)	Amphotericin B	1 – 4	1		2.00
	Caspofungin acetate Prominent	≤0.015 – 0.25	0.03		0.05
	Caspofungin acetate Complete	0.06 – 0.5	0.25		0.25
	Fluconazole	0.25 – 1	0.5		0.59
	Voriconazole	≤0.015 – 0.06	0.03		0.03

† Broth Microdilution method (CLSI formerly NCCLS Document: M27-A); RPMI 1640 (Biowhittaker) medium; inoculum 0.5 to 2.5 x 10_3 CFU/mL; incubation at 35 to 37°C. MIC for caspofungin was defined as the lowest concentration showing significant reduction (prominent inhibition) in visible growth (MIC-80) at 24 hours, and complete inhibition of visible growth (MIC-100) at 48 hours. The MIC for Amphotericin B was defined as the lowest concentration inhibiting visible growth (MIC-100) at 48 hours (complete inhibition). The MIC for Fluconazole and Voriconazole was defined as the lowest concentration of antifungal showing significant reduction (prominent inhibition) in visible growth (MIC-80) at 48 hours.
§ At least 2 isolates are required to calculate MIC_{50}.
‡ At least 10 isolates are required to calculate MIC_{90}.

1 J Clin Microbiol. 2002 March; 40(3): 852–56.
2 Intensive Care Med. 2007 Jul;33(7):1272-83
3 CID 2008;46:1206–13

For geometric mean, when the MIC value was δ0.015 or >32 or >64 or >128 ⌈g/mL, a value of 0.015 or 64 or 128 or 256 ⌈g/mL, respectively, was used for the geometric mean calculation.

MO comment: *MICs of all Candida isolates to caspofungin at 24 hour reading (prominent) are low (≤1ug/ml), and are in the susceptible range <2ug/ml. The 24 hour reading of Candida breakpoints for caspofungin was found to correlate better with clinical outcome. For 48 hour reading (complete) only C. tropicalis and C. guillermondii have MICs for caspofungin in 32ug/ml range the rest of the species continue to retain MICs at or below 1ug/ml.*

Esophageal Candidiasis

The only subject with esophageal candidiasis in the study has C. albicans isolated from the original biopsy specimen; however, the isolate was mishandled during transport to the central lab and no MICs were determined.

Table 28 Discontinuations from study therapy (043)

	Number of Subjects (%)	
Category/Reason	**Caspofungin N = 49**	
Treatment Completed	**43**	**(94)**
Discontinued Prematurely	**6**	**(6)**
Reason Discontinued		
Adverse Event	4	(6)
Lost to Follow-up	2	(2)

MO comment: *Clinical adverse events that lead to study drug discontinuation occurred only in subjects with invasive aspergillosis and upon closer examination were related to the progression of the disease. 2 candidemia subjects were discharged/transferred from the study site hospital. No adverse events were associated with their early dismissal from the study.*

Overall, 43 (87.8%) patients completed the study, defined as completing at least the Day 14 posttherapy follow-up visit. The percentages of patients with invasive aspergillosis, invasive candidiasis, and esophageal candidiasis who completed the study were 60%, 94.7%, and 100%, respectively. Among the 6 patients who discontinued the study, 4 discontinued due to clinical adverse experiences not related to caspofungin therapy, 1 patient moved, and 1 discontinued due to being discharged from the hospital.

Table 29 Patient Accounting by Treatment Group (043)

	Invasive Aspergillosis		Invasive Candidiasis		Esophageal Candidiasis		Total	
	(N = 10)		(N = 38)		(N = 1)		(N = 49)	
	n	(%)	n	(%)	n	(%)	n	(%)
PATIENTS ENTERED:	**10**		**38**		**1**		**49**	
COMPLETED THERAPY†:	**5**	**(50.0)**	**23**	**(60.5)**	**1**	**(100)**	**29**	**(59.2)**
DISCONTINUED THERAPY:	**5**	**(50.0)**	**15**	**(39.5)**	**0**	**(0.0)**	**20**	**(40.8)**
clinical AE	2	(20.0)	0	(0.0)	0	(0.0)	2	(4.1)
lack efficacy	3	(30.0)	6	(15.8)	0	(0.0)	9	(18.4)
other	0	(0.0)	9	(23.7)	0	(0.0)	9	(18.4)
COMPLETED STUDY‡:	**6**	**(60.0)**	**36**	**(94.7)**	**1**	**(100)**	**43**	**(87.8)**
DISCONTINUED STUDY:	**4**	**(40.0)**	**2**	**(5.3)**	**0**	**(0.0)**	**6**	**(12.2)**
clinical AE	4	(40.0)	0	(0.0)	0	(0.0)	4	(8.2)
other	0	(0.0)	1	(2.6)	0	(0.0)	1	(2.0)
patient moved	0	(0.0)	1	(2.6)	0	(0.0)	1	(2.0)

†"Completed Therapy" is defined as having a status of "patient continuing trial" on the last day of caspofungin study therapy.
‡"Completed Study" is defined as completion of the 14 Day posttherapy Follow-up visit period.

MO comment: *Clinical adverse events that lead to study drug/study discontinuation occurred only in subjects with invasive aspergillosis and upon closer examination were related to the progression of the disease. 9 candidemia subjects have not completed full course of caspofungin treatment in the study center: 1 subject lost IV access, 5 upon parental request (3 continued to receive marketed caspofungin and 2 oral fluconazole as outpatients), 1 was found to have Trichosporon infection rather than candidemia, 1 subject AN 6189 was discharged home on voriconazole on Day 10 due to unfavorable clinical response (should be considered as discontinued due to efficacy failure), 1 subject AN 6002 was discharged due to being uncooperative with study procedures (continued to receive marketed caspofungin as outpatient). The Reviewer did not identify any additional adverse events that might have lead to premature therapy discontinuation.*

Treatment Compliance

Only 3 patients (6.1%) missed 1 dose of intended study drug during the treatment period. In 2/3 cases (ANs 6001, 6105), the patient received oral fluconazole instead of study drug due to loss of venous access. AN 6019 missed 1 dose due to a technological error.

Concomitant Antifungal Medications

16 (32.7%) subjects received systemic antifungal therapy during the treatment period, 15 of them received the antifungal either before or after the treatment period but on the same calendar day; this was permissible by protocol.

Two subjects with candidemia (ANs 6001, 6105) received fluconazole instead of caspofungin study therapy due to lost of venous access for 1 day. Only 1 subject with invasive aspergillosis (AN 6082) received concomitant voriconazole in error one day prior to discontinuing study therapy due to lack of efficacy

EFFICACY

6.2.1.4 Efficacy in Invasive Aspergillosis (primary, secondary endpoints, and subgroup analyses)

Invasive Aspergillosis

Table 30 Proportion of Invasive Aspergillosis Patients With a Favorable Clinical Response at the End of Caspofungin Therapy (MITT), Study 043

Time Point	Complete Response n/m (%) (95% CI)	Partial Response n/m (%) (95% CI)	Total n/m (%) (95% CI)
End of caspofungin therapy	3/10 (30.0) (6.7, 65.2)	2/10 (20.0) (2.5, 55.6)	5/10 (50.0) (18.7, 81.3)

n/m = Number of patients with a favorable response/number of patients in the subgroup.
CI = Confidence interval.

MO comment: *Caspofungin is approved for second line treatment of invasive aspergillosis in adults. Success of caspofungin monotherapy as salvage therapy in invasive aspergillosis was ~45% in both Protocols 019 and 024/025. The efficacy demonstrated in the study under review for pediatric subjects with refractory invasive aspergillosis is comparable to that observed in the adult caspofungin trials.*

Five patients (50%) with invasive aspergillosis were classified as having an unfavorable clinical response at the end of caspofungin therapy. These patients were treated with caspofungin for 6 (AN 6146), 8 (AN 6162), 10 (AN 6161), 29 (AN 6145), and 85 (AN 6082) days. Two of the patients had invasive aspergillosis involving multiple sites, and 3 were neutropenic at study entry. All 5 patients died either during the study or shortly after study completion due to aspergillosis progression and its complications.

Table 31 Proportion of Invasive Aspergillosis Patients With a Favorable Clinical Response† at the End of Caspofungin Therapy by Various Demographic Subgroups (MITT), Study 043

	Favorable Response† n/m (%)
Age (years)	
2-6	2/3 (66.7)
7-11	2/5 (40.0)
12-17	1/2 (50.0)
Gender	
Male	4/8 (50.0)
Female	1/2 (50.0)
Race	
White	4/6 (66.7)
Asian	1/4 (25.0)
Ethnicity	
Not Hispanic or Latino	5/10 (50.0)

n/m = Number of patients with a favorable response/number of patients in the subgroup.

MO comment: *The number of subjects in each subgroup is small to perform meaningful comparison of the efficacy results between them. Fewer Asian subjects achieved favorable clinical response than whites.*

Table 32 Proportion of Invasive Aspergillosis Patients With a Favorable Clinical Response† at the End of Caspofungin Therapy by Various Subgroups (MITT), Study 043

	Favorable Response† n/m (%)
Site of Infection	
Definite pulmonary	2/2 (100)
Probable pulmonary	1/4 (25.0)
Definite CNS (intracranial)	1/1 (100)
Definite middle ear (with lytic bone lesion)	1/1 (100)
Multiple sites	0/2 (0.0)
Underlying Disease	
Hematologic Malignancy	1/4 (25.0)
Allogeneic BMT or Stem Cell Transplant	1/2 (50)
Solid Tumor	2/2 (100)
Other	1/2 (50)
Prior Antifungal Therapy (refractory patients)	
Amphotericin B	3/5 (60.0)
Itraconazole	0/1 (0.0)
Voriconazole	1/1 (100)
>1 antifungal	0/2 (0.0)
Prior Antifungal Therapy (intolerant/refractory patients)	
Amphotericin B	1/2 (50)
Neutropenia status	
Neutropenic	0/3 (0.0)
Non-neutropenic	5/7 (71.4)

n/m = Number of patients with a favorable response/number of patients in the subgroup.

MO comment: *It is reassuring that greater number of subjects with definite diagnosis of invasive aspergillosis had favorable response (4/5) as compared to those with probable diagnosis (1/5).*

Microbiologic Response at End of Caspofungin Therapy

Microbiological response was assessed in all patients who had culture confirmation of infection. Six patients did not have a baseline culture and are excluded from this analysis. Of the 4 patients with a baseline culture, 2 (ANs 6139, 6153) had a favorable microbiological and clinical response at the end of caspofungin therapy.

Table 33 Microbiological Response by pathogen, IA, Study 043

Pathogen	Caspofungin acetate n/m (%)
Aspergillus flavus	0/1 (0.0)
Aspergillus fumigatus	1/1 (100)
Aspergillus niger	0/1 (0.0)
Aspergillus terreus	1/1 (100)

n/m = Number of patients with a favorable response/number of patients in the subgroup.

MO comment: *Limited number of Aspergillus isolates precludes from drawing any conclusions on isolate specific activity of caspofungin.*

Relapses

No relapses were documented in any of 5 successfully treated subjects at the 14 and 28 days follow-up study visits.

6.2.1.5 Efficacy in Invasive Candidiasis (primary, secondary endpoints, and subgroup analyses)

Candidemia and other invasive *Candida* infections

Table 34 Proportion of Invasive Candidiasis Patients with a Favorable Clinical Response, MITT Population, Study 043

Time Point	Complete Response n/m (%) (95% CI)
End of caspofungin therapy	30/37 (81.1) (64.8, 92.0)

n/m = Number of patients with a favorable response/number of patients in the subgroup.
CI = Confidence interval.

MO comment: *Caspofungin is approved for treatment of candidemia, intra-abdominal abscesses, pleural space infections, and peritonitis in adult patients based on 1 randomized controlled blinded study 014 (efficacy of 73% for caspofungin versus 62% for Ambisome) and 2 supportive compassionate use studies 024/025 and 045. Clinical response rates in candidemic pediatric patients are comparable to those seen in adult caspofungin trials.*

Table 35 Proportion of Invasive Candidiasis Patients With a Favorable Clinical Response at the End of Caspofungin Therapy by Various Demographic Subgroups (MITT), Study 043

	Favorable Response† n/m (%)
Age	
3 to 23 months	3/3 (100)
2 to 6 years	12/15 (80.0)
7 to 11 years	6/6 (100)
12 to 17 years	9/13 (69.2)
Gender	
Female	13/16 (81.3)
Male	17/21 (81.0)
Race	
American Indian or Alaska Native	2/2 (100)
Asian	3/4 (75.0)
Black, of African heritage	5/6 (83.3)
White	18/23 (78.3)
Multi-racial	2/2 (100)
Ethnicity	
Hispanic or Latino	6/7 (85.7)
Not Hispanic or Latino	24/30 (80.0)

n/m = Number of patients with a favorable response/number of patients in the subgroup.

MO comment: *Adolescents had somewhat lower clinical response rates as compared to other pediatric subgroups. Otherwise, there are no significant numerical differences between various subgroups in clinical response rates.*

Table 36 Proportion of Invasive Candidiasis Patients With a Favorable Therapeutic Response at the End of Caspofungin Therapy by Various Subgroups (MITT), Study 043

	Favorable Response† n/m (%)
Infection Site	
Psoas muscle abscess	1/1 (100)
Multiple Sites	1/2 (50)
Blood	28/34 (82.4)
Underlying Disease (SOC/PT**)**	
Cardiac Disorders	1/1 (100)
Congenital, Familial and Genetic Disorders	7/8 (87.5)
Gastrointestinal Disorders	5/5 (100)
Immune System Disorders	1/1 (100)
Infections and Infestations	1/1 (100)
Neoplasms Benign, Malignant and Unspecified	7/12 (58.3)
Hematologic malignancy	2/5 (40.0)
Solid tumor	5/7 (71.4)
Nervous System Disorders	2/2 (100)
Renal and Urinary Disorders	1/1 (100)
Chronic renal insufficiency	1/1 (100)
Respiratory, Thoracic and Mediastinal Disorders	1/1 (100)
Transplantation (solid organ)	4/5 (80.0)
Neutropenic (ANC <500/mm3)	2/5 (40.0)
Non-neutropenic	28/32 (87.5)
Reason for enrollment	
Primary therapy	25/30 (83.3)
Salvage therapy	5/7 (71.4)

n/m = Number of patients with a favorable response/number of patients in the subgroup.

MO comment: *Efficacy rates observed in this study are in line and slightly higher than those observed in caspofungin study of adult patients with candidemia (73%). Also, caspofungin efficacy in neutropenic pediatric subjects was similar to the observed caspofungin efficacy in neutropenic adult subjects with candidemia (42.9%).*

Upon closer examination of the outcomes of candidemia in neutropenic subjects the following inconsistencies were identified:
Subject AN 6010 a 2yo white female with history of medulloblastoma on chemotherapy with ANC of 1 developed *C. tropicalis* candidemia (Day -2) manifested itself with fever up to 39C and tachycardia. While on caspofungin therapy her blood cultures have cleared from Day -1 on; however fever and tachycardia have not resolved upon treatment discontinuation on Day 10 (last day of study therapy). Investigator though documented complete clinical and mycological response on Day 10. The subject continued to receive caspofungin through Day 18, although neutropenia was documented to be resolved on Day 10. On Day 23 the subject was again neutropenic and febrile (Temp 38.3C) and was started on fluconazole, then switched to Ampho B on Day 26.

MO comment: *It appears that the subject failed clinically.*

Subject AN 6184, a 2yo black male with atypical teratoid tumor on chemo and radiation therapy profoundly neutropenic with ANC of 0 developed *C. topicalis* fungemia on Day -2 manifested by

fever. While on caspofungin treatment his fever resolved on Day 5, his cultures sterilized on Day 1 and then remained negative for the duration of the study. His neutropenia resolved on Day 8. He had a deterioration of his respiratory status requiring brief ICU admission on Day5 (Chest X-ray and CT revealed atelectasis vs pneumonia suspicious of fungal etiology). However, the subject was afebrile and in stable clinical condition on Day 10 (last day of study treatment). He was started on voriconazole on Day 11 upon hospital discharge through Day 48, and Amphotericin B was added on Days 33 and 34. His chest CT findings were improving/worsening on Day 18, then finally improving on Day 26. Coincidental recovery of the subject's neutrophil count might have contributed to the self-limiting brief clinical deterioration while on caspofungin treatment. It appears that the subject received insufficient duration of study therapy for the disseminated Candida infection (pulmonary and blood) to achieve a complete cure. However, due to premature discontinuation of the study drug the clinical outcome for the subject will have to remain a failure.

MO comment: *The Reviewer therefore assesses the efficacy in candidemia in neutropenic subjects as 1/5 (20%).*

Subject AN 6106, 17 year old black female with Crohn's disease and history of bacterial psoas abscess on ciprofloxacin prophylaxis developed RLQ tenderness and CT documented interim abscess size increase. Abscess was drained on Day -4 and the culture revealed *C. albicans.* The subject, however, was on piperacillin-tazobactam since D -9, limiting investigator's and Reviewer's ability to judge if the etiology of the abscess was due to any other concomitant bacterial organisms rather than Candida albicans alone. The subject underwent laparotomy and further debridement of the abscess, cecectomy, and intestinal re-anastomosis on Day 4 of the study. She received both caspofungin and piperacillin-tazobactam through Day 10 of the study. Complete response was documented by the investigator on Day 10, and mycological eradication was presumed on the same day. No relapses were documented on the Day 14 and 28 posttreatment follow-up visits.

MO comment: *The Reviewer identified the following confounding factors of the successful outcome in this case, where the subject was not neutropenic or fungemic at study enrollment or during study therapy: piperacillin-tazobactam pretreatment, concomitant broad spectrum antibacterial treatment, and surgical debridement of the abscess.*

Subject AN 6001, a 6 year old black female with cerebral palsy and recent surgery had candidemia due to *C. parapsilosis* received caspofungin for 5 days was discharged from the study site early on marketed caspofungin therapy for an additional 9 days. The study investigator documented complete clinical response and mycological eradication on Day 5, while the subject was still febrile. His fungal culture was negative on Days 1 and 4.

MO comment: *The Reviewer assesses this subject's clinical response as failure due to absence of fever resolution at the time of study treatment discontinuation. Mycological response remains eradication.*

Subject AN 6002, a 13 year old male with Down syndrome and feeding intolerance developed candidemia due to *C. albicans*. He received total of 9 days of study treatment with caspofungin. He could not complete caspofungin therapy due to being uncooperative with study procedures and was discharged home on marketed caspofungin therapy for additional 2 days. At the time of study drug discontinuation the investigator assigned him an outcome clinical success and mycological eradication. However, on Day 9 the subject was still febrile, and the only negative fungal blood culture that was drawn on Day 7.

MO comment: *The Reviewer assesses this subject's clinical response as failure due to absence of fever resolution at the time of study treatment discontinuation. Mycological response is indeterminate as there was only single negative blood culture available.*

MO comment: *Overall clinical response in candidemia, therefore, should be 26/36 (72.2%) instead of 30/37in pediatric patients with candidemia. It still remains comparable to that seen in adults (73%).*

Table 37 Proportion of Invasive Candidiasis Patients With a Favorable Clinical Response at the End of Caspofungin Therapy by Baseline Pathogen, MITT, Study 043

Pathogen	Caspofungin acetate (N = 37) n/m (%)
Candida albicans	11/13 (84.6)
Candida glabrata	4/4 (100)
Candida guilliermondii	1/1 (100)
Candida krusei	0/1 (0.0)
Candida lambica	2/2 (100)
Candida lusitaniae§	3/3 (100)
Candida parapsilosis§	7/8 (87.5)
Candida tropicalis	2/5 (40.0)

n/m = Number of patients with a favorable response/number of patients in the subgroup.

MO comment: *Lower clinical response rates were observed in subjects with C. tropicalis fungemia as compared to infections with other Candida isolates. As compared to adults clinical response rates were better for pediatric subjects with fungemia due to C. albicans (85 vs. 63%), C. glabrata (100 vs. 70%), C. parapsilosis (88 vs. 68%), while worse for infections due to C. tropicalis (40 vs. 84%) and C. krusei (0 vs. 100%).*

Table 38 Proportion of Invasive Candidiasis Patients with a Favorable Mycological Response,

MITT Population, Study 043

Time Point	Eradication n/m (%) (95% CI)	Presumptive Eradication n/m (%) (95% CI)	Total n/m (%) (95% CI)
End of caspofungin therapy	31	1	32/37 (86.5) (71.2, 95.5)

MO comment: *Overall there was a great degree of agreement between clinical and mycological outcomes. Discordant outcomes between clinical and mycological successes were observed in 2 subjects: subject AN 6189 with eradication of C. tropicalis from the bloodstream (Cx negative on Day 4 an 6) was discontinued from the study therapy due to suspected fungal pneumonia (clinical failure); subject AN 6020 with C. tropicalis fungemia achieved eradication of the pathogen from the bloodstream (Cx negative Days 1-7); however, he developed CNS lesions characteristic of disseminated candidiasis (clinical failure).*

Table 39 Proportion of Invasive Candidiasis Patients With a Favorable Mycological Response at the End of Caspofungin Therapy by Baseline Pathogen and its MIC, MITT, Study 043

Pathogen	Caspofungin MIC	Caspofungin acetate 70/50 mg/m2 (N = 37) n/m (%)
Candida albicans	0.03	3/4 (75.0)
	0.06	5/6 (83.3)
	0.12	2/2 (100)
Candida glabrata	0.03	1/1 (100)
	0.06	2/2 (100)
	0.12	1/1 (100)
Candida guilliermondii	0.25	1/1 (100)
Candida krusei	0.12	0/1 (0)
Candida lambica	0.12	1/1 (100)
	0.25	1/1 (100)
Candida lusitaniae	0.25	1/1 (100)
	0.5	1/1 (100)
	1	1/1 (100)
Candida parapsilosis	≤0.015	1/1 (100)
	0.12	1/2 (50.0)
	0.5	5/5 (100)
Candida tropicalis	≤0.015	1/1 (100)
	0.03	1/1 (100)
	0.06	1/1 (100)
	0.25	1/1 (100)

MO comment: *No apparent correlation of mycological response to baseline caspofungin MIC is apparent from the above tabulated data.*

Relapses

1 documented relapse among 28 successfully treated and followed for the duration of the study follow-up subjects occurred in a subject with candidemia due to *C. albicans.* He developed chills and fever on Day 27 posttreatment, and his blood culture was positive for *C. albicans, P. mirabilis, and S. aureus.*

6.2.1.6 Efficacy in Esophageal Candidiasis

Esophageal candidiasis

17 year old non-neutropenic male subject with history of allogeneic BMT for recurrent AML was symptomatic at study entry with dysphagia and odynophagia with both oropharengeal and esophageal lesions. He received caspofungin 70mg for 32 days and had complete resolution of his symptoms and pathologic lesions on esophagoscopy. Day 25 histopathology report on endoscopy specimen was free of fungal forms and the fungal culture was negative. The fungal isolate (*C. albicans* from local laboratory) was mishandled during shipping to the central laboratory; therefore, it was not available for MIC analysis. Relapse was not assessed at the 14 and 28 days posttherapy while the subject was on prophylactic therapy with sequential antifungals: fluconazole, voriconazole, and caspofungin through Day 88.

6.2.1.7 MO Conclusion on Efficacy

CONCLUSION

The efficacy data in pediatric patients with documented Candida and Aspergillus infections from Protocol 043 are compared with the corresponding efficacy data in adult patients in the following table.

Table 40 Comparative Assessment of Caspofungin Efficacy in Clinical Trials of Adults and Children for the Indications of Invasive Aspergillosis, Candidemia and other Candida Infections, and Esophageal Candidiasis, Study 043

	Caspofungin Treated Groups					
Treatment Indications	**Pediatrics Study 043 (open label, non-comparative)**			**Adult Studies (compassionate use and comparative)**		
	Protocol/dose	**n/m**	**Therapeutic Response % (95% CI)**	**Protocol/dose**	**n/m**	**Therapeutic Response % (95% CI)**
Invasive Aspergillosis	043 50 mg/m^2 ‖	5/10	50% (18.7, 81.3)	019 50mg#	46/96	47.9% (37.6, 47.9)
				50mg# (EP) ‡	37/83	44.6% (33.7, 55.9)
Invasive Candidiasis	043 50 mg/m^2 ‖	30/37	81.1% (64.8, 92.0)	014 50mg#	80/109	73.4% (65.1, 81.7)
Esophageal Candidiasis	043 50 mg/m^2 ‖	1/1	100% N/A	020 50mg	66/81	81.5% (71.3, 89.2)

n/m = Number of patients with a favorable response / Number of patients in the analysis.
‖ Patients received a loading dose of caspofungin 70 mg/m2 (maximum dose for treatment period =70 mg/day) on Day 1.
Patients received a loading dose of caspofungin 70 mg on Day 1.
‡ EP = Expert Panel assessment

This open-label non-comparative study provided supportive information, albeit limited, on efficacy of caspofungin at 70mg/m^2 LD /50mg/m^2 MD regimen in candidemia in non-neutropenic patients and in refractory invasive aspergillosis in 3 months to 17 years old pediatric patients. The efficacy rates were numerically similar to those historically observed in adult patients with similar indications treated with caspofungin at 70mg LD and 50mg MD regimen.

6.2.2 Study 044

Study Report 044: A Multicenter, Double-Blind, Randomized, Comparative Study to Evaluate the Safety, Tolerability, and Efficacy of Caspofungin versus AmBisome for Injection as Empirical Therapy in Pediatric Patients with Persistent Fever and Neutropenia.

6.2.2.1 Methods

INVESTIGATORS: 20 investigators, 17 of whom enrolled subjects

STUDY CENTERS: 20 centers 17/20 centers (8 U.S., 4 Germany, 4 Spain, and 1 Belgium) enrolled patients.

STUDY PERIOD: 11-June-2004 to 20-September-2006

OBJECTIVES: The **primary** objective was to estimate in pediatric patients, aged 2 to 17 years, with persistent fever and neutropenia, the proportion of patients treated with caspofungin reporting one or more clinical and/or laboratory drug-related adverse experience(s) during the study drug therapy period plus 14 days posttherapy.

Secondary objectives were to estimate:

1. The proportion of patients reporting one or more clinical and/or laboratory drug-related serious adverse experience(s) during the study drug therapy period plus 14 days posttherapy;
2. The proportion of patients reporting one or more clinical and/or laboratory drug-related adverse experience(s) leading to discontinuation of study therapy;
3. The proportion of patients with a favorable overall efficacy outcome.

Exploratory objectives were to evaluate:

1. The proportion of patients who reported one or more clinical or laboratory drug-related adverse experience(s) during the study drug therapy period;
2. The proportion of patients who meet each of the 5 individual criteria that make up the overall efficacy outcome;
3. The proportion of patients with a favorable composite efficacy outcome, based on 4 of the 5 individual criteria. Resolution of fever during the period of neutropenia will not be included in this composite efficacy outcome. In this way, the potentially disproportionate influence of fever resolution on the composite outcome will be removed. In the adult Phase III study, an exploratory analysis with the fever resolution endpoint excluded was performed and those results will serve as the comparison.

METHODOLOGY: A Multicenter, Double-Blind, Randomized, Comparative Study

NUMBER OF SUBJECTS: Total enrollment was 82 subjects.

STUDY DRUG: IV caspofungin acetate given as a loading dose of 70mg/m² on Day 1 and 50 mg/m² on Day 2 onward. The batch numbers for the caspofungin acetate and AmBisome are presented in the table below.

Table 41 The Appearance, Formulation, and Dosage Strength of the Study Drugs and respective placebo used in the Study 044

Study Drugs	Appearance	Formulation	Dose Unit	Batch numbers
Caspofungin acetate	white cake	Lyophilized Powder for injection	50mg/vial	MK-0991-HLS016B003 MK-0991-HLS016B005, MK-0991-HLS017B001, MK-0991-HLS017B004, MK-0991-HLS017B005, MK-0991-HLS017B006, MK-0991-WL00017427
Caspofungin placebo (Normal saline**)**	Clear liquid	Solution for infusion	0.9%	n/a
AmBisome (liposomal Amphotericin B)	Yellow cake	Lyophilized Powder for solution	50mg/vial	042350AA, 042347AD, 042455AD

AmBisome placebo (Multi-Vitamin Infusion (MVI) 5 mL/vial)	Yellow liquid	solution	5 mL/vial	119835, 122633

DURATION OF TREATMENT: Patients were treated until the resolution of neutropenia (absolute neutrophil count 500 cells/μL), and for up to 72 hours later. The maximum duration of empirical treatment was 28 days (up to 90 days if patient had documented invasive fungal infection).

TREATMENT COMPLIANCE: Study drug infusion information, including dosage and volume prescribed, and volume administered was collected daily.

STUDY DESIGN: This study was designed as a double-blind, double-dummy, and in-house blind, randomized, comparative study to evaluate the safety, tolerability, and efficacy of caspofungin versus AmBisome (liposomal amphotericin B) in the treatment of pediatric patients (2-17 years) with persistent fever and neutropenia.
Patients were stratified at study entry by risk status (high-risk or low-risk). Patients at high-risk were those who have undergone allogeneic hematopoietic stem-cell transplantation or those who have received chemotherapy for a relapse of acute leukemia. All others were low-risk. All patients received either: (1) caspofungin and placebo to AmBisome, or (2) AmBisome and placebo to caspofungin. Patients were assigned to a treatment group via a 2:1 (caspofungin to AmBisome randomization schedule.
Patients randomized to the caspofungin group received a 70 mg/m^2/day loading dose on day 1, followed by 50 mg/m^2/day on subsequent treatment days (maximum daily dose permitted was 70 mg). Patients in the AmBisome group were treated with 3mg/kg/day.
Patients without invasive fungal infection were treated until the resolution of neutropenia (absolute neutrophil count 500 cells/μL), and for up to 72 hours later. The maximum duration of empirical treatment was 28 days. If a longer duration of empirical therapy for an individual patient was warranted, the case was discussed with the Merck clinical monitor before Day 23 of therapy. For patients with documented invasive fungal infection, the duration of therapy was at the discretion of the investigator, but the recommended duration was at least 14 days, and at least 7 days after resolution of neutropenia and of symptoms, and for no longer than 90 days.
If, in the opinion of the investigator, a patient required dose escalation of study therapy, the dose could have been increased to either 70 mg/m^2/day for caspofungin plus placebo to AmBisome or to 5 mg/kg/day for AmBisome and placebo to caspofungin.
An Adjudication Committee (composed of external experts) reviewed blinded data from all cases of suspected invasive fungal infection for final determination of the presence of documented invasive fungal infection and clinical outcome of baseline invasive fungal infections.

SAMPLE SIZE
In previous adult studies, the rates of clinical and laboratory drug-related adverse experiences, respectively, were: 12.7% and 13.7% in invasive aspergillosis (Study 019); 28.9% and 23.7% in invasive candidiasis (Study 014); and, 41.0% and 28.9% in esophageal candidiasis (Study 020).Assuming the experience in children would be similar to that observed in the adult studies, one would expect, with 50 patients, rates of 29.9±12.7% (95% confidence) for clinical and 23.5±11.8% (95% confidence) for laboratory drug-related adverse experiences.

INCLUSION CRITERIA:

- Patient had received chemotherapy for leukemia, lymphoma, or other cancers or had undergone hematopoietic stem-cell transplantation.
- Patient has had an absolute neutrophil count <500/μL for at least 96 hours (the patient must not be expected to recover from neutropenia in the next 48 hours), and has received at least 96 hours of parenteral broad spectrum systemic antibacterial therapy preceding randomization, and has fever >38.0°C within the last 24 hours prior to randomization. Appropriate antibiotics included those that provide broad spectrum Gram-positive and Gram-negative coverage.
- Male or female patients were at least 2 years of age and less than 18 years of age at the time of initial screening.
- For female adolescents of childbearing potential, patient had a negative serum or urine pregnancy test sensitive to 25 IU HCG prior to enrollment into the study and subsequently use adequate birth control measures as defined by the investigator. (Note: Oral contraceptives were not to be used as the sole method of birth control because the effect of caspofungin on the efficacy of oral contraceptives has not yet been established. Patients who became pregnant during the study were to be discontinued from the study.)

EXCLUSION CRITERIA:

- Patient had an inadequately managed bacterial infection at the time of enrollment. In order to be eligible for enrollment, patients with documented bacterial infections must have had:
  - Negative blood culture results at the time of screening;
  - Received antibiotics to which any bacterial isolates were sensitive for at least 5 days prior to enrollment;
  - Surgical drainage of any abscess fluid or surgical debridement of infected tissues;
  - Removal of infected catheters
- Patients with bacterial infections who did not meet ALL of these criteria were considered to have inadequately managed bacterial infections and were not eligible for enrollment.
- Patient had a known documented invasive fungal infection at the time of enrollment.
- Patient had abnormal laboratory values:
  - Platelet count <5000/μL.
  - INR >1.6 (if patients were receiving anticoagulants, INR>4.0).
  - Bilirubin >3 times upper limit of normal for age.
  - AST (SGOT) or ALT (SGPT) >5 times the upper limit of normal for age.
- Patient had a history of allergy, hypersensitivity, or any serious reaction to echinocandin antifungal or an amphotericin B formulation.
- Patient had received any formulation of parenteral amphotericin B or any echinocandin within 10 days before the administration of the study drug.
- Patient was pregnant or breast-feeding.
- Patient had a diagnosis of acute or chronic hepatic disease or cirrhosis due to any cause.
- Patient had participated or was participating in any other clinical study involving the administration of an investigational antibiotic, antifungal, or immunosuppressive drug, within 14 days prior to study entry or during the course of the study. Use of investigational antineoplastic agents was prohibited only during the course of study therapy. Use of investigational drugs for cancer supportive care could be used only after discussion with the Merck clinical monitor.

- Patient had previously participated in this study.
- Patient had any condition or concomitant illness which, in the opinion of the investigator, might confuse the results of the study or pose additional risk in administering the study drugs to the patient.
- Patient was taking rifampin, cyclosporin A, or concomitant systemic antifungal therapy.

STUDY PROCEDURES: The schedule of clinical and laboratory assessments for study 044 is presented in the following table.

Table 42 Study 044 Flowchart

Clinic Visit ID:	Preliminary Screening	Randomization	Treatment Days								Follow-Up Assessment	
	Pre study Visit	Treatment Day 1	2	3	4	5	6	7	Continuing IV Antifungal Tx Past Day 7	Last Day of IV Antifungal Therapy†	7 Days After Discontinuation of Antifungal Tx	14 Days After Discontinuation of Antifungal Tx
Informed consent	X											
Medical history	X											
ECG‡	X											
Chest x-ray§	X											
Blood cultures	X%											
Physical examination	X	X			X			X	Every 3 days (twice weekly)	X	X	
Body temperatures (noninfusion and infusion)	X	X	X	X	X	X	X	X	Daily	X	X	
WBC and ANC#	X	X	X	X	X	X	X	X	Daily	X		X
Blood for safety#	X				X			X	Every 3 days (twice weekly)	X		X
Urine for safety#	X									X		
Monitor for adverse events	X	X	X	X	X	X	X	X	Daily	X	X	X
Plasma for drug levels††	X††				X ††			X	X††			
Assessment of signs and symptoms‡‡		X	X	X	X	X	X	X	Daily	X	X	

† Duration of IV treatment should have been according to criteria specified in text of protocol.
‡ ECG was to be completed within 4 weeks of study entry.
§ Chest radiograph (x-ray or CT) was to be completed within 2 days of study entry.
% Performed at screening and as clinically indicated.
¶ Procedures performed twice weekly during IV treatment.
# Safety labs excluding PT, PTT, INR, and hepatitis serology were to be completed within 2 days of study entry. PT/PTT/INR were to be completed within 4 days. For hepatitis serology, if there was documentation of positive serology anytime in the past, the tests did not need to be repeated. If serologic tests were negative and performed over 1 month from the date of randomization, they were to be repeated. Female adolescents of childbearing potential must have had a negative serum or urine pregnancy test (sensitive to 25 IU hCG) within 2 weeks of study entry.
†† A plasma blank for caspofungin drug levels was drawn at screening at all study sites. Pharmacokinetic samples were collected at all study sites preinfusion and within 5 minutes after the end of caspofungin/placebo infusion on Days 4, 7, 14. At a subset of study sites, 5-point plasma sampling for pharmacokinetics (predose, 1 hour, 2 hour, 4 hour, and 24 hour) was done on Day 4. Results of the pharmacokinetic analyses from blood (plasma) are summarized separately from this report.
‡‡ Assessment of signs and symptoms included radiographic studies/biopsies/cultures as clinically indicated.

EVALUATION OF EFFICACY

Efficacy assessments were based upon a 5-part composite endpoint.

A successful outcome, or favorable overall response, was defined as meeting all of the following endpoints:

1. Successful treatment of baseline invasive fungal infection, if any;
2. Absence of breakthrough invasive fungal infection up to 7 days posttherapy;
3. Survival to 7 days posttherapy;
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 counted as an unfavorable overall response.

Adjudication Committee assessments provided the basis for evaluation of 2 of the 5 endpoints: successful treatment of baseline invasive fungal infections, and absence of breakthrough invasive fungal infections up to 7 days posttherapy. As described in the protocol, the Adjudication Committee was responsible for the determination of likelihood ("possible", "probable", or "proven") of the invasive fungal infection, the timing of onset, and if baseline infection, the response to treatment (complete response and partial response successful treatment outcomes of baseline infections). Since all breakthrough invasive infections were considered as failures, the Adjudication Committee did not evaluate clinical responses for breakthrough infections.

Only probable and proven invasive fungal infections were considered to be documented infections and included in the study analyses.

REASONS FOR WITHDRAWAL:

1. The patient develops a serious clinical or and laboratory adverse experience related to study medication.
2. The patient or guardian refuses further treatment or follow-up and withdraws consent.
3. The patient requires treatment with investigational drugs other than the patient's antineoplastic or supportive care regimen.
4. Patient develops a breakthrough proven a probable fungal infection
5. Progression of pulmonary infiltrates on high dose study medication.
6. Any other reason, which may significantly affect the quality of the data.

STATISTICS:

This study was analyzed as an estimation study. Results were summarized by treatment group.

Sample size determination:

The primary safety evaluation was estimation of the proportion, and its associated 95% exact confidence interval, of pediatric patients in the caspofungin treatment group that reported any clinical or laboratory drug-related adverse experience during the study drug therapy period plus 14 days post-therapy. This evaluation was also done for the AmBisome group.

The actual incidence rates for clinical and laboratory drug-related adverse experiences in pediatric patients with persistent fever and neutropenia who were treated with caspofungin is unknown. In a previous study (Study 026) conducted in adults with persistent fever and neutropenia and treated empirically with caspofungin, the rates for clinical and laboratory drug-related adverse experiences were 47% and 22.5%, respectively. Using these figures as a guide and assuming the experience in children is similar to that of the adults, it was expected, with 67 patients in the caspofungin treatment group, rates of 47±12% (95% confidence) for clinical and 22.5±10% (95% confidence) for laboratory drug-related adverse experiences.

The main efficacy evaluation was the proportion of patients with a favorable overall response. A favorable overall response was defined as meeting each of the 5 individual criteria listed in the evaluation of efficacy section.

- For those patients with an invasive fungal infection (probable or proven) present at baseline (defined as those with onset up to the second day of study therapy), successful treatment outcome of the baseline invasive fungal infection. Patients without probable or proven baseline invasive fungal infections were assigned a successful outcome for this endpoint.
- Absence of breakthrough invasive fungal infections (probable or proven) (defined as those with onset on or after the third day of study therapy) during administration of the study drug or within 7 days after the end of treatment. Patients without probable or proven breakthrough invasive fungal infections were assigned a successful outcome for this endpoint.
- Survival for at least 7 days after the end of study drug therapy.
- Absence of premature discontinuation of the study drug because of study drug-related toxicity or lack of efficacy.
- Resolution of fever for 48 hours during the period of neutropenia.

Adjudication Committee assessments provided the basis for evaluation of 2 of the 5 endpoints: successful treatment of baseline invasive fungal infections, and absence of breakthrough invasive fungal infections up to 7 days posttherapy. The remaining endpoints were assessed based on data reported by the investigator in the patient database.

Analysis populations:

Modified Intention-to-Treat (MITT) Patient Population

Patients who:

1. During the prestudy period, either received chemotherapy for leukemia, lymphoma, or other cancers or had undergone hematopoietic stem-cell transplantation
2. Received at least 1 dose of active study therapy
3. Met the protocol-defined criteria for persistent fever and neutropenia.

The MITT patient population was the primary population for all efficacy evaluations.

Evaluable-Patient Population

The Merck Clinical Monitor, while still blinded to the patient treatment group assignments, identified those patients to be included in the evaluable-patient population, based on prespecified criteria. As outlined below, patients who had persistent fever and neutropenia, received the proper course of study therapy, and did not commit any protocol violations that would interfere with the assessment of efficacy were included in this population.

The following evaluability criteria were used to determine those patients to be included in the evaluable-patient population:

- The patient met the protocol-defined definitions for persistent fever and neutropenia.
- The patient must not have received:
  - Any parenteral formulation of amphotericin B or any echinocandin within 10 days prior to study drug receipt.
  - Systemic investigational antifungal within 14 days prior to study entry or during the course of study therapy.
  - Systemic antifungal treatment during study therapy or within 7 days poststudy therapy (unless the patient has already failed at least 1 of the 5 efficacy endpoints defined earlier

in this section). Note: Patients could receive antifungal medication as prophylaxis after the end of study therapy.

- The patient must have had a 7-day post-therapy follow-up visit (unless the patient had already failed at least 1 of the 5 efficacy endpoints defined earlier in this section).
- The patient received at least 4 doses of active study therapy.
- The patient did not commit any protocol violations that interfered with the assessment of efficacy.

The evaluable-patient population is supportive to the MITT patient population for assessing efficacy. Only the overall response (composite efficacy endpoint) and its 5 individual endpoint components were assessed using the evaluable-patient population.

EVALUATION OF SAFETY:

Safety and tolerability were assessed by statistical and clinical review of all safety parameters, including adverse experiences and laboratory values. To address the safety and tolerability, the following endpoints were assessed:

Primary Endpoint:

Clinical or laboratory (separately) drug-related adverse experience during the study drug therapy period plus 14 days post-therapy

Secondary Endpoints

- Clinical or laboratory (separately) drug-related serious adverse experience during study therapy and the 14-day post-therapy period;
- Clinical or laboratory (separately) drug-related adverse experience leading to discontinuation of study therapy;
- Systemic infusion-related adverse event during study drug infusion or within 1 hour following infusion;
- Development of nephrotoxicity during the study drug therapy period or within 14 days post-therapy.

Nephrotoxicity, as defined for this study, was a doubling of the serum creatinine relative to baseline or an increase of 1 mg/dL in serum creatinine if baseline serum creatinine was above the upper limit of normal for age. Any patient with renal failure and on dialysis at study entry was excluded from the evaluation of nephrotoxicity.

PROTOCOL CHANGES:

Protocol 044 was written and approved in 2003. There were no subsequent amendments to the protocol.

RESULTS

6.2.2.2 Patient Disposition

Study centers: 20 study centers; subjects were enrolled at 17/20 centers (8 U.S., 4 Germany, 4 Spain, and 1 Belgium).

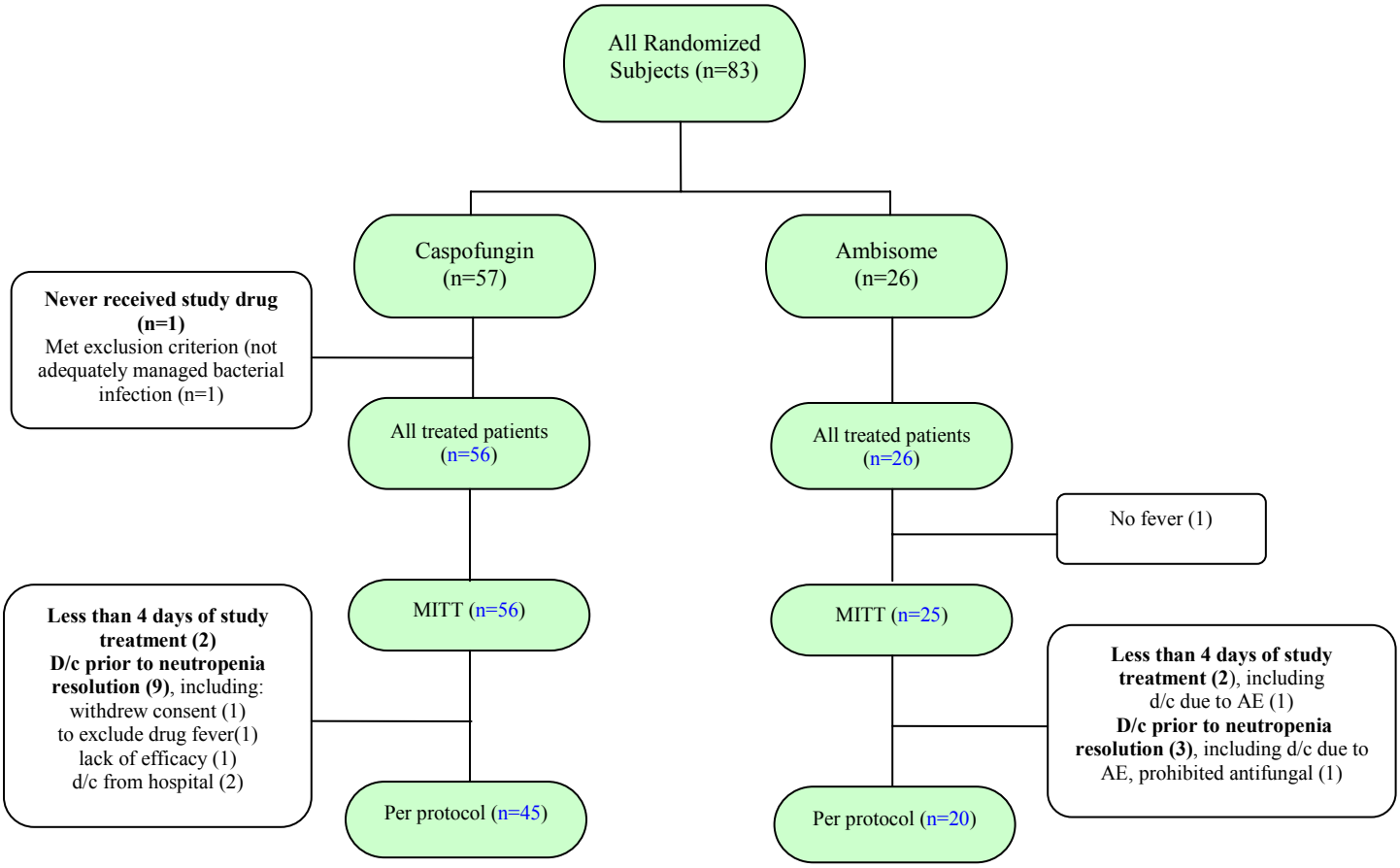
Total patients enrolled: 83 (82 received study treatment).

The subjects were from diverse geographical areas, represented by the following countries: 32 subjects (39%) from USA, 19 (23%) from Spain, 18 subjects (22%) from Germany, and 14 subjects (17%) from Belgium. Each of the following 2 study sites randomized more than 10% of all study subjects: 1 and 9 (clinical investigators: ---------- and ---------- .
Total of 4/17 clinical investigators have disclosed their financial interests.

The following flowchart and the tables summarize the composition of the applicant's populations for analysis, the primary reasons for exclusion and the demographics of the study population.

Figure 2 Subject's Disposition

Appears This Way On Original



MO comment: *The Reviewer identified 2 subjects on Ambisome arm that discontinued study therapy after the first dose of the study medication due to hypersensitivity reaction (4120 and 4154), but were included in the evaluable population. The Sponsor was requested to clarify.*

6.2.2.3 Demographic and Baseline Characteristics

Table 44 Demographic characteristics, All Treated Subjects (044)

	Caspofungin 70/50 mg/m2 (N = 56)		AmBisome™ 3.0 mg/kg (N = 26)		Total (N = 82)	
	n	(%)	n	(%)	n	(%)
Gender						
Male	35	(62.5)	20	(76.9)	55	(67.1)
Female	21	(37.5)	6	(23.1)	27	(32.9)
Race						
American Indian or Alaska Native	2	(3.6)	3	(11.5)	5	(6.1)
Black, of African heritage	4	(7.1)	2	(7.7)	6	(7.3)
Multi-racial	2	(3.6)	0	(0.0)	2	(2.4)
White	48	(85.7)	21	(80.8)	69	(84.1)
Ethnicity						
Hispanic or Latino	5	(8.9)	4	(15.4)	9	(11.0)

Not Hispanic or Latino	51	(91.1)	22	(84.6)	73	(89.0)
Age (years)						
2 to 6	29	(51.8)	14	(53.8)	43	(52.4)
7 to 11	15	(26.8)	4	(15.4)	19	(23.2)
12 to 17	12	(21.4)	8	(30.7)	20	(24.4)
Mean ± SD		7.4±4.5		7.4±4.9		7.4±4.6
Median		6.0		5.5		6.0
Range		2 to 16		2 to 16		2 to 16

MO comment: *study subjects tend to be white males under 7 years of age. Overall there were no significant imbalances in demographic characteristics between the study arms.*

Table 45 Baseline Patient Characteristics (044)

	Caspofungin 70/50 mg/m2 (N = 56)		**AmBisome™ 3.0 mg/kg (N = 26)**		**Total (N = 82)**	
	n	**(%)**	**n**	**(%)**	**n**	**(%)**
Primary Condition †						
Acute Leukemia						
Acute myelogenous leukemia	18	(32.1)	10	(38.5)	28	(34.1)
Acute lymphocytic leukemia	16	(28.6)	7	(26.9)	23	(28.0)
Lymphoma						
Hodgkin's lymphoma	1	(1.8)	0	(0.0)	1	(1.2)
Non-Hodgkin's lymphoma	5	(8.9)	4	(15.4)	9	(11.0)
Solid tumor	16	(28.6)	4	(15.4)	20	(24.4)
Other	0	(0.0)	1	(3.8)	1	(1.2)
Transplant Type ‡						
Allogeneic hematopoietic stem cell transplant						
Bone marrow	3	(5.4)	0	(0.0)	3	(3.7)
Peripheral stem cell	3	(5.4)	3	(11.5)	6	(7.3)
Autologous hematopoietic stem cell transplant						
Bone marrow	4 (7.1)		0 (0.0)		4 (4.9)	
Peripheral stem cell	10 (17.9)		1 (3.8)		11 (13.4)	
Risk Category						
High Risk	15	(26.8)	7	(26.9)	22	(26.8)
Allogeneic HSCT §	6	(10.7)	3	(11.5)	9	(11.0)
Chemotherapy for relapse of acute leukemia	9	(16.1)	4	(15.4)	13	(15.9)
Low Risk	41	(73.2)	19	(73.1)	60	(73.2)
Antifungal Prophylaxis Status						
Antifungal prophylaxis	28 (50.0)		14 (53.8)		42 (51.2)	
No antifungal prophylaxis	28 (50.0)		12 (46.2)		40 (48.8)	
Neutropenic Status (cells/microliter)						
ANC < 100	40 (71.4)		19 (73.1)		59 (72.0)	
ANC 100 to 250	13 (23.2)		7 (26.9)		20 (24.4)	
ANC 251 to 500	3 (5.4)		0 (0.0)		3 (3.7)	
Duration of Neutropenia Prior to Study Entry (days)						
4 to 7	23 (41.1)		13 (50.0)		36 (43.9)	
>7	33 (58.9)		12 (46.2)		45 (54.9)	

† Primary Condition Categories: "Solid tumor" includes Bone sarcoma, Brain neoplasm malignant, Cerebellar tumour, Ewing's sarcoma, Medulloblastoma, Medulloblastoma recurrent, Nephroblastoma, Neuroblastoma, Rhabdomyosarcoma. "Other" includes Aplastic anaemia.
‡ Patients with more than one type of transplant are counted under each specific type of transplant.
§ Patients with allogeneic hematopoietic stem cell transplant (HSCT) who had received chemotherapy for relapse of acute leukemia are counted only in the Allogeneic HSCT row.
AN 4157 had 3 days of documented neutropenia and is not included in the "Duration of Neutropenia Prior to Study Entry" count.

MO comment: *Both groups were comparable in baseline patient characteristics: risk category, prior antifungal prophylaxis, neutropenia degree.*

Table 46 Secondary Diagnoses (044)

	Caspofungin 70/50 mg/m2 (N = 56)		AmBisome™ 3.0 mg/kg (N = 26)	
	n	**(%)**	**n**	**(%)**
Patients With One Or More Secondary Diagnoses	56	(100.0)	26	(100.0)
Patients With No Secondary Diagnoses	0	(0.0)	0	(0.0)
Blood And Lymphatic System Disorders	31	(55.4)	15	(57.7)
Cardiac Disorders	20	(35.7)	7	(26.9)
Eye Disorders	11	(19.6)	1	(3.8)
Gastrointestinal Disorders	48	(85.7)	20	(76.9)
General Disorders And Administration Site Conditions	39	(69.6)	16	(61.5)
Hepatobiliary Disorders	11	(19.6)	5	(19.2)
Immune System Disorders	17	(30.4)	5	(19.2)
Infections And Infestations	37	(66.1)	18	(69.2)
Injury, Poisoning And Procedural Complications	8	(14.3)	2	(7.7)
Metabolism And Nutrition Disorders	29	(51.8)	14	(53.8)
Musculoskeletal And Connective Tissue Disorders	10	(17.9)	6	(23.1)
Neoplasms Benign, Malignant And Unspecified (Including Cysts And Polyps)	56	(100.0)	25	(96.2)
Nervous System Disorders	20	(35.7)	9	(34.6)
Psychiatric Disorders	10	(17.9)	3	(11.5)
Renal And Urinary Disorders	13	(23.2)	8	(30.8)
Reproductive System And Breast Disorders	3	(5.4)	3	(11.5)
Respiratory, Thoracic And Mediastinal Disorders	28	(50.0)	13	(50.0)
Skin And Subcutaneous Tissue Disorders	31	(55.4)	10	(38.5)
Vascular Disorders	21	(37.5)	8	(30.8)

MO comment: *The study population was sufficiently sick at baseline with almost all subjects having > 1 secondary diagnoses.*

Table 47 Number (%) of Patients with Specific Prior Therapies (Incidence ≥9.0% in One or More Treatment Groups) by Drug Category (044)

	Caspofungin 70/50 mg/m2 (N = 56)		AmBisome™ 3.0 mg/kg (N = 26)	
	n	(%)	n	(%)
Antiinfectives For Systemic Use				
Antibacterials For Systemic Use	***56***	***(100.0)***	***26***	***(100.0)***
Antimycotics For Systemic Use	***33***	***(58.9)***	***17***	***(65.4)***
Amphotericin B	8	(14.3)	5	(19.2)
Fluconazole	25	(44.6)	11	(42.3)
Itraconazole	8	(14.3)	5	(19.2)
Antivirals For Systemic Use	***20***	***(35.7)***	***5***	***(19.2)***
Immune Sera And Immunoglobulins	***8***	***(14.3)***	***3***	***(11.5)***
Globulin, Immune	6	(10.7)	2	(7.7)
Antineoplastic And Immunomodulating Agents				
Antineoplastic Agents	***55***	***(98.2)***	***26***	***(100.0)***
Immunostimulants	***27***	***(48.2)***	***11***	***(42.3)***
Filgrastim	18	(32.1)	9	(34.6)
GCSF	5	(8.9)	2	(7.7)
Systemic Hormonal Preparations, Excl. Sex Hormones And Insulin				
Corticosteroids For Systemic Use	***39***	***(69.6)***	***21***	***(80.8)***

MO comment: *there were no differences noted between the study arms with regard to the groups of the antibiotics used, i.e. penicillins, cephalosporins, glycopeptides, aminoglycosides, etc. The study arms were also well balanced in terms of immunosuppressive and immunostimulant medications received.*

Table 48 Discontinuations from study therapy, All Treated Subjects population (044)

	Caspofungin 70/50 mg/m2 (N = 56)		AmBisome™ 3.0 mg/kg (N = 26)		Total (N = 82)	
	n	(%)	n	(%)	n	(%)
COMPLETED THERAPY†:	**46**	**(82.1)**	**19**	**(73.1)**	**65**	**(79.3)**
DISCONTINUED THERAPY:	**10**	**(17.9)**	**7**	**(26.9)**	**17**	**(20.7)**
clinical AE	3	(5.4)	5	(19.2)	8	(9.8)
lack efficacy	3	(5.4)	1	(3.8)	4	(4.9)
patient discontinued for other‡	3	(5.4)	1	(3.8)	4	(4.9)
patient withdrew consent	1	(1.8)	0	(0.0)	1	(1.2)
DISCONTINUED THERAPY Protocol defined as a part of the primary endpoint	**6**	**(10.8)**	**4**	**(15.3)**	**10**	**(12.3)**
Lack of efficacy	3	(5.4)	1	(3.8)	4	(4.9)
Drug related toxicity*	2	(5.4)	3	(11.5)	6	(7.4)
COMPLETED STUDY§:	**56**	**(100)**	**25**	**(96.2)**	**81**	**(98.8)**
DISCONTINUED STUDY:	**0**	**(0.0)**	**1**	**(3.8)**	**1**	**(1.2)**
clinical AE	0	(0.0)	1	(3.8)	1	(1.2)

† "Completed Therapy" is defined as having a status of "patient continues trial" on the last day of study therapy.
‡ "Other" reasons for discontinuation of study therapy were as follows: caspofungin group – patient discharged from hospital (AN 4170 and AN 4225) and 'to exclude drug-induced fever' (AN 4007); AmBisome™ group- 'primary MD stopped antifungal therapy'
* AEs that were reported by the investigator definitely, probably, or possibly related to the study drug.
§ "Completed Study" is defined as completion of the 14 Day Follow-up visit period.

MO comment: *greater number of subjects on Ambisome arm discontinued study therapy and they did so primarily due to clinical adverse events. On caspofungin arm the reasons for discontinuation were more diverse; however, there were more treatment discontinuations due to lack of efficacy (total of 5(8.9%)): 3 listed in the table above and 2 additional patients: AN 4007 who is listed as discontinued on Day 20 to r/o drug-fever obviously continued to be febrile and neutropenic and AN 4009 listed as withdrawn consent on Day 7 also continued to be febrile on Day 14 when he expired due to probable pulmonary aspergillosis. Discontinuations on Ambisome arm due to drug related toxicity (part of a composite primary endpoint were hypersensitivity reactions and LFT abnormalities which could have been attributed to either study drug. On caspofungin arm drug related toxicities resulted in treatment discontinuation were rash and hypotension, latter experienced during Ambisome placebo (multivitamin solution) infusion. The frequency of adverse event discontinuations is comparable to the adult ETFN study 026.*

Table 49 Number (%) of Patients with Specific Concomitant Therapies (Incidence ≥9.0% in One or More Treatment Groups) by Drug Category - Treatment and Follow-Up Phases (044)

	Caspofungin 70/50 mg/m2 (N = 56)		AmBisome™ 3.0 mg/kg (N = 26)	
	n	(%)	n	(%)
Antiinfectives For Systemic Use				
Antibacterials For Systemic Use	***56***	***(100.0)***	***26***	***(100.0)***
Antimycotics For Systemic Use	***31***	***(55.4)***	***16***	***(61.5)***
Amphotericin B	8	(14.3)	4	(15.4)
Caspofungin Acetate	3	(5.4)	4	(15.4)
Fluconazole	19	(33.9)	6	(23.1)
Itraconazole	6	(10.7)	4	(15.4)
Antivirals For Systemic Use	***26***	***(46.4)***	***5***	***(19.2)***
Immune Sera And Immunoglobulins	***7***	***(12.5)***	***6***	***(23.1)***
Globulin, Immune	***6***	***(10.7)***	***6***	***(23.1)***
Antineoplastic And Immunomodulating Agents				
Antineoplastic Agents	***19***	***(33.9)***	***12***	***(46.2)***
Immunostimulants	***29***	***(51.8)***	***15***	***(57.7)***
Filgrastim	21	(37.5)	13	(50.0)
Granulocyte Colony Stimulating Factor (Unspecified)	8	(14.3)	2	(7.7)
Systemic Hormonal Preparations, Excl. Sex Hormones And Insulin				
Corticosteroids For Systemic Use	***25***	***(44.6)***	***18***	***(69.2)***

MO comment: *there were no significant differences noted between the study arms with regard to the groups of the antibiotics used during the study treatment and follow-up. It appears that on caspofungin arm immunosuppressive and immunostimulant medications were used on a smaller scale as compared to Ambisome.*

Concomitant use of systemic antifungal therapy during study therapy was prohibited by the protocol; however, patients were permitted to receive antifungal therapy as secondary prophylaxis after the conclusion of the study therapy regimen. Patients who failed study therapy were also frequently changed to an alternative antifungal regimen. 10 patients received non-systemic Amphotericin B preparations. In 2 patients, the use of systemic amphotericin B was limited to the period after the completion of study drug therapy. Only 1 patient received sustained treatment with prohibited

antifungal therapy during the period of study therapy. Patient AN 4012 received itraconazole concurrently with AmBisome™ during the entire study therapy period. This patient was excluded from the evaluable patient population.

Table 50 Duration of Study Therapy by Treatment Group, Risk Category, and Prior Antifungal Prophylaxis Status (044)

	Caspofungin 70/50 mg/m2				AmBisome™ 3.0 mg/kg			
	n	**Range**	**Mean**	**Median**	**n**	**Range**	**Mean**	**Median**
All Patients Treated	56	3 to 36	11.6	9	26	1 to 55	11.4	9
High Risk (overall)	**15**	**3 to 36**	**13.6**	**10**	**7**	**1 to 55**	**13.9**	**9**
Prophylaxis	7	8 to 36	13.4	10	7	1 to 55	13.9	9
No prophylaxis	8	3 to 28	13.8	10	0			
Low Risk (overall)	**41**	**3 to 33**	**10.9**	**9**	**19**	**2 to 50**	**10.5**	**9**
Prophylaxis	21	4 to 28	10.9	9	7	2 to 50	14.7	9
No prophylaxis	20	3 to 33	10.9	9	12	2 to 13	8.1	9

MO comment: *The duration of the study therapy did not significantly differ between the study arms regardless of the risk category or prophylaxis status in the high risk category. In the lower risk category subjects on the Ambisome arm tend to have longer study treatment duration 14.7 vs. 10.9 days*

The dosage of study drug could have been increased, at the discretion of the investigator, for patients who tolerated study drug, if (1) fevers persisted for at least 5 days of study therapy and (2) there was clinical deterioration (defined as the development of hypotension, tachypnea, hypoxemia, worsening fevers or rigors not associated with drug infusion, new infiltrates on chest radiographs, or new signs or symptoms of lung consolidation); and if appropriate radiographic studies, cultures, biopsies, and/or histopathology studies did not provide an alternative explanation for the clinical deterioration. Three patients had study drug increased due to inadequate clinical response; 1 (1.8%) (AN 4156) of the 56 patients in the caspofungin group and 2 (7.7%) (patients: AN 4012 and AN 4152) of the 26 patients in the AmBisome™ group.

RESULTS

Efficacy

6.2.2.4 Efficacy, Primary Endpoint, Sensitivity Analyses

The main efficacy outcome measure for this study was the proportion of patients with a favorable overall response at the end of study therapy.

Table 51 Proportion of Patients with a Favorable Overall Response Adjusted for Risk Category Modified Intention-to-Treat Patient Population, MITT (044)

per updated efficacy dataset (mittover) submitted 4/25/08

Endpoint	**Caspofungin 70/50 mg/m2 (N = 56) Estimated Response n (%), [95% CI]**	**AmBisome™ 3.0 mg/kg (N = 25) Estimated Response n (%),[95% CI]**

Favorable Response (overall)	26 (46.4), [33.4, 59.5]	8 (32.0), [13.7, 50.3]
High Risk	9/15 (60.0)	0/7 (0.0)
Low Risk	17/41 (41.5)	8/18 (44.4)
Successful treatment of baseline infection†	0/1 (0.0)	----
Absence of breakthrough fungal infection	56/56 (100)	24/25 (96.0), [88.3, 100]
Survival to 7-day follow-up	56/56 (100)	25/25 (100)
Completed therapy or non-endpoint discontinuation	51/56 (91.1), [83.6, 98.5]	21/25 (84.0), [69.6, 98.4]
Resolution of fever during neutropenia	27/56 (48.2), [35.1, 61.3]	9/25 (36.0), [17.2, 54.8]

MO comment: *Caspofungin arm performed overall better than Ambisome on the composite endpoint and each of its individual components. Slightly better outcome was noticed on Ambisome arm only in the subgroup of subjects in low risk category. This finding is of unknown clinical significance especially in lieu of small sample size.* ------------- ---------------------------- --------------------------
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The review team has identified 4 subjects where the closer look at the primary endpoint components and listings for resolution of fever, neutropenia and reason for study discontinuation did not match. Subject 4121 on Ambisome arm in the analysis datasets is reported as have received 1 day worth of study treatment and therefore had been assigned an outcome of failure due to premature discontinuation and inability to resolve fever for 48h prior to discontinuation. In the listings dataset this subject was reported to have received 13 days worth of study therapy and the fever has resolved on day 7. Subject' neutropenia was not recorded after day 6; however the subject recovered his neutrophil count on Day 20 (7 day follow-up visit). One might argue that this subject should not have been evaluable, but should have had an outcome of success.

MO comment: *in the revised MITT analysis dataset the Sponsor converted this subject's outcome to success.*

In subject 4135 on Ambisome arm ANC was recorded at 500/mm3 on Day 5 of therapy; however, it dipped at 456 on Day 7, then completely recovered at >500 on Day 8 and subsequent follow-up. The fever in this subject also resolved on Day 5. The study drug was continued to be administered until day 8, when fever was resolved for >48h in the subject who was still neutropenic. The Sponsor assigned an outcome of failure to this subject, although he met definition of success.

Subject 4155 on caspofungin arm was determined to have a possible baseline fungal infection (pneumonia) by Adjudication committee that has not improved while on study treatment. Clinical investigator reported an adverse event of fungal infection on Day 14 that eventually lead to treatment discontinuation, as the event would not resolve by Day 36 of study treatment. The Sponsor determined the outcome for this subject to be a success despite the fact that the subject discontinued due to the failure of the study drug to cure/improve concomitant fungal infection whether baseline or breakthrough.

Subject 4159 on caspofungin arm has achieved ANC of >500/mm3 on Day 6, while his fever resolved on Day 4. The study treatment was continued through Day 7. Although there was no record on the subject's neutropenia status on Day 5, certainly on the last day of study therapy the subject

was not neutropenic or febrile (for >48h). The Sponsor assigned a failure outcome to this subject. It appears that favorable outcome is more prudent in this case.
The Sponsor was asked to clarify the above discrepancies. Even if the outcomes were to be re-assigned for the above subjects, it will not affect the total number of successes on the caspofungin arm. Two additional favorable outcomes on Ambisome arm will improve overall response rates for the comparator arm; however it will still be numerically lower than that of caspofungin. The overall response to study treatment for both study arms is numerically higher than the response documented from the historical trials of the same design in adults, which is consistent with published epidemiologic data on antifungal treatment of candidemia.1 As determination of caspofungin efficacy is an exploratory objective of the study and it was planned to be and is not statistically substantiated, Reviewer elects to retain Sponsor's assignments of the outcomes from now on for the duration of the review.

Table 52 Overall Response with Alternative Definitions of Fever Resolution, MITT (044)

per updated efficacy dataset (mittover) submitted 4/25/08

	Cancidas™ (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)

MO comment: *Slight numerical difference in overall response between the study groups favoring caspofungin remained fairly constant throughout application of various definitions of fever resolution except for elimination of fever resolution from the endpoint definition where the difference was the smallest of 5%. Of note, in adults, exclusion of fever resolution from the composite endpoint statistically favored caspofungin over Ambisome.*

Table 53 Proportion of Patients with a Favorable Overall Response Adjusted for Risk Category Modified Intention-to-Treat Patient Population, Evaluable (044)

per updated efficacy dataset (evalover) submitted 4/25/08

Endpoint	Caspofungin 70/50 mg/m2 (N = 45) Estimated Response n (%), [95% CI]	AmBisome™ 3.0 mg/kg (N = 20) Estimated Response n (%),[95% CI]
Favorable Response (overall)	18 (40), [25.7, 54.3]	6 (30.0), [9.9, 50.1]
High Risk	8/14 (57.1)	0/6 (0.0)
Low Risk	10/31 (32.3)	6/14 (42.9)
Successful treatment of baseline infection†	----	----
Absence of breakthrough fungal infection	45/45 (100), [92.1, 100]	19/20 (95.0), [75.1, 100]
Survival to 7-day follow-up	56/56 (100) , [92.1, 100]	25/25 (100) , [83.2, 100]
Completed therapy or non-endpoint discontinuation	41/45 (91.1), [78.8, 97.5]	17/20 (85.0), [62.1, 96.8]
Resolution of fever during neutropenia	18 (40), [25.7, 54.3]	7/20 (35.0), [14.1, 55.9]

MO comment: *Overall response results and the results of the individual components of the composite primary endpoint in the evaluable population closely follow results in the MITT population.*

Dose adjustment for inadequate clinical response

At the discretion of the investigator, the dosage of blinded study drug could be increased for patients who tolerated study drug, if (1) their fevers persisted for at least 5 days of study therapy; (2) there was clinical deterioration (defined as the development of hypotension, tachypnea, hypoxemia, worsening fevers or rigors not associated with drug infusion, new infiltrates on chest radiographs, or new signs or symptoms of lung consolidation); and (3) if appropriate radiographic studies, cultures, biopsies, and/or histopathology studies could not provide an alternative explanation for the clinical deterioration. For caspofungin, the dosage was increased from 50 to 70 mg/m2/day (with a maximum daily dose of 70 mg), and for AmBisome™, from 3 to 5 mg/kg/day. The higher dose was maintained until therapy was discontinued or drug-related toxicity occurred. If drug-related toxicity developed, the dose could be reduced to the standard dose.

Table 54 Treatment outcome after dose adjustment for inadequate clinical response (044)

Subject AN	Day of dose increase	Day of Rx discontinuation	Overall Response	Reason for Unfavorable Response
		Caspofungin		
4156	15	26	Favorable	n/a
		Ambisome		
4012	6	10	Unfavorable	Early d/c due to toxicity (hyperbili)
4152	52	55	Unfavorable	Early d/c due to lack of efficacy

The size of the study is sufficiently small to meaningfully evaluate therapeutic response in different age, race, ethnic subgroups. However, descriptive subgroup analyses are provided in the table below. Additional sensitivity analyses were performed to include "possible" infections into the definition of failure whether failure to treat "possible" baseline fungal infection or having a "possible" breakthrough fungal infection.

Sensitivity analyses

Additional sensitivity analyses were performed to include "possible" infections into the definition of failure whether failure to treat "possible" baseline fungal infection or having a "possible" breakthrough fungal infection.

Table 55 Proportion of Patients with a Favorable Overall Response (including possible fungal infections) Modified Intention-to-Treat Patient Population, MITT (044)

	Study 044 (Pediatric subjects 2-17 years)		**Study 026 (Adult subjects)**	
Endpoint	**Caspofungin 70/50 mg/m2 (N = 56) Estimated Response n (%), [95% CI]**	**AmBisome™ 3.0 mg/kg (N = 25) Estimated Response n (%),[95% CI]**	**Caspofungin 70/50 mg (N = 556) Estimated Response n (%)**	**AmBisome™ 3.0 mg/kg (N = 539) Estimated Response n (%)**
Favorable Response (overall)	25 (44.6), [31.3, 58.5]	8 (32.0), [13.7, 50.3]	171 (30.8)	171 (31.7)
Successful treatment of baseline infection	0/4 (0.0)	1/1	32/73 (43.8)	38/85 (44.7)
Absence of breakthrough fungal	55 (98.2)	24 (96.0),	491 (88.3)	497 (92.2)

infection		[88.3, 100]	
Survival to 7-day follow-up	56 (100)	25 (100)	515 (92.6)
Completed therapy or non-endpoint discontinuation	51 (91.1), [83.6, 98.5]	21/ (84.0), [69.6, 98.4]	499 (89.8)
Resolution of fever during neutropenia	27 (48.2), [35.1, 61.3]	9 (36.0), [17.2, 54.8]	229 (41.2)

MO comment: *The numbers of fungal infections whether confirmed, probable, or possible are small due to the study size. One of the subjects with a possible baseline fungal infection (pneumonia) AN 4155 remained febrile on and off for the duration of her neutropenia and discontinued the drug due to adverse event of fungal infection, although not considered drug related toxicity, but clearly representing a failure of caspofungin to cure/improve the fungal infection at baseline. Overall favorable treatment response was greater and sustained through the sensitivity analyses on the caspofungin arm as compared to Ambisome. Absence of successful treatment outcome in any of 4 subjects with suspected baseline fungal infection (primarily fungal pneumonia) is of some concern. However, the study was not designed to evaluate caspofungin efficacy in invasive aspergillosis which would require significantly longer treatment duration than that of empiric coverage of febrile neutropenia. Also, additional information on estimates of efficacy in refractory aspergillosis in children is available from an open-label study of invasive fungal infections, study 043, where successful treatment was observed in 5/10 pediatric subjects ages 2-17 years with invasive aspergillosis.*

The size of the study is sufficiently small to meaningfully evaluate therapeutic response in different age, race, and ethnic subgroups. However, descriptive subgroup analyses are provided in the table below.

6.2.2.5 Efficacy, Subgroup analyses

Table 56 Subgroup Analyses Overall Response, MITT (044)

Subgroups	Treatment Group	
	Caspofungin	Ambisome
Gender		
Male	15/35 (42.9)	5/19 (26.3)
Female	11/21 (52.4)	3/6 (50.0)
Ages		
2-6	10/29 (34.5)	7/14 (50.0)
7-11	6/15 (40.0)	0/4 (0.0)
12-17	10/12 (83.3)	1/7 (14.3)
Race		
White	20/48 (41.7)	7/20 (35.0)
Other	6/8 (75.0)	1/5 (20.0)
Antifungal Prophylaxis		
Prior prophylaxis	11/28 (39.3)	4/13 (30.8)
No prophylaxis	15/28 (53.6)	4/12 (33.3)
Risk Category		
High Risk	9/15 (60.0)	0/7 (0.0)
Low Risk	17/41 (41.5)	8/18 (44.4)

MO comment: *Overall results of subgroup analyses are comparable but numerically higher than previously reported in adults. The overall numerically higher rates of favorable response are seen in caspofungin arm as compared to Ambisome across the different subgroups with the exception of subjects younger than 6 years and those in the low risk category. Of interest, a trend towards increasing efficacy with the increasing age is seen in caspofungin treated subjects. The Sponsor did not provide efficacy analyses by age, race, or gender; therefore, the study report also does not bear any discussion on the above finding. The Reviewer examined the reasons for failure among the younger (2-6year olds and 7-11 year olds) versus 12-17year olds in both study arms. No imbalances in premature discontinuations (part of the efficacy endpoint) overall and discontinuations due to adverse events were identified. All subject survived through 7 day follow-up. The primary reason for failure was persistent fever while on study therapy (part of the efficacy endpoint) which is reflected in the overall efficacy outcome. PK analyses demonstrated sufficiently similar levels of caspofungin exposure in pre-adolescents (2-11year olds) compared to adolescents (12-17 year olds). The table below describes the reviewer findings.*

Table 57 Comparative assessment of the risk factors in pediatric age groups (044)

Factors examined	2-6 year olds		7-11 year olds		12-17 year olds	
	Caspofungin N=29 (%)	Ambisome N=14 (%)	Caspofungin N=15 (%)	Ambisome N=4 (%)	Caspofungin N=12 (%)	Ambisome N=7 (%)
Hematologic malignancies	13 (45)	9 (64)	11 (73)	4 (100)	10 (83)	4 (57)
High risk category	2 (7)	2 (14)	9 (60)	2 (50)	4 (33)	3 (43)
Discontinuation all causes	3 (10)	1 (7)	2 (13)	2 (50)	0	1 (14)
Discontinuations due to AEs	1 (3)	1 (7)	1 (7)	2 (50)	0	1 (14)

MO comment: *As presented in the above table, the younger subgroup of caspofungin subjects had the lowest number of hematologic malignancies, the lowest number of subjects in high risk category, as compared to the older age subgroups on caspofungin arm and as compared to Ambisome arm in the same age subgroup. Also, a single subject in the youngest subgroup on caspofungin arm had discontinued due to adverse event as a part of the overall response as compared to a single subject in 7-11 year old subgroup on caspofungin arm and none in 12-17 year old subgroup. The lowest efficacy outcome in the youngest age group does not appear to be dependent either on unfavorable safety profile of caspofungin in this age group (also not supported by close similarity of caspofungin exposures across age groups), or on the higher incidence of underlying conditions predisposing subjects for poor outcome (hematologic malignancies or overall high risk category). As the efficacy endpoint is a composite and the study population by definition excludes cases of confirmed fungal infection, the Reviewer interprets the lower caspofungin efficacy in the youngest age subgroup as a reflection of greater uncertainty of fungal etiology of febrile neutropenia in this age group.*

MO Conclusion on Efficacy

CONCLUSION

This small randomized double blind study of caspofungin at 70 mg/m^2/day LD /50mg/m^2/day MD in empiric therapy of presumed fungal infections in febrile neutropenic pediatric subjects as compared to Ambisome 3-5mg/kg/day, demonstrated favorable outcomes in caspofungin arm that are comparable and numerically higher than that of historical trials of a similar design in adults. The study was not designed nor powered to show non-inferiority or superiority of caspofungin regimen

to that of Ambisome. However, the results of this study maintain caspofungin response rate numerically above the rate of Ambisome as was seen in adults. It holds true for the overall composite response, each individual component of the response, and in the majority of the subgroup analyses.
The study provides supportive evidence of caspofungin efficacy in ETFN in pediatric patients that is comparable to that seen historically in adults.

7 Review of Safety by Julie-Ann Crewalk, M.D.

Safety Summary

Overall, the caspofungin dose of 50mg/m^2/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 clinical trial safety data between the pediatric and the adult population and between the study treatment and the comparator treatment group, we found an overall similar profile of adverse events. None of the 12 caspofungin treated patients, who died, appeared to do so from the study drug itself, nor was there a higher incidence of deaths in this population compared to the comparator (AmBisome) or the adult population. The causes of death in the pediatric patients were consistent with that observed adult studies, where the major causes of deaths were: AML, respiratory failure, septic shock, and aspergillosis. Discontinuations in the caspofungin treated patients were attributed to: pyrexia, hypotension, and rash. In adults, the main reasons for discontinuation were: respiratory failure, septic shock, and aspergillosis. Serious adverse events such as: pyrexia, hypotension, and hypoxia were higher in the caspofungin treated patients and highest in the pediatric caspofungin treated patients when compared to adult patients. In regards to common adverse events: the most common clinical adverse experiences across the caspofungin groups were pyrexia (29.2%), diarrhea (14.0%), rash (11.7%), chills (11.1%) and hypotension (11.1%). Pyrexia was the most common clinical adverse experience reported at each of the caspofungin dose levels and demonstrated the largest difference in incidence between pediatrics and adult population that had only a 1.2% incidence. Rash and chills was also higher in the pediatric population compared to adults (8.3% and 0.1% respectively). There were no demographic issues with regards to safety, except for the possibility within the Asian race. While the numbers enrolled were small and it is difficult to make major conclusions on the effect of caspofungin within the Asian race, it would be helpful to assess for any possible increase in adverse events, including deaths in post-marketing studies. Postmarketing events observed in pediatric patients not currently described in the label include pancreatitis, hypotension, erythema, erythema multiforme, Steven's Johnson and skin exfoliation. Post-marketing evaluation for liver toxicity including liver failure, and clinically significant decreases in serum potassium and platelets is warranted. The potential role of the drug transporter OATP1B1 in these toxicities should be considered should additional hepatic failure events emerge.

7.1 Methods

This safety review was conducted using the following studies: Protocols 033, 042, 043, 044, and 058. Additionally postmarketing safety assessments were made based on the data submitted by the

sponsor in the supplemental NDA (see review by Eileen Navarro) and from the FDA AERS (see review by Chris Jones).

7.1.1 Clinical Studies Used to Evaluate Safety

This safety review was conducted using the following studies: Protocols 033, 042, 043, 044, and 058. The review is based on all the 5 pediatric studies where data was pooled together for event rates. Three PK studies evaluated the empiric use of caspofungin in pediatric patients ages 0-3 months with proven or suspected invasive candidiasis and pediatric patients ages 3 months to 17 years with new onset fever and neutropenia. Two safety and efficacy studies examined caspofungin safety and efficacy profile in pediatric patients 3 months to 17 years with invasive mycoses and new onset of fever and neutropenia.

PK Studies:

Protocol 033 was a multi-center, open, sequential dose-escalation study to investigate the safety and tolerability and pharmacokinetic of caspofungin in children and adolescents 2 to 17 years of age. The patients were stratified into two separate age groups: 2- 11, and 12- 17 year olds. Immunocompromised children with a history of underlying hematological or solid organ malignancies and documented fever received caspofungin starting on Day 1. Three different dosage levels were studied: 1 mg/kg/day, 50 mg/m^2/day, and 70 mg/m^2/day. Patients were allowed to continue study therapy until their absolute neutrophil count (ANC) post nadir value was ≥ 250/mm^3. In general, patients were to be treated for a minimum of 4 days and a maximum of 28 days. A total of 39 patients were enrolled and were included in the safety analyses. Per the sponsor, there were no serious drug-related adverse experiences or discontinuations in caspofungin therapy due to drug-related adverse experiences reported.

Protocol 042 was a multicenter, open, sequential dose-escalation study to investigate the safety, tolerability, and pharmacokinetics of caspofungin in children between the ages of 3 to 24 months with new onset fever. Clinically stable immunocompromised children with a history of underlying hematological or solid organ malignancies with persistent fever and neutropenia received caspofungin starting on Day 1 of therapy. A caspofungin dose level of 50 mg/m^2/day was studied with a maximum daily dose of 70 mg. Patients were allowed to continue study therapy until their ANC post nadir value was ≥ 250/mm^3. In general, patients were to be treated for a minimum of 4 days and a maximum of 28 days. Per the sponsor, a total of 9 patients were enrolled and were included in the safety analyses. There were no serious drug-related adverse experiences or discontinuations in caspofungin therapy due to drug-related adverse experiences reported.

Protocol 058 was a multicenter, sequential-panel, open-label, noncomparative study to evaluate the safety, tolerability, and pharmacokinetics of caspofungin in neonates and infants <3 months of age. Patients with culture-confirmed or highly suspected *Candida* infections were enrolled in one of the two sequential treatment panels: Panel A (Single Dose) or Panel B (Multiple Dose). In both panels, all patients received caspofungin at 25 mg/m^2 along with an intravenous amphotericin B formulation. Patients in Panel A received a single dose of caspofungin 25 mg/m^2 on Day 1. Blood for plasma pharmacokinetic sampling was collected at the screening visit, at 1 hour post caspofungin infusion (peak concentration), and at 24 hours post caspofungin infusion (trough concentration). Patients enrolled in Panel B received multiple doses of caspofungin at 25 mg/m^2 daily. The

minimum duration of caspofungin in Panel B was expected to be 4 days. In these patients, blood for plasma pharmacokinetic sampling was also collected at screening, 1 hour and 24 hours post caspofungin infusion on Day 1, and 1 hour and 24 hours post caspofungin infusion on Day. An additional trough sample may have been collected following the Day 9 infusion, provided the patient was still receiving caspofungin therapy and the collection was deemed appropriate by the investigator. All patients who received one or more doses of caspofungin in either panel were evaluated for safety. All patients were assessed for safety while on caspofungin therapy and for 14 days post caspofungin therapy.

Safety and Efficacy Studies:

Study 043 was an open-label, non-comparative study to evaluate the safety, tolerability and efficacy of caspofungin in children ages 3 months to 17 years with documented *Candida* or *Aspergillus* infection. Patients with proven esophageal candidiasis or invasive candidiasis were enrolled into the study as primary or rescue therapy. Patients with proven or probable invasive aspergillosis were only enrolled if they had failed or were intolerant to standard antifungal treatment. All patients received caspofungin monotherapy 50 mg/m^2 daily after a 70-mg/m^2 loading dose on Day 1. The maximum daily dose was 70 mg/day. At the end of study therapy, all patients were scheduled to have a 14-day follow-up visit. Patients who responded clinically well at the end of study therapy were also observed for relapse of the fungal infection at 14- and 28-days post-therapy.

Study 044 was a multicenter, double-blind, randomized, comparative study to evaluate the safety, tolerability, and efficacy of caspofungin versus liposomal amphotericin B (AmBisome™) as empirical therapy in pediatric patients (2-17 years) with persistent fever and neutropenia. Patients were stratified at study entry by risk status (high-risk or low-risk). Patients at high-risk were those patients who underwent allogeneic hematopoietic stem-cell transplantation or those who have received chemotherapy for a relapse of acute leukemia. All patients received either: (1) caspofungin and placebo to AmBisome™, or (2) AmBisome™ and placebo to caspofungin. Patients were assigned to a treatment group via a 2:1 (caspofungin to AmBisome™) randomized schedule. Patients randomized to the caspofungin group received a 70 mg/m^2/day loading dose on day 1, followed by 50 mg/m^2/day on subsequent treatment days (maximum daily dose permitted was 70 mg). Patients in the AmBisome™ were treated with 3mg/kg/day. Patients without invasive fungal infection were treated until the resolution of neutropenia (absolute neutrophil count 500 cells/μL), and for up to 72 hours later. The planned maximum duration of empirical treatment was 28 days. The recommended duration for patients with documented invasive fungal infection was at least 14 days, and at least 7 days after resolution of neutropenia and of symptoms, and for no longer than 90 days.

7.1.2 Adequacy of Data

The data submitted by the sponsor appeared adequate and complete. We did request a revision of their adverse event tables to include all adverse events (AEs) despite investigator input of causality.

7.1.3 Pooling Data across Studies to Estimate and Compare Incidence

Comparisons are made by pooling the data in the three PK studies (033, 042, and 058) and the Safety and Efficacy Studies (043, 044).

7.2 Adequacy of Safety Assessments

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

The mean duration of exposure across all the studies for the 171 caspofungin-treated pediatric patients was 12.1 days (median 9.0 days; range of 1 to 87 days). Sixty-six patients received at least one dose of caspofungin in the 3 pharmacokinetic studies (Protocols 033, 042, and 058). An additional 105 patients received caspofungin in the safety/efficacy studies (Protocols 043 and 044). Of the 171 caspofungin recipients, 132 of the patients (77.2%) received caspofungin at a daily maintenance dose of 50 mg/m^2. The remaining 39 patients received caspofungin at a daily maintenance dose of 1 mg/kg (9 patients in Protocol 033), 25 mg/m2 (18 patients in Protocol 058), or 70 mg/m2 (12 patients in Protocol 033).

Twenty-six patients enrolled in the pediatric empirical therapy study (Protocol 044) were treated with AmBisome™ at 3.0 mg/kg daily.

Pharmacokinetic Studies (Protocols 033, 042, 058)
Overall, the mean duration of caspofungin therapy for the 66 patients enrolled in the pharmacokinetic studies was 7.8 days with a median of 5 days (range 1 to 28 days).

In Protocol 033, the mean duration of treatment for all patients (N=39) who received caspofungin was 8.2 days (range of 2 to 28 days). Only 4 (10.3%) of the 39 patients received <4 days of study therapy: 3 patients (7401, 7473, 7501) had resolution of both their fever and neutropenia prior to Day 4 and 1 patient (7432) who did not receive further therapy after Day 3 because it was felt, a fungal etiology for the fever and neutropenia was unlikely. Among the subjects between the ages of 2 and 11 years, the mean duration of therapy was 8.6 days, 8.1 days, and 4.8 days for patients in the 1.0-mg/kg, 50-mg/m^2, and 70-mg/m^2 treatment groups, respectively. Similarly, among the children aged 12 to 17 years, the mean duration of therapy was 3.5 days and 14.1 days for the patients in the 1.0-mg/kg and 50- mg/m^2 treatment groups, respectively.

In Protocol 042, a total of 9 patients received caspofungin study therapy once at a daily dose of 50 mg/m^2 (Pharmacokinetic Study in Patients 3 to 24 Months of Age). The mean duration of study therapy was 9.6 days (range 2 to 21 days). The median duration of therapy was 9 days. Five (55.6%) patients received >7 days of caspofungin study therapy, and two (22.2%) patients received >14 days of caspofungin study therapy.

In Protocol 058, (Pharmacokinetic Study in Patients 0 to 3 Months of Age), 18 neonates and infants received caspofungin therapy. Six were enrolled and received a single dose (Panel A) of caspofungin study therapy. The remaining 12 patients were enrolled in the multiple-dose panel

(Panel B). The mean duration of caspofungin therapy for patients enrolled in Panel B was 8.7 days (range 4 to 36 days). The median duration of therapy for patients in Panel B was 5 days. The majority of the patients (50%) in Panel B received between 4 and 7 days of treatment, while two patients received >14 days of caspofungin therapy.

Safety/Efficacy Studies (Protocols 043 and 044)

Protocol 043

A total of 49 patients were enrolled in Protocol 043 (Safety/Efficacy Study of Documented *Candida* and *Aspergillus* Infections in Pediatric Patients 3 Months to 17 Years of Age). All 49 patients were included in the safety analyses. The degree of caspofungin exposure is discussed separately below for the 3 different indications (invasive aspergillosis [N=10], invasive candidiasis [N = 38], and esophageal candidiasis [N=1]).

Invasive Aspergillosis

Ninety percent of the 10 patients with invasive aspergillosis received between 8 and 87 days of therapy. Six of these patients received >28 days of therapy, including 3 (30.0%) who received >60 days of therapy. Overall, the mean duration of therapy for patients with invasive aspergillosis was 42.7 days. For children 2 to <7 years of age, the mean duration of therapy was 61 days, while for children 7 to <12 years had a mean duration of therapy was almost half at 31.6 days. There was one patient age 12 to <15 years who was treated for 29 days and one patient 15 to 17 years who was treated for 57 days.

MO Comment: *It is not clear why the younger age group had a longer duration of caspofungin treatment. The longer duration may possibly reflect a decrease in efficacy in that age group; however, given the small numbers within the population it is difficult to make this assessment. The longer duration may also be due to the reluctance on part of the physician to terminate a medication prematurely in younger patients.*

Invasive Candidiasis

Overall, the mean duration of therapy for patients with invasive candidiasis was 11.8 days. Twenty-eight (73.7%) of the 38 patients with invasive candidiasis, received ≤ 14 days of therapy. The remaining 10 (26.3%) patients received between 15 and 42 days of therapy. There was one patient in each of the following age groups: 3 to <7 months with 13 days of therapy, 13 to <19 months with 16 days of therapy, and 19 to <24 months with 14 days of therapy. Children 2 to <7 years of age had a mean duration of therapy of 12.6 days, while those ages 7 to <12 years had a mean duration of therapy of 9 days. The mean durations of therapy for children in the 12 to <15 years and 15 to 17 years was 8.6 days and 15 days, respectively.

Roughly 10% (N=5) of the 49 patients had their caspofungin dose escalated to 70 mg/m^2 daily as permitted by the protocol. These patients included 1 patient with invasive aspergillosis and 4 patients with invasive candidiasis.

Esophageal Candidiasis

The one patient with esophageal candidiasis was a 17 year-old Caucasian male with recurrent acute myelogenous leukemia (AML) and a history of allogeneic bone marrow transplant. The patient received caspofungin study therapy as primary treatment for a total of 32 days.

Protocol 044

Eighty-two patients were enrolled in Protocol 044 (Pediatric Empirical Therapy Study in Pediatric Patients 2 to 17 Years of Age). All 82 patients received at least one dose of study therapy with either caspofungin or AmBisome™. Fifty-six patients were treated with caspofungin 50 mg/m^2 (following a 70 mg/m^2 loading dose on Day 1) and 26 patients received AmBisome™ 3 mg/kg/day. The mean durations of the standard dose of study therapy were similar for the 2 treatment groups. Per the protocol, 3 patients were dose escalated in the caspofungin (N=1) and AmBisome™ (N=2) treatment groups. Among these 3 patients, the duration of the increased dose ranged from 4 to 12 days.

7.2.2 Explorations for Dose Response

Not Applicable

7.2.3 Special Animal and/or In Vitro Testing

Per the protocol, caspofungin showed dose-dependent efficacy against confirmed disseminated candidiasis with CNS involvement in a juvenile mouse model. Caspofungin administered by daily intraperitoneal injection at doses of 1, 2, 4 or 8 mg/kg/day for 7 days significantly reduced kidney and brain *Candida* burden compared to control mice by both with regards to microbiological and histopathological endpoints. Caspofungin treatment also resulted in 100% survival through Day 28 as compared to 100% mortality in controls by Day 11 after challenge.

"Previously submitted repeat-dose intravenous toxicity studies have shown that the toxicity profile of caspofungin consists of signs of:

1) histamine release in rats and rhesus monkeys,
2) irritation at the injection sites in rats and monkeys, and
3) very slight elevations in serum transaminase values with or without very slight to slight subcapsular liver necrosis in monkeys.
4) In addition, there were very slight decreases in fetal weights in a developmental toxicity study in rats, which correlated with an increased incidence of fetuses with cervical rib and incomplete ossifications of the torso and/or skull at a maternally toxic dosage of 5 mg/kg/day."

With regard to toxicity in infant rhesus monkeys, there were no treatment-related findings in either caspofungin treatment group (2 mg/kg/day or 5 mg/kg/day). Body weight changes, CBCs, clinical biochemical assessments, urinalyses, ophthalmologic examinations, and gross and microscopic findings were all within normal limits for the animals. The rhesus monkeys were administered caspofungin doses that achieved exposures approximately 2.5 to 4.5 greater than that achieved in children administered caspofungin at a maintenance dose of 50 mg/m^2 daily, without toxicity observed in antemortem or postmortem assessments.

MO Comment: *Based on this pre-clinical information, this reviewer assessed the hepatic adverse event closely and recommend events be assessed prospectively in post marketing studies. For a more detailed evaluation of animal studies, please refer to Dr. Taylor's review.*

7.2.4 Routine Clinical Testing

Routine clinical testing while on caspofungin should include evaluation of parameters which may be affected by the medication, such as: complete blood count, and comprehensive metabolic panel (to evaluate for increase in AST, ALT, and alkaline phosphatase).

7.2.5 Metabolic, Clearance, and Interaction Workup

Caspofungin is metabolized slowly in the liver by nonenzymatic peptide hydrolysis and N-acetylation into two inactive metabolites (M1 and M2). There does not appear to be any metabolism through the P450 system. The majority of drug-drug interactions in echinocandins as a whole include immunosuppressive medications which are commonly seen in patients with fever and neutropenia for which this drug is seeking an indication (Cappelletty et al). Caspofungin specifically, due to its metabolism, does not have many drug-drug interactions. However, interactions have been shown with cyclosporine in adults. In Phase 1 trials, there was some evidence of increase in hepatic enzyme when the two medications were used concomitantly. In a retrospective review of 40 patients who received both medications, there were two who discontinued therapy due to hepatotoxicity. Four other patients again, showed hepatic abnormalities.

The interactions of rifampin and nelvinavir stem from their method of action (MOA) as strong CYP inducers. Nelvinavir caused significant increases in caspofungin's AUC and C_{min} on the first day of therapy, but there was no significant change on day 14 noted between the treatment and control groups. Rifampin, on the other hand greatly increases the AUC and C_{min} of caspofungin on day 1 of therapy, but again no significant change was noted by day 14 between the treatment and control groups (cappelletty). It has been recommended, however to increase the dose of caspofungin in adults to 70mg / day when rifampin is started 14 days before caspofungin, as this has shown to decrease caspofungin's C_{min} by 30%. Caspofungin interacts with tacrolimus by reducing its AUC, C_{max}, C_{min}, by 20%, 16% and 26% respectively. Routine tacrolimus monitoring is therefore advised.

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

Overall the side effects from this drug class are similar and well tolerated. Table 58 from Cappelletty's et al. (2007) article on echinocandins presents the most common adverse events in this class of antifungal medication from adult studies which should be monitored. Caspofungin, according to this has a higher incidence of liver-related laboratory abnormalities, infusion related pain, and phlebitis than the other two medications in this class of drug. This is compared to our own table, Table 58 which includes all causality AEs from the anidulafungin, micafungin label and the ---- submitted by Merck for caspofungin based on their submitted studies.

Table 58 Cappelletty's Frequency of Common Adverse Drug Reactions and Laboratory Abnormalities Associated with the Echinocandins

Adverse Reaction	Caspofungin (%)	Micafungin (%)	Anidulafungin (%)
Phlebitis	**3.5–25**	**1.6**	**< 1**
Fever	**4–40**	**1–14**	**< 1**
Abdominal pain	**3.6**	**1**	**< 2**
Nausea or vomiting	**1–6, 2–4**	**2–7, 1–5**	**1, < 1**
Diarrhea	**3.6**	**1.6**	**3.1**
Headache	**4–15**	**2–17**	**1.3**
Rash or pruritus	**1–10, < 2**	**1–12, < 1**	**1, < 2**
Leukopenia	**6.2**	**1.6**	**< 1**
Neutropenia	**1.9**	**1.2**	**1**
Thrombocytopenia	**3.1**	**< 1**	**< 2**
Hypokalemia	**2–10**	**1.2**	**3–10**
Abnormal liver function tests	**1–15**	**1–8**	**3–5**

Table 58 shows a higher percentage of AEs such as phlebitis, fever, abdominal pain, leukopenia, thrombocytopenia, hypokalemia and abnormal LFTs in the caspofungin treated group when compared to micafungin and anidulafungin. The data, however, is based on a small number especially in the anidulafungin category and adverse reactions were reported based on the investigator's judgment. Compare this with FDA Table 59, where the percentages are very similar between the three groups. Incidences of gastrointestinal disturbances (i.e. nausea, vomiting and diarrhea) have a much lower incidence in the caspofungin group than in the micafungin and anidulafungin groups. Leukopenia is comparable between the three groups, while thrombocytopenia has an incidence approximately 5 times less compared to the micafungin group. Table 2 gives a more thorough look at the potential adverse events by taking into account more recent events and all causality events not just investigator reported drug related events.

Table 59 (FDA) Frequency (%) of Adverse Events and Laboratory Abnormalities Associated with Echinocandins Based on All Causality

Adverse Reaction	Caspofungin N=1747	Micafungin N=3083	Anidulafungin N=204
Phlebitis	4.0	5.6	< 3
Fever	21.1	20	15.2
Abdominal pain	6.2	9.7	5.9
Nausea or Vomiting	8.8, 7.4	22, 21.7	26.1, 16.4
Diarrhea	14.9	23.3	18.1
Headache	10.5	2–17	7.8
Rash or Pruritus	8.6, 4.1	8.7, 6.1	3.9, < 3
Leukopenia	2.6	1.6	< 3
Neutropenia	1.3	14.1	< 3
Thrombocytopenia	3.6	15.1	5.4
Hypokalemia	11.8	18	19.6
Abnormal LFTs	14.1	5.6	3.1

***MO comment**: A cross study comparison of all causality adverse events shows a high frequency of abnormal LFTs within the caspofungin treated patients. Direct comparison is needed to make relative hepatic safety statements. Merck has conducted a normal volunteer study in normal volunteers of Japanese descent comparison safety of Cancidas to micafungin. When this study is submitted, we should be able to assess whether this observed difference in LFT abnormalities is sustained.*

7.3 Major Safety Results

7.3.1 Deaths

Across all the studies, 13 patients died. Of the 171 pediatric patients treated with caspofungin, 11 (6.4%) died during the treatment and follow-up phase. Of these 11 patient deaths, 5 deaths occurred in patients enrolled in the PK studies (033, 042, 058) and 6 occurred in patients enrolled in the safety/efficacy studies (043, 044). Of the 5 deaths in the PK studies, 3 deaths occurred in the neonatal PK study (058). One additional caspofungin-treated patient enrolled in Protocol 044 died during the post study period. None of the adverse experiences resulting in death were considered by the reporting investigator to be related to caspofungin study therapy. One (3.8%) of the 26 pediatric patients treated with AmBisome™ had a serious clinical adverse experience resulting in death. This death was also not considered by the reporting investigator as related to AmBisome™ study therapy. See Table 60 for a listing of all 13 fatal cases.

Table 60 Listing of Patients with Clinical Adverse Experiences Resulting in Death

Protocol	PT #	Sex	Race	Age	AE	Intensity	Drug Relation	Action	Day of Death
Caspofungin 25 mg/m2									
058	7635	M	Native American	5 wk	Escherichia sepsis	severe	def not	discon PRx	Day 10
					Intestinal	severe	def not	discon PRx	
					perforation				
					Necrotizing enterocolitis	severe	def not	discon PRx	
058	7613	F	Multi	1 wk	Hypoaemia	severe	def not	none	Day 2
058	7617	M	Asian	6 wk	Patent ductus	severe	def not	none	Day 4
					arteriosus				
					Cardiac failure	severe	def not	none	
					congestive				
					Fungal endocarditis	severe	def not	none	
					Pneumonia	severe	def not	none	
033	7531	M	White	12 yr	Pneumonia fungal	severe	def not	discon PRx	Day 23
042	3600	M	White	13mo	Pneumonia cytomegaloviral	severe	def not	none	Day 22
043	6082	M	White	7 yr	Pulmonary hemorrhage	severe	def not	none	Day 93
043	6161	M	Asian	9 yr	Fungal sepsis Acute lymphoblastic leukemia	severe severe	def not def not	none none	Day 43
043	6162	M	White	7 yr	Multi-organ failure	severe	def not	none	Day 21
043	6145	M	Asian	12 yr	Pneumonia Acute myelocytic leukemia Sepsis	severe severe severe	def not def not def not	discon PRx discon PRx discon PRx	Day 29

043	6146	F	Asian	11 yr	Pneumonia aspergillus	severe	prob not	none	Day 11
044	4009	M	White	13 yr	Pneumonia	severe	def not	none	Day 21
044	4225†	M	White	6 yr	Septic shock	severe	def not	none	Day 58
AmBisome™ 3.0 mg/kg									
044	4012	M	White	7 yr	Leukemia recurrent Respiratory failure	severe severe	def not def not	none none	Day 22

Drug Relationship: def = definitely, def not = definitely not, poss = possibly, prob = probably, prob not = probably not † Patient death occurred during post study period Adverse experience terms are from MedDRA Version 9.1.

MO Comment: *Two patients (7613, 7617) who died within days of receiving caspofungin therapy were in the neonatal study (058). They were not only premature, but also had multiple comorbid conditions that may have explained their rapid deterioration and death. Although it is possible that the deaths may have been due to caspofungin, I feel it is unlikely that caspofungin was related directly to their deaths given the degree and severity of illnesses in these two patients.*
The deaths in children < 2 months of age accounted for about 25% of the total caspofungin deaths. This may have been due to their multiple co-morbid conditions, such as prematurity and congenital heart defects. In comparing the deaths to the comparator group, there was little difference in deaths between caspofungin and AmBiosome. There was one death in the AmBisome (N=26) groups and two deaths in the Caspofungin group (N=56) when comparing the same population in Protocol 044 (3.9% and 3.6% respectively). In the adult caspofungin studies (N=1576) there were 211 subjects (13.4%) who died compared to the pediatric studies where approximately 7% (12/171) of those treated with caspofungin died. Overall, caspofungin does not seem to contribute to the patients' deaths, nor is there a higher incidence of deaths in the pediatric caspofungin treated groups.

Patient 7531 Study 033 was admitted for fever and neutropenia and continued with low fevers during the first two days of treatment. Study Days 3-23 he continued to spike daily from 38.6^{o}C – 40.2 ^{o}C. His initial chest x-ray was notable for a right 7th rib fracture; however there was no concern for fungal infection until his diagnosis on study day 9. Study day 15, he was intubated for respiratory distress. Amphotericin was started on study day 17. The next day he was noted to have a 4 cm ulcerated lesion on the nape of his neck, and was treated with Baltroban for 4 days. This lesion was ultimately biopsied with pathology showing angio-invasive fungal hyphae.

MO Comment: *While the patient's death may not be a direct safety cause of caspofungin, it may be an indication of lack of efficacy with regards to either a fungal breakthrough infection or worsening of the fungal infection while on the study medication.*

His concomitant antibiotics while on caspofungin therapy included oral fluconazole (Days 1 – 10), cefepime (Days 1 – 8), amikacin (Days 5 – 22), vancomycin (Days 7 – 18), meropenem (Days 9 – 22), and rifampin (Days 18 – 22). Infusion related adverse events (AEs) experienced included separate occasions of indigestion (Day 2) and fever (Day 4 and Day 7) and chills (Day 7). They were considered to be possibly related to the medication, but no action was taken and the AEs resolved. Non-infusion related AEs included an episode of flushing on Days 3-4, fever on Day 4, and intermittent sinus tachycardia on Days 7-23. These adverse events were

considered to be mild to moderate in intensity and were either not related to the medication, or possibly related in regards to flushing and fever. Loose stools which were reported from study Days 7 - 16 and were also considered possibly related to the medication. Hypotension was noted on Days 15 – 23 and was considered to be severe and unrelated to the medication. The medication was discontinued on day 9 due to lack of efficacy. The patient expired on study day 23 from fungal pneumonia. His fungal pneumonia was not considered by the reporting investigator to be due to the study drug. Autopsy confirmed zygomycetes in lungs.

MO Comment: *Given the concomitant use of antibiotics, it is difficult to ascertain the etiology of some of these AEs. It is possible that some of the side effects were due to the concomitant antibiotics that were prescribed and not necessarily caspofungin. Hypotension is a known AE associated with sepsis.*

Protocol 042 also had one patient who died from cytomegalovirus (CMV) pneumonia. Patient 3600 was a 13 month-old Hispanic male patient with acute myelogenous leukemia (AML). The patient was a recipient of an unrelated cord blood transplant prior to study entry. The patient received caspofungin at 50 mg/m^2/day (daily dose, 24 mg) for 12 days. At study entry, the patient also had known respiratory distress and was seropositve for CMV based on PCR results. This patient was consistently febrile for the first five days of the study with a maximum temperature of 39^{o}C on Day 4.

On Day 4 of caspofungin study therapy, the patient had worsening respiratory distress from baseline tachypnea with a respiratory rate >100 breaths/min, necessitating oxygen therapy. The patient was transferred to the pediatric intensive care unit (PICU) and was subsequently intubated and ventilated. The patient completed caspofungin study therapy on Day 12, with resolution of fever and neutropenia. The patient remained in the PICU due to continued respiratory distress following completion of caspofungin study therapy. On Day 22 (10 days following the completion of caspofungin study therapy), the patient expired. CMV pneumonia was considered to be the cause of death. No autopsy was performed. The serious clinical adverse event of CMV pneumonia was determined to be life-threatening and resulted in prolonged hospitalization and death. The investigator considered CMV pneumonia to be definitely not related to caspofungin study therapy. The non-fatal serious clinical adverse experience of worsening respiratory distress was determined to be life-threatening and resulted in prolonged hospitalization. The investigator considered respiratory distress to be probably not related to caspofungin study therapy.

Of note, there was a drug-prescribing error on Day 1 in which the patient inadvertently received 2 doses of caspofungin study therapy due to a pharmacy/nursing error. This ultimately resulted in an unintentional study drug overdose. No safety findings were noted after either of the two doses administered on Day 1.

MO Comment: *CMV pneumonia is a common infection in immunocompromised children. It is doubtful that the caspofungin caused this pulmonary infection. While side effects caused by overdoses of caspofungin are not fully known, it is doubtful that this medication error attributed to, or caused a worsening in the CMV.*

The third PK study (058) reported 3 deaths, again all unrelated to treatment per the reporting investigator. Three (16.7%) of the 18 patients who received caspofungin study therapy died as a result of a clinical adverse experience that occurred during the course of the study. Two patients enrolled in the single-dose panel (Panel A) died, while only one patient enrolled in the multiple dose panel (Panel B) died. Summaries of the 3 patients who died are presented by below:

Panel A (Single Dose)

Patient 7613 was a 10 day old female patient (gestational age 24 weeks, weight 0.69 kg, and length 30.0 cm) with a high suspicion for candidemia who was enrolled into the single-dose panel of this study. At study entry, the patient had known sepsis, respiratory failure, pulmonary hypertension, patent ductus arteriosus, and hypoxemia. She received a single 25mg/m^2 dose of caspofungin for a total dose of 1.9 mg. On Day 1 of caspofungin study therapy, the patient developed progressive signs of sepsis with increased white blood cell count to 37.9 x10^3 cells / μL and persistent hypotension in the range of 47 – 71 systolic over 27-36 diastolic. At that time, the patient was hypoxic and acidemic. On Day 2 (1 day following the completion of caspofungin study therapy), the patient died as a result of hypoxemia. The primary investigator did not consider the serious adverse experience of hypoxemia to be related to caspofungin study therapy. No autopsy was performed.

Patient 7617 was a 6 week-old male patient (gestational age 30 weeks, weight 1.69 kg, and length 43 cm) with highly suspected *Candida* endocarditis who was enrolled into the single-dose panel of this study. The patient received caspofungin at 25 mg/m^2/day for a total dose of 3.54 mg. At study entry, the patient had known patent ductus arteriosus, bacterial pneumonia, hyponatremia, and congestive cardiac failure. On Day 2 (1 day following the completion of caspofungin study therapy), the investigator reported a worsening of the patient's congestive cardiac failure, and the patient was placed on ventilatory support. An echocardiograph showed an increase in the size of the fungal mass and reopening of the ductus arteriosus. Despite supportive measures, on Day 4 (3 days post caspofungin study therapy), the patient expired. The primary investigator considered the serious adverse experiences of worsening patent ductus arteriosus, worsening congestive cardiac failure, pneumonia, and worsening fungal endocarditis to be definitely not related to caspofungin study therapy. No autopsy was performed.

The patient's lab results were also elevated including an increase in transaminases, creatinine, bilirubin, and potassium. Table 61 shows the values of the mentioned serum chemistry values in relation to the patient's therapy.

Table 61 Laboratory Results for Patient 7617

Day of Study	AST (IU/L)	ALT (IU/L)	Creatinine (mg/dL)	Potassium (mm/dL)	Total Bilirubin (mg/ dL)	Direct Bilirubin (mg/dL)
-1	44	13	0.3	3.3	3.7	.94
4	4423	2018	2.2	7.2	7.4	4.19

MO Comment: *Given there was only one dose of the study medication, it is difficult to fully attribute the AEs to the study drug given the severity of prematurity and other comorbidities in both infants. The elevation in laboratory values for patient 7617 is unlikely due to one dose of caspofungin, and is probably more indicative of multi-organ failure from the underlying fungal sepsis.*

Panel B (Multiple Doses)

Patient 7635 was a 4 week-old Native American male patient (gestational age 33 weeks, weight 1.4 kg, and length 40 cm) with documented *Candida* peritonitis who was enrolled into the multiple-dose panel of this study. The patient received caspofungin at 25 mg/m^2/day (daily dose 3 mg Days 1 to 7 and 4.3mg Days 8 to 10) for a total of 10 days. The patient had multiple co-morbidities prior to study drug infusion, including brain atrophy and retinopathy due to prematurity, necrotizing enterocolitis, bowel perforation, *E. coli* sepsis with confirmed *E. coli* meningitis, and right lower extremity necrosis. Due to the severity of the prognosis and the on going illnesses, the patient's parents decided to withdraw life support. The patient died on Day 10 of caspofungin study therapy. The primary investigator felt the serious adverse experiences of worsening sepsis, worsening necrotizing enterocolitis, and worsening bowel perforation were definitely not related to caspofungin study therapy. No autopsy was performed.

MO Comment: *Given the multiple co-morbid factors including prematurity, it is difficult to determine if death was related to lack of efficacy with the drug. Gram negative sepsis and meningitis alone have a high mortality rate in this age population.*

In study 043, a total of 5 patients died. All 5 deaths were in patients with invasive aspergillosis and all were due to clinical adverse experiences. Their deaths were attributed to their worsening aspergillosis infections. The following are the patient summaries of their clinical outcomes and deaths:

Patient 6082 was a 6-year-old white male with a history of Acute Lymphoblastic Leukemia (ALL) and AML who was treated with consecutive allogenic bone marrow transplants. At the time of admission, he was diagnosed with definite skin and probable pulmonary aspergillosis, and was had progression of disease while on at the time of enrollment. Caspofungin therapy was started at 50 mg/m^2 (50 mg) daily following a 70 mg/m^2 (70 mg) loading dose on Day 1. The severity of his cough decreased to mild by Day 7 and resolved by Day 12. On Day 51, the patient's cough returned and persisted into the follow-up period.

On Day 42, a needle biopsy showed a relapse of ALL which was considered life-threatening. Aggressive chemotherapy was administered on Days 59 - 63. On Day 65, he experienced a vertebral collapse which was considered a significant disability. On Day 71, the patient became febrile. From Days 71 -Day 85, his cough and radiological findings worsened. He developed chest pains and a papular nodule on his skin. On Day 85, caspofungin study therapy was discontinued due to lack of efficacy. The patient was treated with voriconazole in the follow-up period. His condition did not improve and on Day 93 the patient expired due to pulmonary hemorrhage attributed to on-going pulmonary aspergillosis. The primary investigator felt that the SAEs of ALL relapse, spinal compression, and pulmonary hemorrhage were not related to study therapy.

MO Comment: *The investigator felt that the aggressive chemotherapy administered created an immunosuppressive state which probably resulted in worsening of the fungal infection. I would agree. Given the severity of his oncological state, I feel the caspofungin had little to no role in his SAEs mentioned or his death.*

Patient 6145 was a 12-year-old Asian male with a history of Trisomy 21 (Down syndrome) and AML who at study entry was neutropenic, febrile, had decreased breath sounds with rales, and severe respiratory failure. He was diagnosed with probably pulmonary invasive aspergillosis by findings on chest CT and positive serology. He was treated with amphotericin B, but failed treatment after 2 weeks. The patient was then enrolled into this study as a refractory patient and was treated with 66 mg (50 mg/m^2) of caspofungin daily. On Day 3, he developed new papular nodules on the skin of both thighs and right leg. Sputum cultures taken after Day 3 were positive for *Aspergillus flavus* and/or *Aspergillus terreus*. During the first 2 weeks of study therapy, the infection, respiratory failure, and rales persisted. On Day 15, he developed severe hemoptysis which persisted. On Day 20, a pneumopericardium was noted. Sputum cultures taken on Day 17 and Day 25 grew *Aspergillus flavus* along with *A. baumanii, S. maltophilia,* and *B. cepacia* complex. The patient's infection worsened until his death on day 29. The primary investigator felt the *Aspergillus* pneumonia, AML and sepsis were not related to caspofungin study therapy. No autopsy was performed.

MO Comment: *This patient had already failed therapy on AmBisome™ and so it is not surprising that there were continued difficulties clearing his fungal infection. Of note, there was a medication error mentioned; on Days 25-27, he received only 52.5 mg of caspofungin as a nursing / pharmacy error. The correct dose of 66mg was re-instated on Day 28 when the error was noted. It is unlikely that the decrease in medication which occurred so late in his treatment course was the cause of his worsening fungal infection. It is also doubtful that caspofungin caused his death given the severity of illness from the beginning.*

Patient 6146, an 11-year-old Asian male with severe aplastic anemia, febrile neutropenia, and a number of other medical conditions was diagnosed with probably pulmonary invasive aspergillosis based on clinical findings, chest x-ray, and sputum culture. He was treated with AmBisome™ for 9 days, but his illness advanced. As a result, he was enrolled into Protocol 043 as a refractory patient and was treated with caspofungin for a total of 6 days. At study entry, the patient had fever, cough, tachypnea, mental status changes, and papular/nodular skin lesions. Caspofungin therapy was administered at 70 mg (50 mg/m^2) daily. The patient continued to have positive sputum cultures and was discontinued from caspofungin therapy on Day 6 due to lack of efficacy. On Day 7, he was placed on AmBisome at 250mg/day. The patient worsened and expired on Day 11. The primary investigator considered the serious adverse experiences of bronchopulmonary aspergillosis and septic embolus not related to study therapy. No autopsy was performed.

MO Comment: *I agree it is unlikely that the caspofungin was the cause of his infection or death. Lack of efficacy may have played a role, however, given he was already refractory to AmBisome™, it is unlikely that the caspofungin would have cleared this invasive infection so late in the clinical study. There was a reactivation of his CMV on Days 9-11. It is unclear what role caspofungin plays in this, however, it is unlikely that caspofungin provoked his CMV re-activation which is more likely due to the patient's neutropenia*.

Patient 6161, a 9-year-old Asian male with ALL relapse and various other medical conditions was diagnosed with probable pulmonary invasive *Aspergillus* based on a BAL culture that grew *A. niger,* and an abnormal chest CT. The patient was enrolled into Protocol 043, as he was refractory to treatment with AmBisome™ and oral voriconazole. Caspofungin study therapy was initiated at 46

mg daily (following a 64.4 mg loading dose on Day 1). At study entry, the patient was neutropenic and presented with fever, cough, abdominal pain and fatigue. Chemotherapy (vincristine and idarubicin) was administered on Day 3. Galactomannan ELISA and PCR of the blood became positive on Day 7. On Day 8, the study therapy was increased to 64.4 mg/day (70 mg/m^2) due to a worsening of his condition. On Day 9, the patient had a seizure after 80% of the study therapy was administered. The study therapy was interrupted and diazepam was administered. Fifteen minutes after the seizure ended, the caspofungin infusion was continued without further incident. The patient's condition rapidly deteriorated over the next day. On Day 10, the study therapy was discontinued due to lack of efficacy and he was placed on IV voriconazole. On the following day, he was given marketed caspofungin as combination therapy. On Day 13, the caspofungin was discontinued when sensitivities revealed *Tricosporon asahii* from a blood culture was resistant to caspofungin. On Day 14, treatment with AmBisome™ was initiated and a granulocyte infusion was given. From Day 15 through Day 38, a combination therapy of IV voriconazole and AmBisome™ was administered. On Day 43, the patient expired. The primary investigator did not consider the serious adverse experiences of ALL, fungal sepsis, and convulsion as related to study therapy. No autopsy was performed.

MO Comment: *It is unlikely that caspofungin was associated with his death as he was refractory to other antifungals during the course of his illness. While the fungal species was resistant to caspofungin, caspofungin had only been administered for 2 days. The cause of his death is most likely due to the overwhelming severity of this patient's clinical illness.*

Patient 6162, a 7-year-old white male with AML refractory to chemotherapy, presented with fever and pulmonary insufficiency and was diagnosed with probable pulmonary invasive aspergillus. The diagnosis was based on lower respiratory symptoms, radiological findings, and positive serology. He was refractory to treatment with amphotericin B and voriconazole and as a result, was enrolled into Protocol 043. Caspofungin therapy was initiated at 54 mg daily (following a 70 mg loading dose on Day 1). He developed a pneumothorax on Day 2 and a cough on Day 5. Additional tests such as chest x-rays, sputum cultures, and serology revealed little improvement of his medical condition. On Day 9, caspofungin therapy was discontinued and other antifungal options were addressed. He was first placed on AmBisome™ on Day 9 after caspofungin therapy discontinuation. On Day 10 voriconazole was added in order to begin a combination regimen. Despite the combination therapy, on Day 21 he expired due to multi-organ failure. The primary investigator considered the serious adverse experiences of multi-organ failure, pneumothorax, and invasive aspergillus as not related to study therapy. An autopsy was not performed.

MO Comment: *Again, it is not likely that caspofungin contributed to his death given the limited duration of therapy and the degree of his fungemia.*

In study 044, there were three deaths; two were in the caspofungin treated arm, and one was in the AmBisome™ treated study. Below are the narratives of these three deaths.

Caspofungin (N=2)
Patient 4009 was a 13-year old white male with multiple medical problems, including, but not limited to a history of Ewing's sarcoma, febrile neutropenia, mucositis, thrombocytopenia, hypokalemia, anemia, pneumonia, hypotension and shock. Chemotherapy was administered from

Days -21 to Day -17. On Day -4, the patient had fever and neutropenia. He was enrolled in Protocol 044 and received caspofungin acetate 70 mg/m^2 on Day 1 and 50 mg/m^2 daily thereafter, for the treatment of febrile neutropenia. Some concomitant therapies included cefotaxime sodium, trimethoprim-sulfa, ceftazidime, amikacin, vancomycin, prednisone, meropenem, methylprednisolone, ranitidine, and furosemide. On Day -1 the patient experienced pneumonia caused by Aspergillus which was confirmed by chest x-ray which revealed multiple patchy bilateral infiltrates. Galactomannan ELISA was positive on Day 1. Study therapy was discontinued on Day 7 due to the parents withdrawing consent. Following discontinuation of blinded therapy, the patient was treated with caspofungin from Days 8 – 21. The patient had chest pain on Day 10 and dyspnea, hypoxia, and tachypnea on Day 12. A chest CT on Day 14 revealed mediastinal lymphadenopathy and patchy pulmonary nodules with surrounding ground glass opacities. Galactomannan ELISAs on Days 8, 12, 16, and 19 continued to be positive and blood cultures Day 8 through Day 14 continued to be negative. On Day 18, the patient experienced a serious adverse event of bilateral pneumonia. The patient was transferred to intensive care and put on a ventilator. On Day 20 the chest x-ray showed a large infiltrate in both lungs with air bronchograms which worsened on Day 21 to include a new area of consolidation in the infrahilar region of the right lung. The patient died on Day 21 with bilateral pneumonia as a cause of death. The investigator felt that bilateral pneumonia was definitely not related to study therapy. This case was adjudicated and found to have a probable case of baseline pneumonia with clinical response of failure. An autopsy was not performed.

MO Comment: *It is possible that the death is more likely due to an untreated aspergillosis. However, there was no identification of the fungal organism to assess for sensitivities, so it is unclear if the organism was susceptible to caspofungin, or if there was another mechanism for its failure.*

Patient 4225 was a 6-year old white male with AML. The patient's medical history included mucositis, sepsis, pancytopenia, hepatomegaly, sinus arrhythmia, and constipation. The patient was enrolled in Protocol 044 and received caspofungin acetate 70 mg/m^2 on Day 1 and 50 mg/m^2 daily thereafter, for the treatment of febrile neutropenia. The patient completed study therapy per protocol on Day 11 and was discharged.

On Day 16, the patient was hospitalized after experiencing fever and neutropenia and was placed on antibiotic therapy with cefepime, teicoplanine, and oral fluconazole as antifungal prophylaxis. On Day 17, a blood culture was performed and was positive for *E. coli*. Teicoplanine and cefepime were discontinued on Day 18 and ceftazidime was added to the treatment plan. A follow-up blood culture on Day 19 was negative and the septicemia was considered resolved, however when the patient experienced recurrence of fever, amikacin was added. Fluconazole therapy was discontinued on Day 20 and replaced by voriconazole on Day 21. A chest x-ray on Day 21 revealed pneumonia. The cefepime was re-added in place of ceftazidime for worsening symptoms. A chest CT on Day 22 confirmed pneumonia with fungal characteristics. AmBisome™ was added and given from Day 23 – Day 51.

Three days later, galactomannan ELISA was performed on 2 blood samples and was positive for *Aspergillus* antigen. Subsequent Galactomannan ELISA on Days 28, 30, 33, 37 and 46 remained positive. A repeat chest x-ray on Day 30 revealed an aspergilloma with a satellite nodule. Voriconazole therapy was discontinued and caspofungin was added. Meropenem was added from

Days 38 –47. The patient was started on methylprednisolone on Day 43. On Day 52, a chest CT showed multiple bilateral focus of aspergillus.

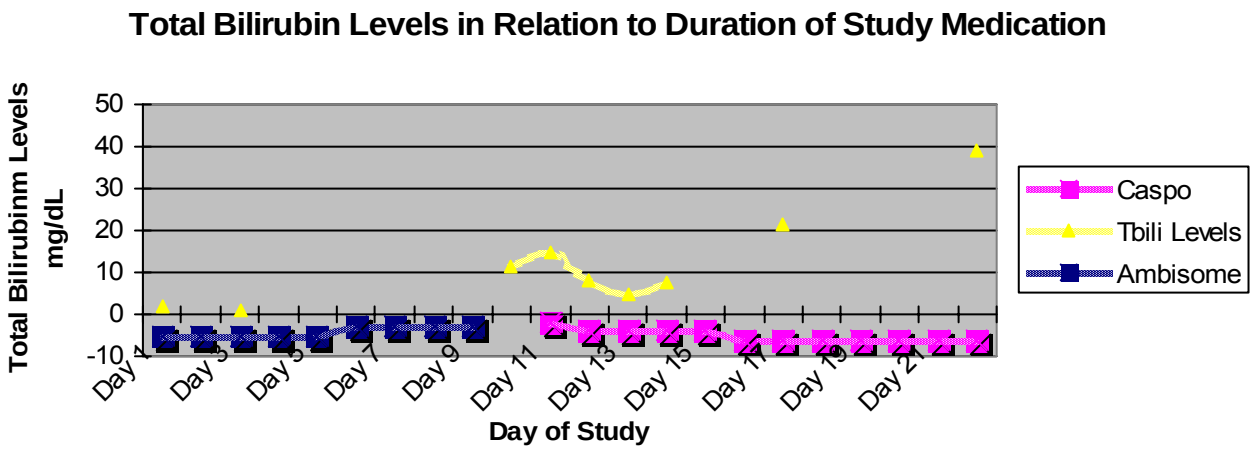
Two blood cultures were performed (on Day 49 and 50) showing positive results for S*treptococcus viridians*. The patient went to the ICU due to the Streptococcus viridians sepsis and was treated with meropenem, teicoplanine and voriconazole. The patient experienced respiratory hypoxia and underwent mechanical ventilation. The patient experienced septic shock and was treated with dopamine, dobutamine and bicarbonate. The patient died on Day 58 due to septic shock. The reporting investigator felt that the *E. coli* septicemia and fungal pneumonia were probably not related to study therapy, and that the anaerobic gram negative bacteremia, acute respiratory hypoxia, *Streptococcus viridians* sepsis and septic shock were definitely not related to study therapy. The cause of death was septic shock. This case was adjudicated and found to be "not a fungal infection" at the efficacy assessment time-point of the 7-day follow-up visit, but later met the criteria for probable infection 12 days after the end of study therapy.
An autopsy was not performed.

MO Comment: *There were too many co-morbid medical conditions that may have contributed to this patient's death. While this may indicate a lack of efficacy of caspofungin, it is unlikely given the degree of other antifungals used without eradication of the organism.*

AmBisome™ (n=1)
Patient 4012 was a 7-year old white male enrolled in Protocol 044 who received 3 mg/kg of AmBisome™ for the treatment of febrile neutropenia. He had a history of relapsed AML, anorexia, bone pain, fungal infection, hepatomegaly, pancytopenia, splenomegaly, tachycardia, and tachypnea. Chemotherapy was administered in two courses: from Day -59 to Day -54 and from Day -9 to Day -4. On Day -4, the patient experienced neutropenic fever.

On study Day 4, patient experienced a possible breakthrough fungal infection which was not confirmed by chest CT. On Day 6, the dose of study drug was increased and the patient was placed on AmBisome™ 5 mg/kg. Study therapy was discontinued on Day 10 due to the serious adverse events of a total serum bilirubin of 11.25 mg/dl and veno-occlusive disease (VOD). The VOD was considered by the investigator to probably not be related to AmBisome™. On Day 11, the total serum bilirubin value was still very elevated (14.63 mg/dl). The patient received marketed caspofungin 60 mg on the evening of Day 11, 40 mg from Day 12 to Day 15, and 20 mg from Day 16 to Day 21. Total serum bilirubin was 8.18 mg/dl on Day 12, and 4.92 mg/dl on Day 13 showing improvement of the hyperbilirubinemia. The hyperbilirubinemia was considered by the investigator to not only be due to the VOD but to be possibly related to AmBisome™. A de-challenge was positive. On Day 14, the total serum bilirubin value was 7.65 mg/dl, but on Day 17, the patient experienced worsening hyperbilirubinemia with a total serum bilirubin value of 21.32 mg/dl. The worsening hyperbilirubinemia was considered by the investigator to probably not be related to AmBisome™ and continued. Below Graph 1 shows a trend in the levels of total bilirubin with regards to duration of treatment with AmBisome and Caspofungin.

Figure 3:



MO Comment: *The bilirubin levels appear to decrease with the withdrawal of AmBisome, however the increase in levels 5 days after the introduction of caspofungin could be due to either caspofungin, or to the underlying illness of the patient.*

Table 62 Bilirubin Levels and Liver Function Tests per Treatment Dose (Subject 4012)

Day of Study	Dose of Medication	AST	ALT	Alkaline Phosphatase	Total Bilirubin (mg/ dL)
0	N/A				1.68
1		9	15		
3	Ambisome 3mg/kg	8	6	105	.86
6	Ambisome 5mg/kg	4	7	94	-
10	Ambisome Discontinued	8	9	**108**	**11.25**
11	Caspofungin 60mg				**14.63**
12	Caspofungin 40mg				8.18
13	Caspofungin 40mg				4.92
14	Caspofungin 40mg				7.65
16	Caspofungin 20mg				-
17	Caspofungin 20mg				**21.32**
22	Caspofungin 20mg	**50**	**83**	**542**	**39.09**

On Day 18, the patient experienced acute respiratory distress syndrome and refractory leukemia and was subsequently intubated. The patient died on Day 22. The cause of death was refractory leukemia and respiratory failure. Total bilirubin levels at time of death, along with AST and ALT were quite elevated as noted in the table above. The reporting investigator felt that the refractory leukemia and respiratory failure were definitely not related to study therapy. This case was adjudicated and found to be "not a fungal infection". An autopsy was not performed.

MO Comment: *While this is an Ambisome treated patient per the protocol, this patient also received marketed caspofungin, which may have increased the total bilirubin. The other liver function tests*

do not seem as affected until the final day when the patient expired. The initial stability of the other liver enzymes with the increase in total bilirubin points more to the veno-occlusive disease as a possible etiology, although caspofungin cannot be excluded. There were also no labs completed to look for hemolysis as a possible etiology of the increase in bilirubin.

7.3.2 Dropouts and/or Discontinuations

Overall, there were 12 patients treated with caspofungin and 5 patients treated with AmBisome who discontinued therapy due to an adverse event. Below is Table 63, which shows the listings of patients who discontinued their medication due to clinical AE, regardless of causality. Comments on patients who died are discussed under deaths, and the two patients whose AEs were thought to be due to caspofungin are discussed below.

Table 63 Pediatric Patients who Discontinued their Medication due to Clinical AEs

Study #	Dose	Day of onset	AE	Duration	Day Rx d/c'd	Intensity	AE Related to Drug	Outcome
CASPOFUNGIN								
7442	32mg	8	Pyrexia	11 days	8	Moderate	Def. Not	Recovered
7457	None[1]	9	Pyrexia	2 days	8	Moderate	Prob Not	Recovered
7458	35mg	4	Pyrexia	3 days	4	Moderate	Prob Not	Recovered
7531	60mg	9	Fungal Pnuemonia	15 days	9	Severe	Def Not	Fatal
7460	56mg	3	Pyrexia	4 days	4	Moderate	Def Not	Recovered
7453	17mg	5	Pyrexia	4 days	5	Moderate	Prob Not	Recovered
7455	None[1]	13	Pyrexia	3 days	12	Moderate	Prob Not	Recovered
6162	54mg	6	Zycomycosis	Cont	8	Severe	Def Not	Not recovered
6145	66mg	29	AML, PNA, Sepsis	1 day	29	Severe	Def Not	Fatal
4221	None	1	Rash	17 days	7	Moderate	Possibly	Recovered
4155	46mg	14	Fungal Infection	1.15 months	36	Mild	Prob Not	Recovered
4172	50mg	6	Hypotension	4 hours	6	Moderate	Possibly	Recovered
AMBISOME™								
4012	110mg	10	Hyperbilirubinemia, Veno-occlusive Disease	4 days Cont	10	Severe	Possibly Probably Not	Recovered Not Recovered
4037	None[1]	3	Rash	9 days	2	Moderate	Prob Not	Recovered
4106	208mg	9	Pneumonia	6 days	9	Mild	Def Not	Recovered
4120	30mg	1	Circumoral edema	3 days	1	Severe	Probably	Recovered
4154	0.24mg	1	Angioedema, Dyspnea, Laryngospasm	10 min 10 min 10 min	1	Severe	Def Probably Def	Recovered

MO Comment: *While the adverse event was not considered to be due to the drug, there is a large percent (50%) of patients who were discontinued due to pyrexia, ----- ---------- ------ ------- ---- t-- ----- l.*

Patient 4172 received caspofungin at 50 mg/m^2/day (following the protocol 70-mg/m^2 loading dose) for the treatment of persistent fever and neutropenia. On the second day - during the second infusion of AmBisome placebo - the patient experienced erythema and flushing of the arms and legs. On Day 3, the infusion nurse noted that the patient had flushed red cheeks while asleep during the first caspofungin infusion of the day; however, no hypotension was noted. Hypotension was noted on Day 4 to with a blood pressure of approximately 80/30 mmHg near the end of the caspofungin infusion. A normal saline solution bolus was administered prior to the infusion of the second infusion (placebo). On Day 5, 10 minutes into placebo infusion, the patient experienced a blood pressure of about 80/30 mmHg with a rash on her arms and legs bilaterally. The placebo infusion was aborted, and caspofungin study therapy was discontinued. The rash resolved after treatment with diphenhydramine. The hypotension resolved with the treatment of a normal saline solution bolus. The reporting investigator felt that hypotension reported on Day 5 was a SAE and was probably related to caspofungin study therapy.

MO Comment: *While caspofungin may have played a role in this SAE, it is unclear as to why the patient experienced hypotension and rash with the placebo infusions as well. Perhaps the infusion of the placebo was also infusing caspofungin that remained in the IV line. It may also be possible that the underlying illness was a cause of the SAE and was unrelated to the study medication. However, given the time line and the severity of the adverse event, I agree with investigator with regards to the possible relation of the study drug with the AEs.*

Patient 4221 received caspofungin at 50 mg/m^2 daily again following a 70-mg/m^2 loading dose on Day 1 for the treatment of persistent fever and neutropenia. The patient developed a rash on his hands and abdomen on Day 1. Although the rash was considered non-serious, the event was considered by the investigator to be possibly related to caspofungin study therapy. This led to discontinuation of caspofungin study therapy on Day 7. The rash resolved 10 days later during the post-therapy follow-up period. Concomitant medications started approximately at the same time as the study drug included: amikacin (Day -3), ciproxine (Day -2); metronidazole (Day -2), vancomycin (Day -1).

MO Comment: *The development of rash occurring after the infusion of caspofungin, points to a possible relation between the study drug and AE. It is unclear as to why the study drug was not discontinued sooner, or why the rash took so long to resolve. Perhaps it was secondary to an immune complex or cell mediated rash rather than an IgE mediated rash. It is also possible that the rash was due to other antibiotics the child had been given. Given that the concomitant medications started around the same time as the caspofungin, it is difficult to attribute the rash solely to caspofungin. The concomitant medications may also explain the long duration of the rash as the other concomitant medications continued past the discontinuation of the caspofungin.*

7.3.3 Serious Adverse Events

Thirty-seven (21.6%) of the 171 pediatric patients treated with caspofungin had at least one serious clinical AE during the study. Most of these SAEs were consistent with the baseline illnesses of the enrolled patients, as there were predisposing factors for invasive fungal infections such as: prematurity, prolonged catheterization, prolonged exposure to antibiotics, malignancies, and neutropenia. Overall, the most common serious clinical adverse experiences among caspofungin-treated patients were pyrexia (2.3%), pneumonia (2.3%), and hypotension (2.3%). Table 64 displays the number (%) of patients with specific serious clinical adverse experiences by study type (PK study or safety/efficacy study), and treatment group.

Of the 66 patients who received caspofungin in the pharmacokinetic (PK) studies, 18 (27.3%) patients had at least one serious clinical AE. Pyrexia (4.5%), hypotension (3.0%), and hypoxia (3.0%) were the most commonly reported serious clinical adverse experiences in the PK studies. Nineteen (18.1%) of the 105 patients in the safety/efficacy studies had at least one serious clinical adverse experience. The most frequently reported SAEs in the safety/efficacy studies were pneumonia (2.9%) and hypotension (1.9%). Based on the data supplied by the sponsor, similar proportions of patients had at least one serious clinical adverse experience in the caspofungin and AmBisome™ groups: 21.6% and 23.1%, respectively. Per the sponsor, there does not appear to be any major differences in degree of serious clinical AEs by initial caspofungin maintenance dose level, study type or treatment group (caspofungin vs. AmBisome™).

Table 64 Serious Adverse Events* by Study Type, Age and Treatment Group

Serious AEs	Pediatric Caspofungin Studies (N= 171)	Pharmacokinetic Studies (N = 66)	Safety/Efficacy Studies (N = 105)	Protocol Caspofungin (N = 56)	044 Ambisome™ (N = 26)	Adult Caspofungin Studies (N=1576)
Total % with SAE	**21.6%**	27.3%	18.1%	21.6%	23.1%	**25.8%**
Pyrexia	**2.3%**	4.5%	1.0%	2.3 %	0%	**1.2%**
Pneumonia	**2.3%**	1.5 %	2.9%	2.3 %	3.8%	**2.1%**
Hypotension	**2.3%**	3.0%	1.9%	2.3%	0%	**0.8%**
Hypoxia	**1.2%**	3.0%	0%	1.2%	0%	**0.4%**

Modified Tables from Appendix 2.7.4:11, 2.7.4:12, and 2.7.4:13 in submitted Summary of Clinical Safety, and Submitted Adult Tables by Sponsor. * All causality

MO Comment: *Overall, with regards to total SAEs, there were very little differences between the pediatric population and the adult population or between caspofungin and AmBisome in the randomized study except for pyrexia, hypotension, and hypoxia which were higher in the caspofungin treated patients and highest in the pediatric caspofungin treated patients.* ---------- . **There were a total of 19 cases of hypotension in the caspofungin pediatric studies. Three of the 19 (15.8%) were considered to be infusion related and are discussed in Section 7.4.11.**

7.3.4 Adverse Events of Special Interest

Hepatic

A total of 10 (5.9%) caspofungin treated patients had a hepatobiliary disorder as defined in Table 65. The incidence of hepatic adverse events was comparable among the PK, safety and efficacy studies and AmBisome groups. The two most common AEs were jaundice (N = 3) and hepatosplenomegaly (N = 3). With regards to clinically significant laboratory abnormalities (CSLA), Table 66 has a breakdown of the lab values for hepatic involvement. The most common hepatic events were associated with abnormal liver function test results, including increases in: the aminotransferases: AST, ALT.

Table 65 Incidence (> 0%) of Hepatic Adverse Events by Study Group and Treatment

	Caspofungin – PK Studies N = 66		Caspofungin – SE Studies N = 105		AmBiome™ N = 26		Caspofungin Adult Studies N = 1576	
	n	%	n	%	n	%	n	%
Hepatobiliary	**5**	**7.6**	**5**	**4.8**	**2**	**7.7**	**17**	**1.1**
Hepatitis	1	1.5	0	0	0	0	1	0.1
Hepatitis Toxic	0	0	0	0	1	3.8		
Hepatomegaly	1	1.5	1	1.0	0	0		
Hepatosplenomegaly	2	3.0	1	1.0	1	3.8		
Hepatotoxicity	0	0	1	1.0	0	0		
Hyperbilirubinemeia	0	0	0	0	1	3.8	4	0.3
Jaundice	2	3.0	1	1.0	1	3.8	1	0.1
Liver Failure	--------		--------		---------		4	0.3
Liver Disorder	0	0	1	1.0	0	0		

Modified from Table 2.7.4:7 from Summary of Clinical Safety

Table 66 Number (%) Patients with CSLA by Protocol

Laboratory Test	CSLA Criteria	Caspofungin PK N = 67		Caspofungin SE N = 106		Protocol 044 Caspofungin N = 56		Protocol 044 AmBisome N = 26	
		n/m	%	n/m	%	n/m	%	n/m	%
AST (units/L)	> 2.5 x ULN	3/56	5.4	9/102	8.8	1/55	1.8	2/24	8.3
	> 5 x ULN	0/56		4/102	3.9	1/55	1.8	0/24	
	> 7.5 x ULN	0/56		2/102	2.0	1/55	1.8	0/24	
	> 2.5 x Baseline	7/56	12.5	19/102	18.6	11/55	20.0	8/24	33.3
ALT (units /L)	> 2.5 x ULN	3/56	5.4	9/102	8.8	2/55	3.6	2/24	8.3
	> 5 x ULN	3/56	5.4	5/102	4.9	3/55	5.5	0/24	
	> 7.5 x ULN	2/56	3.6	3/102	2.9	1/55	1.8	0/24	
	> 2.5 x Baseline	7/56	12.5	21/102	20.6	13/55	23.6	8/24	33.3
Alkaline Phosphatase (units/L)	> 2.5 x ULN	0/46		2/96	2.1	0/51	1.8	0/24	
	> 5 x ULN	0/46		1/96	1.0	0/51	1.8	0/24	
	> 7.5 x ULN	0/46		0/96	0	0/51	1.8	0/24	
	> 2.5 x Baseline	1/46	2.2	6/96	6.3	4/51	7.8	2/24	8.3
Total Bilirubin (mg/dL)	> 2.5 x ULN	1/55	1.8	3/99	3.0	2/53	3.8	2/22	9.1
	> 5 x ULN	0/55		2/99	2.0	1/53	1.9	1/22	4.5
	> 7.5 x ULN	0/55		1/99		0/53		1/22	4.5

	> 2.5 x Baseline		1.0	8/53 15.1	5/22	22.7

Modified from Appendix 2.7.4:23 from Summary of Clinical Safety

MO Comment: *The CSLA laboratory results show a higher incidence of abnormal lab AEs within the safety and efficacy studies. Overall, however, they are still lower than the AmBisome compared group and when the two treatment groups within Protocol 044 are compared, AmBisome continues to have higher incidences of abnormal hepatic labs.*

Hypersensitivity

Table 67 Incidence of Hypersensitivity AEs among Studies and Treatment

Organ Class Preferred Term	Caspofungin PK (N = 66)	Caspofungin SE (N =105)	AmBisome™ (N = 26)
Skin and Subcutaneous Tissue Disorders			
Rash NOS	5 (7.6%)	15 (14.3%)	2 (7.7%)
Pruritis NOS	6 (9.1%)	5 (4.8%)	2 (7.7%)
Erythema	1 (1.5%)	8 (7.6%)	0
Rash Pruritic	1 (1.5%)	0	0
Red Man Syndrome	1 (1.5%)	0	0
Immune System Disorders			
Anaphylactic Reaction	0	0	1
Drug Hypersensitivity	5 (7.6)	0	0
Vascular Disorders			
Flushing	1 (1.5)	6 (5.7)	0

MO Comment: *There is a higher incidence of rash in the caspofungin treated patients. When I compared the AmBisome treated group to the Caspofungin treated group for the same protocol, "Rash" had been reported by 13 patients (23.2%), which is still higher than the AmBisome™ treated group. Patients with fungal infections do have a tendency to have a rash, however given the patient population was the same in both groups; we would expect similar number of patients with rash in AmBisome™ as well. Caspofungin may therefore play a role in the higher incidence of rash. In the adult studies, rash was noted in 5 patients (0.3%) and anaphylactic reaction and hypersensitivity were each seen in 1 patient (0.1%).*

Renal

Table 68 Number and % Adverse Events and Abnormal Renal Labs by Study and Treatment

Adverse Events	Caspofungin – PK Studies N = 66		Caspofungin – SE Studies N = 105		AmBiome™ N = 26		Caspofungin Adult Studies N = 1576	
	n	%	n	%	n	%	n	%
Renal and Urinary	**8**	**12.1**	**5**	**4.8**	**1**	**3.8**	**28**	**1.8**
Acute (Pre)-Renal Failure	1	1.5	0	0	0	0	7	0.4
Azotemia	1	1.5	0	0	0	0		
Dysuria	2	3.0	0	0	1	3.8		
Hematuria	1	1.5	2	1.9	1	3.8	1	0.1
Oliguria	1	1.5	0	0	0	0		
Proteinuria	1	1.5	0	0	0	0		

Renal Failure	1	1.5	2	1.9	0	0	20	1.3
Renal Impairment	0	0	1	1.0	0	0		
Urinary Retention	1	1.5	1	1.0	0	0		
CSLA BUN (mg/dL)								
> 2x ULN	0/56		3/103	2.9	1/25	4.0		
> 5 x ULN	0/56		2/103	1.9	0/25			
CSLA Serum Creatinine								
> 2 x ULN	0/56		1/103	1.0	0/25			
> 3 x ULN	0/56		0/103	0	0/25			
> 2 x Baseline	1/56	1.8%	3/103	2.9	1/25	4.0		
> 3 x Baseline	0/56		1/103	1.0	0/25			

MO Comment: *There were 13 patients who had a reported renal incident compared to 1 patient in the AmBisome group. In comparing the breakdown of AEs, however, there does not seem to be a major difference between the caspofungin and AmBisome groups. In protocol 044, there were 4 (7.1%) of caspofungin treated patients with a renal AE. Elevation in blood creatinine ws noted in only one patient. The proportion of patients who developed nephrotoxicity during IV study therapy in Protocol 044 was assessed. Per the sponsor, nephrotoxicity was defined as a doubling of serum creatinine, or an increase in creatinine by 1 mg/dL, if the creatinine was already elevated at study entry. All patients who met these criteria were included; patients with preexisting renal failure and on dialysis were excluded from the analysis. The results showed that all patients had baseline creatinine clearance levels >30 mL/min and only 5 (6.1%) of these patients had nephrotoxicity, as defined per the protocol. Per the sponsor, the rates of nephrotoxicity were similar for the 2 treatment groups: caspofungin 5.5% versus AmBisome™ 8.0%. In comparing with adults, again we have included in this population healthy volunteers. Children with infections, sepsis or even fevers may have proteinuria, and trace hematuria which may account for some of the adverse events.*

Vascular

The following table shows the adverse events associated with the vascular system.

Table 69 Incidence of Vascular AEs by Study and Treatment

Adverse Events	Caspofungin – PK Studies N = 66		Caspofungin – SE Studies N = 105		AmBiome™ N = 26		Caspofungin Adult Studies N = 1576	
	n	%	n	%	n	%	n	%
Vascular								
Jugular Vein Thrombosis	0	0	1	1.0	0	0	2	0.1
Thrombosis	1	1.5	1	1.0	0	0	3	0.2
Phlebitis	1	1.5	1	1.0	0	0	68	4.3
Thrombophlebitis	0	0	1	1.0	0	0	3	0.2
Veno-Occlusive Disease	0	0	0	0	1	3.8	2	0.1

MO Comment: *There does not appear to be any major differences between the treatment groups. There is actually a higher incidence of phlebitis in the adult population.*

7.3.5 Submission Specific Primary Safety Concerns

Across all adult studies, caspofungin has had a favorable safety profile, with few serious, drug-related adverse experiences, and few discontinuations due to drug-related AEs. In previous adult studies, the following drug-related clinical AEs of concern, reported in at least 3% of adult patients, were nausea, vomiting, fever, chills, headache, and phlebitis. Additionally, the following drug-related laboratory AEs have been reported in at least 3% of adult patients: increased ALT, AST, increased alkaline phosphatase, and decreased potassium. Possible allergic reactions have been reported in clinical studies, including isolated reports of rash, facial swelling, pruritus, sensation of warmth, or bronchospasm. Cases of anaphylaxis during administration of caspofungin have also been reported. In the pediatric studies, specific attention was given to infusion reactions.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

One hundred fifty-seven (91.8%) of the 171 patients who received caspofungin had at least one clinical AE. Per the submitted protocol, the most common clinical adverse experiences across the caspofungin groups were pyrexia (29.2%), diarrhea (14.0%), rash (11.7%), chills (11.1%) and hypotension (11.1%). Pyrexia was the most common clinical adverse experience reported at each of the caspofungin dose levels. The number (%) of patients with specific clinical adverse experiences (occurring at an incidence of 0% in any treatment group) is presented by study group in the Table 70 below. Patients enrolled in the PK studies, reported common clinical AEs such as pyrexia (37.9%), diarrhea (21.2%), mucosal inflammation (18.2%), hypotension (15.2%) and chills (15.2%). Pyrexia (23.8%), rash (14.3%), diarrhea (9.5%), vomiting (9.5%) and hypertension (9.5%) were the most frequently reported clinical adverse experiences among the patients in the 2 safety/efficacy (S/E) studies. As noted above, pyrexia (29.2%), diarrhea (14.0%), rash (11.7%), chills (11.1%) and hypotension (11.1%) were the most commonly reported clinical adverse experiences in caspofungin-treated patients. Pyrexia (23.1%) was also the most frequently reported clinical adverse experiences in patients treated with AmBisome™. Other common clinical adverse experiences reported in AmBisome™-treated patients included tachycardia (19.2%) and diarrhea (15.4%). Per the sponsor, after reviewing the data, there were no apparent differences in rates of clinical AEs by initial caspofungin maintenance dose level, study type or treatment group.

Table 70 Percent of Patients with Specific Clinical AE*s (Incidence >0.0% in One or More Treatment Groups) by System Organ Class

Common AEs	Pediatric Caspofungin Studies (N= 171)	PK Studies (N = 66)	Safety/Efficacy Studies (N = 105)	STUDY Caspofungin (N=56)	044 AmBisome™ (N= 26)	Adult CaspofunginStudies (N = 1576)
≥ 1 more AE	**91.8%**	**92.4%**	**91.4%**	**94.6%**	**73.1%**	**84.6%**
Cardiac	**15.8%**	16.7%	15.2%	**12.5%**	**19.2%**	**11.8%**
Tachycardia	10.5% [2]	10.6% [2]	10.5% [2]	10.7%[3]	19.2%[3]	5.2%[2]
General Disorders	**50.3%**	**54.5%**	**47.6%**	**57.1%**	**42.3%**	**44.1%**

Chills	11.1%	15.2%	8.6%	12.5%	7.7%	10.9%
Mucosal Inflammation	8.2%	18.2%	1.9%	3.6%	3.8%	2.5%
Pyrexia	29.2%	37.9%	23.8%	30.4%	23.1%	20.2%
GI Disorders	**41.5%**	**48.5%**	**37.1%**	**41.1%**	**34.6%**	**39.3%**
Diarrhea	14.6% [1]	22.7% [1]	9.5% [1]	7.1%	15.4%	15.0%
Vomiting	8.8%	7.6%	9.5%	10.7%	11.5%	7.2%
Skin Disorders	**35.7%**	**34.8%**	**36.2%**	**41.1%**	**38.5%**	**27.2%**
Rash	11.7%	7.6%	14.3%	23.2%	7.7%	8.3%
Vascular Disorders	**23.4%**	25.8%	21.9%	**21.4%**	**19.2%**	**16.9%**
Hypertension	9.4%	9.1%	9.5%	8.9%	3.8%	4.1%
Hypotension	11.1%	15.2%	8.6%	8.9%	7.7%	5.6%

Modified Table from Appendix 2.7.4:7 and 2.7.4:8, Table 2.7.4:16 from submitted Summary of Clinical Safety, Table 14-11 from Protocol 044, and submitted adult tables from the Sponsor; * All causality; 1 Includes AE of *frequent bowel movements*; 2 Includes both AEs of *sinus tachycardia* and *tachycardia*; 3 all *tachycardia*

MO Comment: *In comparing the pediatric caspofungin treated patients with the adult patients, there is a difference of 7.2% between the two groups with a higher incidence of adverse events in the caspofungin treated patients. This slight increase may be explained by the difference in population at enrollment. The adult caspofungin studies include subjects who were healthy volunteers, which may account for a lower incidence of reported adverse events. Why the incidence of pyrexia, diarrhea and mucosal inflammation as an AE is higher in the PK studies is unclear. There were a total of 19 cases of hypotension in the caspofungin pediatric studies. Three of these 19 (2 were reported as hypotension and 1 was reported as blood pressure decrease) were considered to be infusion related and are discussed in Section 7.4.11. The remaining 17 were not necessarily attributed to caspofungin. The higher incidence of hypotension in the pediatric population could again be due to their underlying illness: immunocompromised children with a history of underlying hematological or solid organ malignancies, immunocompromised children with a history of underlying malignancies with persistent fever and neutropenia, neonates and infants <3 months of age, and patients with known fungal or presumed fungal infections. Children with these underlying illnesses can become hypotensive if they are septic from other infections or their fungemia. The breakdown of hypotension by study is shown below in Table 14A. The highest incidence of hypotension was seen in Protocol 033 in the 2-11 year age group receiving 50 mg/m^2.*

Table 71 Incidence of Hypotension by Protocol

Protocol 033 N = 39		Protocol 042 N = 9		Protocol 058 N = 18		Protocol 043 N= 49		Protocol 044 Caspofungin N = 56		Protocol 044 AmBisome N = 26	
n	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
8	**20.5**	**1**	**11.1**	**1**	**5.6**	**4**	**8.2**	**5**	**8.9**	**2**	**7.7**

Table 72 Incidence of Hypotension in Protocol 033 by Age and Dose of Caspofungin

2-11 year olds 1mg/kg N = 7		12-17 year olds 1mg/kg N = 2		2–11 year olds 50 mg/m^2 N = 10		12-17 year olds 50 mg/m^2 N = 8		2-11 year olds 70 mg/ N = 12	
n	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
2	**28.6**	**0**		**3**	**30**	**2**	**25**	**1**	**8.3**

Modified Table 27 from Protocol 033

7.4.2 Laboratory Findings

Below is Table 73 demonstrating the main laboratory AEs (> 2%) in either the PK or SE caspofungin treated studies in comparison to the laboratory AEs in the AmBisome™ treated group. Per the sponsor, there were no patients in the pediatric studies who had serious laboratory AEs or discontinued due to drug-related laboratory adverse experiences.

Table 73 Specific Laboratory AEs (> 0%) by Study, Population and Treatment Type

Laboratory Result	Pediatric Caspofungin Studies (N = 171)		Protocol 044 Caspofungin (N = 56)		AmBisome (N=26)		Adult Caspofungin Studies (N = 1576)	
	n/m	%	n/m	%	n/m	%	n/m	%
≥ 1 Laboratory AE	**78/171**	**45.6**	**18/56**	**32.1**	**13/26**	**50**	**580/1576**	**36.8**
Blood Chemistry	**72/171**	**42.1**	**15/56**	**26.8**	**13/26**	**50**		
Increased ALT	19/170	11.2	3/56	5.4	3/26	11.5	228/1576	14.5
Increased AST	20/170	11.8	1/56	1.8	3/26	11.5	198/1576	12.6
Increased Alkaline Phosphatase	5/155	3.2	---	---	0/26		206/1576	13.1
Increased Blood Bilirubin	8/169	4.7	1/56	1.8	1/25	4.0	103/1576	6.5
Increased Blood Creatinine	4/170	2.4	1/56	1.8	0/26		59/1576	3.7
Increased Blood Glucose	9/152	5.9	2/53	3.8	0/24		67/1576	4.3
Increased Blood Phosphorus	4/152	2.6	1/56	1.8	0/26		35/1576	2.2
Decreased Blood Calcium	6/154	3.9	2/56	3.6	0/26		50/1576	3.2
Decreased Blood Phosphorus	6/152	3.9	1/56	1.8	0/26		51/1576	3.2
Decreased Blood Potassium	26/170	15.3	5/56	8.9	7/26	26.9	180/1576	11.4
Hematology Lab Tests	**24/170**	**14.1**	**1/56**	**1.8**	**0/26**			
Increased ANC Count	2/169	1.2	-----	----	0/26		---------	-----
Increased Band Neutrophils	4/145	2.8	-----	----	0/19		---------	-----
Increased Eosinophil Count	3/167	1.8	-----	----	0/25		14/1576	0.9
Increase Platelet Count	3/170	1.8	1/56	1.8	0/26		18/1576	1.1
Increase White Blood Cell Count	5/170	2.9	-----	----	0/26		24/1576	1.5
Decrease Hemoglobin	7/170	4.1	-----	----	0/26		88/1576	5.6
Decrease Hematocrit	4/170	2.4	-----	----	0/26		75/1576	4.8
Decrease Lymphocyte Count	2/169	1.2	-----	----	0/25		10/1576	0.6
Decrease Platelet Count	7/170	4.1	-----	----	0/26		56/1576	3.6
Decrease White Blood Cell Count	1/170	0.6	-----	----	-----	----	44/1576	2.8
Hemostatic Function Tests	**5/147**	**3.4**	**1/52**	**1.9**	**0/25**			
Prolonged aPTT	2/144	1.4	1/51	2.0	0/25		41/1576	2.6
Prolonged PT	3/145	2.1	-----	----	0/25		43/1576	2.7
Urinalysis Test	**7/135**	**5.2**	**2/48**	**4.2**	**1/24**	**4.2**		
Glucosuria	2/135	1.5	1/48	2.1	0/24		15/1576	1.0
Hematuria (microscopic)	2/75	2.7	1/19	5.3	0/9		22/1576	1.4
Pyuria	2/58	3.4	0/20		1/9	11.1	43/1576	2.7

MO Comment: *Overall, there were very little difference between patients experiencing laboratory associated AEs between the caspofungin treated and AmBisome treated groups (45.6% and 50% respectively). Overall, there was a higher incidence of children with laboratory adverse events compared to adults (45.6% and 36.8% respectively) which can be accounted for by the healthier population enrolled in the adult studies. When looking at the specific lab values, however, there were little differences between the adult and the pediatric population. Hypokalemia was higher in*

the pediatric population and was the biggest difference between the two groups. Increase in AST and ALT in the caspofungin treated patients were similar to the elevations seen in the AmBisome treated patients, and are consistent with increases seen in the echinocandin class family. There were more differences in the caspofungin treated patients with regards to electrolyte changes (i.e. hypocalcemia, hypophosphatemia, and most noticeably hypokalemia). In the hematology section, there are higher percentages of anemia and thrombocytopenia (4.1% for both compared to 0% in the AmBisome treated population). However, when these variables are compared between the caspofungin and AmBisome treated patients in Protocol 044, there is again almost no difference between the two groups. There is mention of increase absolute neutrophil count (ANC) during treatment with caspofungin, but no AEs associated with decreasing ANC. Overall the laboratory adverse events are consistent with echinocandin class; and careful monitoring should be applied to monitoring LFTS (AST, ALT), and potassium levels.

7.4.3 Vital Signs

See below for systemic-infusion related events.

7.4.4 Electrocardiograms (ECGs)

The majority of patients had only baseline ECGs per study protocol. No follow-up ECGs were planned or collected. The possibility of QT prolongation in pediatric patients, therefore, cannot be ascertained. In the adult studies, there was only 1 (0.1%) patient with a prolonged QT.

7.4.5 Special Safety Studies

7.4.5.1 Systemic Infusion-Related Events

Systemic infusion-related events, defined as systemic symptoms such as fever or chills beginning during caspofungin study drug infusion or within one hour following infusion, were recorded daily during IV infusion of the study therapy. Overall, 37 (21.6%) of the 171 caspofungin-treated patients enrolled in the pediatric studies had at least one systemic infusion-related event. The most common systemic infusion-related events were fever (10.5%), headache (2.9%), chills (1.8%) and hyperventilation (1.8%). Per the investigators, the majority of these infusion-related events were of mild or moderate intensity. Per the sponsor, systemic infusion-related events were reported in patients treated with caspofungin 25 mg/m^2 and caspofungin 50 mg/m^2 (22.2% and 25.0%, respectively). Six (9.1%) of the 65 patients who received caspofungin in the pharmacokinetic studies experienced a systemic infusion related event. The most commonly reported systemic infusion related event in this population was hyperventilation (4.5%). Thirty-one (29.5%) of the patients in the safety/efficacy studies experienced fever (16.2%). The incidence of systemic infusion related events was numerically higher in patients receiving caspofungin in the safety/efficacy studies (29%) than in patients receiving caspofungin in the pharmacokinetic studies (9%).

MO Comment: *The sponsor attributes this higher incidence of systemic infusion-related events in the safety/efficacy studies to the increase in duration of caspofungin among the patients enrolled in*

this study (mean duration 14.8 days and 7.8 days, respectively). It does seem reasonable that the longer duration would incur more potential for incidences of infusion related events. ----------

Based on the information provided by the sponsor, the overall incidence of systemic infusion related events was numerically higher in the AmBisome™ group (34.6%) than in the caspofungin group (21.6%). However, when we compare the caspofungin treated patients within the same protocol as the AmBsiome treated patients, we find a higher percentage within that group (41.1% vs. 34.6%). Fever (including temperature elevation) was the most common systemic infusion-related event in both the caspofungin group (11.1%), and AmBisome™ treated patients (26.9%). Chills were reported as a systemic-infusion (SIR) related event in 7.7% of the patients in the AmBisome™ group. In contrast, chills were reported in only 1.8% of the patients in the caspofungin group within that same protocol. Table 74 shows the percent of patients with Infusion-Related Events by age, and treatment group. Similar events were grouped together to make a better assessment of the findings.

Table 74 Systemic Infusion Related (SIR) Adverse Events by Study, Population, and Treatment

SIR Adverse Event	**Pediatric Caspofungin Studies (N = 171)**	**Protocol 044**	
		Caspofungin (N = 56)	**AmBisome (N = 26)**
N/% of patients with ≥ 1 SIR AE	37 (21.6%)	23 (41.1%)	9 (34.6%)
Chills / Shivering	3 (1.8%)	1 (1.8%)	3 (11.5%)
Exanthem /Rash/Rash maculo-papular rash/ Skin rash	5 (2.9%)	3 (5.4%)	0
Fever / Temperature Elevation	19 (11.1%)	14 (25.0%)	7 (26.9%)
Flushing / Redness in Face / Facial Erythema / Skin Flushed	5 (2.9%)	5 (8.9%)	1 (3.8%)
Headache	5 (2.9%)	5 (8.9%)	0
Hyperventilation	3 (1.8 %)	-----	------
Hypotension / BP Decrease	3 (1.8%)	2 (3.6%)	0
Vomiting	2 (1.2%)	2 (3.6%)	2 (7.7%)

7.4.5.2 Concentration-Effect Relationships for AEs and Laboratory Abnormalities in Pediatric Patients

The potential for the area under the curve ($AUC_{0\text{-}24hr}$), C_{1hr} (peak), and C_{24hr} (trough) to predict the incidence and or absence of certain clinical AEs or laboratory abnormalities was also investigated in a pooled analysis of data from Protocols 033, 042, 043, and 044 by the sponsor. The results propose that the occurrence of AEs is not increased by higher caspofungin plasma concentrations over the range of pharmacokinetic parameter values examined. However, the possibility that $C_{24\ hr}$ may be an indicator of the occurrence of ALT >2.5 times baseline can not be ruled out for pediatric patients who were treated for persistent fever and neutropenia. This is based on the fact that the point estimate of the odds ratio for $C_{24\ hr}$ was considerably greater than 1 with p=0.011. However, the

effect of trough concentration ($C_{24\ hr}$) on ALT elevation for pediatric patients empirically treated for persistent fever and neutropenia is not anticipated to be clinically meaningful since the findings were not consistent across all liver function test biomarkers and across all indications for laboratory abnormalities.

The reviewer also conducted sensitivity analyses for adverse reactions that were seen in pediatric patients at the rates higher as compared to adults, such as hypotension (11.1% versus 5.6%) and rash (11.7% versus 8.3%) to indirectly assess exposure-event relationship. As none of the studies in this supplemental NDA explored a range of doses for pediatric patients, the reviewer addresses the incidence of the adverse events of interest per following age subgroups: 3-24 months, 2-11 years, and 12-17 years. This approach has been taken due to the fact that significant differences in C1hour were observed between these age subgroups and adults. The following table reflects the reviewer findings.

Table 75 Incidence of Hypotensive and Rash Adverse Reactions by Age and Caspofungin C1h

	Adults	Pediatric Patients 12-17 years	Pediatric Patients 2-11 years	Pediatric Patients 3-24 months	Pediatric Patients 0-3 months
N (safety database)	1576	38	104	12	18
C1h (GMR)	9.39 (1.0)	12.9 (1.37)	15.61 (1.66)	17.21 (1.83)	11.7 (1.25)
Hypotension AR	88 (5.6%)	4 (10.5%)	13 (12.5%)	1 (8.3%)	1 (5.5%)
Rash AR	131 (8.3%)	10 (26.3%)	30 (28.8%)	2 (16%)	0

GMR geometric mean ratio

MO Comment: *It appears that there was no increase in incidence of the hypotension and rash adverse reactions with the decreasing age and corresponding increase in C1h. These findings are consistent with conclusions of the clinical pharmacology review done by Dr. Dakshina Chilukuri. While the area under the curve (AUC) and C_1 values are higher in the pediatric population compared to adults, there has been no significant increase in adverse events to accompany this increase in C1h concentrations. There are, however, some limitation to the data including the small number of patients and the fact that only one medication dose was studied.*

7.4.6 Immunogenicity

Not Applicable. Nothing in the pediatric studies suggests there is an immunogenic reaction.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Protocols 043 and 044 permitted an increase in the initial dose of caspofungin therapy in certain patients who met the criteria for poor clinical response. The caspofungin dose was increased from 50 to 70 mg/m^2/day (up to a maximum of 70 mg/day). Overall, 6 patients enrolled in these studies were dose-escalated: 5 in Protocol 043 and 1 in Protocol 044. Four of the 6 patients who had their caspofungin dose increased to 70 mg/m^2/day subsequently experienced at least one drug-related clinical and/or laboratory adverse experience. All of these drug-related adverse experiences

subsequently resolved during the caspofungin therapy period. Per the sponsor, none of the drug-related adverse experiences were considered serious or led to discontinuation of caspofungin therapy.

7.5.2 Time Dependency for Adverse Events

Not Applicable

7.5.3 Drug-Demographic Interactions

7.5.3.1 Gender

There were more male patients (N = 124) than female patients (N= 73) enrolled in both the caspofungin and AmBisome™ treatment groups. The incidence of clinical and laboratory AEs was similar for both male and female patients in the caspofungin treatment group (89.4% / 43.3% and 95.5% / 49.3%, respectively). The incidence of clinical AEs in male and female patients in the AmBisome treatment groups however showed a larger difference between the two genders (85% and 33.3%, respectively). Table 76 shows the clinical and laboratory adverse AEs by gender in the capofungin treated group.

Table 76 Clinical and Laboratory AEs in Male and Female Caspofungin Pediatric Treated Patients

Number / % Patients	Male N = 104		Female N = 67	
With ≥ 1 Clinical AE	93	89.4%	64	95.5%
With Serious Clinical AE	20	19.2%	17	25.4%
Who Died due to Clinical AE	9	8.7%	2	3.0%
Who Discontinued due to Clinical AE	11	10.6%	2	3.0%
Who Discontinued due to Serious Clinical AE	4	3.8%	1	1.5%
With ≥ 1 Lab AE	45	43.3%	33	49.3%
With Serious LAB AE	1	1.0%	0	
Who Died due to Lab AE	0		0	
Who Discontinued due to Lab AE	0		0	
Who Discontinued due to Serious Lab AE	0		0	

MO Comment: *The main differences seen are a higher death incidence and higher discontinuation due to clinical adverse events in the male population. Given the small number of females enrolled, the difference is likely due to chance.*

7.5.3.2 Race

The majority of the patients enrolled in the caspofungin and AmBisome™ treatment groups were White (67.8% and 80.8%, respectively). A similar proportion of Black patients were enrolled in the two treatment groups (7.6% and 7.7%, respectively). A higher proportion of patients with other races were enrolled in the caspofungin group (24.6%) than in the AmBisome™ group (11.5%). Overall, the incidences of drug-related clinical AEs were higher for White, Black, and Other race patients in

the AmBisome™ group (47.6%, 50% and 33.3% respectively) than for each of the races in the caspofungin group (27%, 15% and 29%, respectively). Within the caspofungin-treated patients, the incidence of drug-related laboratory AEs was similar for White, Black, and Other race patients (15.5%, 23.1% and 16.7% respectively). A similar number of White patients had one or more drug-related laboratory AE in the caspofungin group (15.5%) and the AmBisome™ group (9.5%). A higher proportion of patients of Black race developed a drug-related laboratory AE in the AmBisome™ group (100%) in comparison to the caspofungin group (23.1%). Below is Table 77 showing death per race demographic.

Table 77 Deaths per Race Demographic in Caspofungin Treated Patients

Race	Number and Percent of Patients Enrolled by Race (N = 171)	Number and Percent of Deaths within each Race category (N = 12)	Percent of Deaths to Number of Patients Enrolled within each Race Category
Native American / Alaskan	12 (7.0%)	1 (8.3%)	(8.3%)
Asian	14 (8.2%)	4 (33.3%)	(28.6%)
Black / African Heritage	13 (7.6%)	0 (0.0%)	(0.0%)
Multi-Racial	16 (9.4%)	1 (8.3%)	(6.3%)
White	116 (67.8%)	6 (50.0%)	(5.2%)

Modified Table from Appendix 2.7.4:2 in submitted Summary of Clinical Safety

MO Comment: *The Asian population accounted for more deaths in the Safety and Efficacy studies with 3 of the 5 Asian patients enrolled resulting in death and one Asian patient dying in the 058 PK study. The main causes of death included, in most cases, an underlying fungal pneumonia. It is however difficult to put major emphasis on the differences in the occurrence of the clinical or laboratory AEs given the small population size. It may be advisable to monitor for ongoing increases in AEs including death in the Asian population during Post-Marketing assessments.*

7.5.3.3 Ethnicity

The majority of patients enrolled in both the caspofungin and AmBisome treatment groups were of non-Hispanic ethnicity (77.8% and 84.6%, respectively). More Hispanic and non-Hispanic patients in the AmBisome™ group had a drug-related clinical AE (25% and 50%, respectively) as compared with the caspofungin group (15.8% and 29.3%, respectively). However, the incidence of drug-related clinical adverse experiences was greater for non-Hispanic patients for both treatment groups. The incidences of drug-related laboratory AEs in the caspofungin group were similar for patients of Hispanic ethnicity (13.2%) and patients of non-Hispanic ethnicity (17.3%). Although the incidence of drug-related laboratory adverse experiences was numerically higher in Hispanic patients who received AmBisome™ (25%) as compared to the Hispanic patients who received caspofungin (13.2%), the incidences of drug-related laboratory were similar for the Non-Hispanic patients across the 2 treatment groups (18.2% in the AmBisome™ group and 17.3% in the caspofungin group).

MO Comment: *Again, meaningful assessments are difficult to make given the small sample size.*

7.5.4 Drug-Disease Interactions

According to the current FDA label for caspofungin, patients with mild hepatic insufficiency (Child-Pugh score 5 to 6) do not need a dosage adjustment. For patients with moderate hepatic insufficiency (Child-Pugh Score 7 to 9), CANCIDAS 35 mg daily is recommended. However, where recommended, a 70-mg loading dose should still be administered on Day 1. There is no clinical experience in patients with severe hepatic insufficiency (Child-Pugh score >9).

MO Comment: *There is also no current information with regards to the pediatric population at this time.*

7.5.5 Drug-Drug Interactions

See Section 7.2.5. for the discussion of Drug – Drug interactions

7.6 Additional Safety Explorations

7.6.1 Human Carcinogenicity

There is limited data on the carcinogenic nature of caspofungin in humans. Dr. Owen McMaster reviewed Micafungin, a similar class of anti-fungal medication that was approved by the FDA on March 16th 2005. It was shown in animal studies that very high doses (5-10 times the clinical dose), when administered for prolonged periods, produced irreversible changes to the liver. Two-year studies in rats were performed to evaluate the reversibility of altered hepatocellular foci observed in rats. In these studies, the rats were treated for three or six months with doses 5 or 8 times the recommended human dose based on AUC comparisons and sacrificed after varying recovery periods. Adenomas and carcinomas were recorded in the rats during the 18- and 21-month follow-up period.

7.6.2 Human Reproduction and Pregnancy Data

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

7.6.3 Pediatrics and Effect on Growth

There is no data regarding the effects of growth in the pediatric population

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

According to the current label for adult patients, the highest dose administered in clinical studies was 210 mg, which was administered as a single dose to 6 healthy subjects. In addition, 100 mg once daily for 21 days has been administered to 15 healthy subjects and was generally well tolerated. The minimum lethal dose of caspofungin in rats was 50 mg/kg, which is 10 times the recommended daily dose based on relative body surface area comparison. Caspofungin is not dialyzable.

Two patients (1%) in the pediatric studies experienced an overdose of caspofungin study therapy. The 2 patient overdoses are described below. In the pediatric pharmacokinetic study Protocol 042, a drug-prescribing error was reported for Patient 3600. The patient inadvertently received 2 doses of caspofungin study therapy on Day 1 (total exposure: 48 mg) due to a pharmacy/nursing error, ultimately resulting in an unintentional study drug overdose. No safety findings were noted after either of the two caspofungin doses administered on Day 1. The patient continued on caspofungin study therapy for 11 additional days.

MO Comment: *Patient 3600 was one of the subjects who died during this study. On Day 4 of caspofungin study therapy, the patient had worsening respiratory distress and was intubated and ventilated. On Day 22 (10 days following the completion of caspofungin study therapy), the patient expired. CMV pneumonia was considered to be the cause of death. While side effects caused by overdoses of caspofungin are not fully known, it is doubtful that this medication error attributed to, or caused a worsening in the CMV.*

In the pediatric empirical therapy study (Protocol 044), patient 4144 was randomized to the caspofungin treatment group and received a single dose of caspofungin at 113 mg. This event was reported and no adverse experience occurred as a result of the overdose. The patient continued on caspofungin study therapy at the protocol-specified dose (80 mg) for 7 additional days and subsequently completed the study.

Since caspofungin is an anti-infective the probability of abuse is considered to be low. No evidence of drug abuse was observed in the current pediatric studies or in previous clinical trials involving adults. Caspofungin is administered intravenously by medical staff and not by patients. No withdrawal or rebound effects were observed in these pediatric studies or in previous adult clinical trials. Given the method of action in this medication, the terms withdrawal and rebound are not applicable to this compound.

7.7 Additional Submissions

Not Applicable

8 Postmarketing Experience

MO Comment: *Please refer to Dr. Eileen Navarro's Full Report Below*

The sponsor submitted a review using the Merck Worldwide Adverse Experience System (WAES) to summarize the postmarketing information involving caspofungin use in pediatrics. Between December 14 2000 and August 31, 2007, a total of 153 AE reports in pediatric patients treated with caspofungin were identified in the database. In 104 (68%) of the 153 reports, adverse experiences were categorized as serious. The most frequently reported SAEs were: (1) those related to the serious, underlying medical conditions and/or concomitant medications of patients receiving caspofungin; (2) events related to the method utilized to code adverse experience reports in the pediatric population (i.e., reports of "prescribed overdose" and "overdose" reflect the local coding convention utilized for off label use of caspofungin in pediatric patients); and (3) pancreatitis.

Per the sponsor, evaluation of the 11 pancreatitis reports does not suggest a contributory role of caspofungin in the development of pancreatitis. Of these 11 cases, 4 (36.4%) reports included 1 other concomitant condition associated with pancreatitis such as: medications (pentamidine, stavudine, trimethoprim-sulfamethoxazole, voriconazole), ethanol ingestion, and/or CMV disease. In 1 report, pancreatitis was reported to develop 2 months after the discontinuation of caspofungin. In the 6 remaining reports, all from the same site, interpretation was difficult due to the limited data that was provided despite attempts to obtain additional information. Overall, the review of the reports does not suggest a causal role for caspofungin in the development of pancreatitis.

MO Comment: *Assuming the concomitant factors played a role in the development of the patients' pancreatitis in the four patients mentioned above, there is still approximately over 50% of the patients were there is no clear cut interpretation of the causality. However, in all the studies of the current submitted protocol, there was only one AE of pancreatitis and that was in the AmBisome™ treated group. Given that the above 6 AEs were all from one site, it may be possible that the reported pancreatitis was reflective of a possible lab or coding error. Given the reports and ambiguity surrounding the limited data, however, it would still be valuable to monitor for pancreatitis in further post-marketing studies.*

A review of the 18 pediatric reports suggestive of hepatic injury and the 10 pediatric reports suggestive of possible allergic or histamine-mediated reactions, was consistent with the AEs observed in adults. Per the sponsor, for serious, hepatic and possible allergic AEs, causality could not be determined due to the presence of concomitant medications or medical conditions associated with these adverse experiences.

8.1 POSTMARKETING SAFETY by Eileen Navarro, M.D.:

The sponsor's aggregate reported postmarketing adverse events from off-label use of Cancidas®® in pediatric patients by body system from the initial marketing approval of Cancidas®® to August 2007 is summarized below.

Table 78 Cancidas®® Postmarketing Adverse Experience Reports in Pediatric Patients from 14-Dec-2000 to 31-Aug -2007 (Sponsor's Table 2)

	Total Number of Reports (% of total	Age				
System Organ Class+	reports)*	0-27 days	28 days to 23 months	2 to 11 years	12 to 17 years	Unknown
Blood and lymphatic system disorders	14 (9%)	0	2	4	8	0
Cardiac disorders	5 (3%)	0	1	2	2	0
Congenital, familial and genetic disorders	1 (1%)	0	0	1	0	0
Gastrointestinal disorders	16 (10%)	0	1	6	3	16
General disorders and administration site	55 (36%)	1	5	14	21	14
Hepatobiliary disorders	9 (6%)	0	2	3	4	0
Immune system disorders	7 (5%)	0	0	2	5	0
Infections and infestations	37 (24%)	0	1	16	11	9
Injury, poisoning and procedural	24 (16%)	1	4	9	3	7
Investigations	24 (16%)	0	5	10	8	1
Metabolism and nutrition disorders	21 (14%)	0	4	10	6	1
Musculoskeletal and connective tissue	3 (2%)	0	0	2	1	0
Neoplasms benign, malignant and unspecified	5 (3%)	0	0	4	1	0
Nervous system disorders	19 (12%)	0	1	5	11	2
Psychiatric disorders	2 (1%)	0	0	0	2	0

Renal and urinary disorders	7 (5%)	0	0	4	3	0
Respiratory, thoracic and mediastinal disorders	16 (10%)	0	1	4	11	0
Skin and subcutaneous tissue disorders	8 (5%)	0	0	4	4	0
Surgical and medical procedures	23 (15%)	1	5	7	4	6
Vascular disorders	7 (5%)	0	0	3	2	0

Distinct number of reports 153 2 16 46 60 29

*A single report may include adverse events in one or more System Organ classes. Therefore the sum of reports from all System Organ Classes can be greater than the total distinct number of reports

Pancreatitis Reported in the Pediatric Population

Pancreatitis was investigated as a significant postmarketing event in pediatric patients and has not been reported with notable frequency in adults. The sponsor reports a total of 11 reports of pancreatitis in off label pediatric use of Cancidas®®. The sponsor presents details on 5 of the 11 reports of pancreatitis.

Table 79 Clinical Detail on 5 of 11 Pancreatic Adverse Experiences in Pediatric Patients Treated

Off Label with Cancidas®® from 14-Dec-2000 to 31-Aug -2007

WAES Number	0201USA00682	0301USA01127	0412USA02392	0602FRA00062	01116011
Age/Sex	11/F	16/M	9/F	4/M	10/M
Dx	ALL/ Invasive Aspergillosis	Not reported	CGD/ Trichosporonosis	AML/Invasive Aspergillosis	HIV/Esophageal Candidiasis
Rx start	29-Nov-2001	Not reported	Not reported	20-Jun-2005	24-Oct-2001
AE onset	Not reported	Not reported	2 months pEOT	------ -------	----------------
Rx end	Not reported	Not reported	2 weeks	01-Jul-2005	26- Oct-2001
AE end	Not reported	Not reported		Not reported	31- Oct-2001
AE severity		Not reported		Severe	Severe
AE outcome		Not reported		Recovered	Recovered
Sponsor Attribution	Not related	Not related	Not related	Not related	Not related
Mo attribution	Insufficient data	Not related	Insufficient data	Related, with hepatic failure	Related
Confounding	Baseline history of pancreatitis Pentamidine	Alcohol binge Imipenem	None	None	Hx of pancreatitis stavudine, TMP-SMX

WAES 01116011

"A 10 year-old boy with AIDS, CMV infection, Haemophilus influenzae infection, and pyocyanosis reported to have a pancreatitis following antiretroviral treatment (stavudine, amprenavir, nevirapine, and ritonavir), trimethoprim-sulfamethoxazole and clarithromycin.
On 24-Oct-2001, Cancidas® was initiated (30-mg loading dose, followed by 20 mg IV once daily) for Candida esophagitis.
On ---------- ----, he developed pancreatitis with severe vomiting: amylase 1207 IU/l and lipase 4900 IU/l. Cancidas® and all other therapies were interrupted.
On ---------- ----, the amylase value was 1135 IU/l, and the lipase value was 2138 IU/l. An abdominal ultrasound showed acute pancreatitis without necrosis and mild ascites; a chest X-ray showed right upper and bilateral lower lobe change attributed to pancreatitis.
On ---------- ----, the amylase value was 141 IU/l, and the patient's clinical status was better. Thereafter, from early November 2001 to mid January 2002, the amylase values remained stable (80-110 IU/l). He was started on amphotericin due to failed Cancidas® therapy.
The patients'' lipase values reportedly rose again (from 174 IU/l on ----------, to 524 IU/l on 1---------- ------).Following is the sponsor's characterization of this AE from this point on "This recurrence led the reporting physician to believe that pancreatitis was not related to therapy with Cancidas® but rather related to CMV reactivation, for which ganciclovir was ***prescribed since early Dec-2001.*** *On ----- ------ ---, serum*

amylase was normal and serum lipase was subnormal. Abdominal CT scan performed on -------- ------- showed improvement of the lesions: resolution of ascites and peripancreatic infiltration but possible pseudocysts in the caudal region of the pancreas.

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***MO comment**: The sponsor points to the concomitant therapies of trimethoprim sulfamethoxazole and stavudine as confounders in this particular case. However, the temporal relationship of the events to treatment initiation and its resolution with discontinuation of Cancidas® and resolution before specific therapy for CMV leads me to believe this adverse event is causally related to Cancidas®. The treating physician appeared to consider Cancidas® as a causal agent as treatment was not resumed because of the elevated amylase.*

Of the 11 cases of pancreatitis 6 were reported from a single investigator in Belgium. The Office of Safety Evaluation was consulted to evaluate these pancreatitis adverse events. Following are the individual AE report numbers from AERS: WAES 0611BEL00003, WAES 0611BEL00013, WAES 0611BEL00014, WAES 0611BEL00015, WAES 0611BEL00016, WAES 0611BEL00017. Merck indicates that these reports, all derived from the same source, represent "*different events in 6 individual pediatric patients"*. The types of infection and the dose/duration of Cancidas® were not documented. Pancreatic enzymes were reported to become elevated after the initiation of Cancidas® (no values provided). The enzyme levels decreased after Cancidas® was discontinued. The timing of Cancidas® initiation and elevation of enzymes or concomitant drugs and disease states were not documented, thus the sponsor concludes that there is insufficient data on which to assess a causal relationship to Cancidas® therapy. The safety evaluator reviewed the cases and concludes that One of these reports had sufficient detail, quoted verbatim from the AE report:

"*This report concerned a 4 year-old boy, weighing 20 kg, with acute myelogenous leukemia (AML, monosomy type 7) and macrophage activation syndrome (with hypertriglyceridemia and hyperferritinemia). In ---- -----5, he was hospitalized for chemotherapy for the AML. On 13-May-2005, the patient was placed on therapy with IV voriconazole at 160 mg daily for the treatment of pulmonary aspergillosis. As a result of persistent abnormalities on chest CT, Cancidas® at 40 mg daily (based on50 mg/m² daily) was added (off label use) on 20-Jun-2005. On -------- ----, the patient experienced hepatitis, hepatic insufficiency (with increased prothrombin time and factor V activity test of 53%), and pancreatitis. On 01-Jul-2005, therapy with Cancidas® and voriconazole were discontinued, and amphotericin B was prescribed. Subsequently, the patient recovered quickly from these adverse events. Voriconazole was administered alone several months later without any problem. The reporting physician felt that hepatic insufficiency, hepatitis, and pancreatitis were related to therapy with Cancidas®. The patient died in ---------- due to leukemic complications. Sponsor Comment: Notably, no information was provided on liver function tests in this child with AML and macrophage activation syndrome before or during treatment with voriconazole, which was taken for approximately 5 weeks prior to the addition of Cancidas®. It is not known if the patient was on additional concomitant medications, and no information was provided on when the patient last had chemotherapy. Hepatic dysfunction is a feature of macrophage activation syndrome, and it is unclear if the patient had hepatic features of this disorder [Ref. 5.4: 1304]. Voriconazole, is known to be hepatotoxic and to be associated with pancreatitis, as reported in clinical trials with this medication [Ref. 5.4: 1426]. In contrast, Cancidas® has not been associated with the development of pancreatitis. Given the limited information in the report about the patient' precise clinical course and laboratory values, it is unclear whether the hepatic insufficiency in this patient was related to the introduction of Cancidas® or to the patient's underlying medical condition (macrophage activation syndrome), concomitant use of voriconazole, and/or another, unreported factor."*

***MO comment:** The history of prolonged exposure (5 weeks) to voriconazole without development of any hepatic or pancreatic adverse reaction, and the onset of such following initiation of therapy with Cancidas®, suggests that the latter drug is more likely to be associated with the event. Furthermore, the positive dechallenge with Cancidas® and successful reinstitution of voriconazole further strengthens the association with the echinocandin.*

Hepatic Adverse Experiences Reported in the Pediatric Population

The sponsor performed an additional review of selected hepatic adverse experiences using the following terms that might indicate hepatic injury: alanine aminotransferase increased, aspartate aminotransferase increased, bilirubin conjugated increased, blood alkaline phosphatase increased, blood bilirubin increased, hepatic enzyme increased, hyperbilirubinemia, transaminases increased, hepatic function abnormal, jaundice, hepatitis and hepatic failure.

A total of 18 reports with 34 hepatic adverse experiences (18 serious) were identified in pediatric patients, as outlined in Table 4. The age breakdown of patients with these reported events was as follows: 8 (44%) were in adolescents between 12-17 years of age, 7 (39%) were in children between 2 to 11 years of age, 3 (17%) were in infants and toddlers between 28 days to 23 months of age. No reports were in preterm or term infants < 28 days of age. There were 2 deaths in these 18 patients, described in detail below. In 10 of 16 with known outcomes (62%), the patients recovered or were recovering following treatment dechallenge, whereas 2 others had partially recovered at the time of the report.

Table 80 Reports of Hepatic Adverse Experiences in Pediatric Patients Treated with Cancidas® from 14-Dec-2000 to 31-Aug -2007 (Sponsor's Table 4)

	Listed	**Number of Reports**		**Breakdown by Age**			
System Organ Class		Total	Serious	0-27 days	28 days -23 months	2 to 11 years	12 to 17years
Alanine aminotransferase increased	Yes	5	2	0	2	2	1
Aspartate aminotransferase increased	Yes	5	3	0	2	2	1
Bilirubin conjugated increased	Yes	3	2	0	1	0	2
Blood alkaline phosphatase increased	Yes	4	3	0	2	1	1
Blood bilirubin increased	Yes	4	0	0	1	3	0
Hepatic enzyme increased	Yes	1	0	0	0	0	1
Hepatic failure	**No**	**2**	**2**	**0**	**0**	**1**	**1**
Hepatic function abnormal	Yes	2	2	0	0	1	1
Hepatitis	**No**	**1**	**1**	**0**	**0**	**1**	**0**
Hyperbilirubinemia	Yes	4	2	0	1	1	2
Jaundice	**No**	**1**	**1**	**0**	**0**	**1**	**0**
Transaminase increased	Yes	2	0	0	0	2	0
Total Number Adverse Experiences		34	**18**	0	9	15	10
Total Number of Reports†		**18**	**9**	0	3	7	8

† Although a report may have had two or more of these adverse experiences listed it was counted only once in the total number of reports or serious reports

Four (22.2%) of the 18 adverse experiences, representing 3 reports in 17 patients (17%) involved serious, unlisted adverse experiences. These consisted of hepatic failure (WAES 0211AUT00005), jaundice (WAES 01032469), and hepatitis and hepatic failure (WAES 0602FRA00062). Of note, 2 of the 9 serious reports (22.2%) were of hepatic failure. These reports are summarized below.

1. Hepatic failure: **WAES 0602FRA00062**

This report is described above and concerned a 4 year-old boy, weighing 20 kg, with acute myelogenous leukemia (AML, monosomy type 7) and macrophage activation syndrome (with hypertriglyceridemia and hyperferritinemia). In ---- ------, he was hospitalized for chemotherapy for the AML. On 13-May-2005, the patient was placed on therapy with IV voriconazole at 160 mg daily for the treatment of pulmonary aspergillosis. As a result of persistent abnormalities on chest CT despite 5 weeks of IV voriconazole, Cancidas® was initiated at 40 mg daily (based on 50 mg/m² daily) on ---- J----- ----. Eleven days later, on ------ ---- ---, the patient experienced hepatitis, hepatic insufficiency (with increased prothrombin time and factor V activity test of 53%), and pancreatitis, for which treatment was discontinued with prompt recovery. The reporting physician felt that hepatic insufficiency, hepatitis, and pancreatitis were related to therapy with Cancidas®. The patient died in ---------- due to leukemic complications.

***MO comment:** Hepatic failure is not currently labeled for Cancidas®. The patients'' death occurred*

remotely from the event of hepatic failure (7 months) and is unlikely to have accounted for the fatality, however, the sequence of events in this case points to Cancidas® as a factor for the development of hepatic failure. Cancidas® was initiated following therapeutic failure with voriconazole and although the risk benefit may still favor the use of Cancidas®, the severity of the event merits stronger labeling of hepatic failure and a reassessment of the factors that could predict for its development in pediatric patients.

2. **WAES 01032469**

This report involved a hospitalized 7 year-old Asian male with ALL in relapse, post failed bone marrow transplant (x2) and a left upper lobe aspergilloma, treated with itraconazole and liposomal amphotericin B. The following hepatic AEs were reported for this patient: hepatotoxicity. abdominal pain, some underlying liver dysfunction of uncertain etiology, increased alkaline phosphatase raised transaminases, hypokalemia, hypochloremia, decreased creatinine clearance, hypocalcemia, protein deficiency, and decreased serum albumin. Jaundice was an unreported AE.
The child had a history of two bone marrow transplants and chemotherapy (including experimental chemotherapy) and was undergoing therapy for an upper lobe aspergilloma with itraconazole and liposomal amphotericin B The report indicates that although the ***treating physician was not convinced the child had failed therapy with liposomal amphotericin, Cancidas® 30 mg intravenous loading dose, followed by 20 mg intravenous daily, was added on ----*** *when a chest computed axial tomography continued to show a cavity. In addition to liposomal amphotericin and itraconazole, concomitant therapy included: vancomycin, meropenem, amikacin (for persistent fever), leucovorin calcium, sulfamethoxazole/trimethoprim, clotrimazole and experimental chemotherapy with HD37-dgA, among other medications.*
Following is the progression of liver function alteration:

Date	Bili	AST	ALT	ALKp	Note
----------	0.7	56	132	205	Pre treatment, Cancidas® started
----- ----------	13	677	337	408	Jaundice, Cancidas® discontinued
---------- -----	3				
---------- -----	<2				Reduced dose Cancidas® restarted
---------- -----	1.7	57	77	550	Intubated for respiratory failure
------- --------	2.9	39	28		DNR
---------- -----					Expired from ALL, IA and multi-organ failure

Baseline (pre-treatment) liver function *(): total bilirubin 0.7, AST 56,* ***ALT 132****, and ALP 205. The report indicates that patient developed an elevated bilirubin in the high teens (not reported) and transaminases that were elevated greater than 10 times normal. No prothrombin time (PT) was done.*
---------- ----, the patient's liver function tests were as follows: total bilirubin 13., AST 677 U/L, ALT ***337 U/L****, and alkaline phosphatase (ALP) 408 U/L. The physician reported they knew the elevated bilirubin was "real" because the patient was jaundiced at that time. Cancidas® was discontinued and the patient's bilirubin "came down immediately" to 3 mg/dL after holding Cancidas®.*
Cancidas® was restarted on 14-Mar-2001 or 15-Mar-2001 ***at 10 mg IV daily and on this dose*** *his bilirubin remained less than 2 mg/dL.*
On 2------- -- ----- were as follows: total bilirubin 1.7 mg/dL, AST 57 U/L, ***ALT 77*** *U/L, and ALP 550 U/L. The patient's ALT during hospitalization was 337 U/L at its peak and 21 U/L at its lowest. The last ALT provided in the patient's medical record was on -------- ------ -, and was 28 U/L. The patient's AST during hospitalization was 677 U/L at its peak and 24 U/L at its lowest. The last AST provided in the patient's medical record was on -------- ----- 1 was 39 U/L. The patient's ALP during hospitalization was 646 U/L at its peak and 205 U/L at its lowest. The value of last ------ - ------- -) documented ALP measurement in the patient's medical record was 237 U/L. The patient's bilirubin during hospitalization was 13.1 mg/dL at its peak, and 0.5 mg/L at its lowest. The last bilirubin provided in the patient's medical record was on -------- ------ -, and was 2.9 mg/dL.*
The patient deteriorated on - - ---- - --------, and was intubated because of respiratory problems that may be due to an infection or "lack of reserve." The patient was listed as do-not-resuscitate DNR and was "dying." The physician stated that the deterioration and respiratory problems were related to ALL and not related to therapy with Cancidas®. The child expired on -------- -------. According to the discharge data the principle diagnosis was acute lymphocytic leukemia, and secondary diagnoses were aspergillosis pneumonia and multisystem organ failure all of which the patient expired from.

MO comment: *This case is notable in that the sequence of onset and decline in hyperbilirubinemia is clearly related to Cancidas® initiation and withdrawal. The sponsor notes that the patient had some underlying hepatic dysfunction prior to initiation of Cancidas® therapy, was on therapy known to cause hepatotoxicity, prior to and during Cancidas® therapy. Nonetheless the positive dechallenge and the timing of onset of these AES with Cancidas® treatment initiation point to a causal relationship for the drug. Although the sponsor notes that the liver functions tests did not increase with rechallenge with Cancidas®, the rechallenge dose was 3 fold lower than the initiation dose. Thus an AE that is dose related may not be evident on rechallenge. Of note, bilirubin competes with echinocandins for the cellular transporter OATP1B1 and theoretically, a low dose of Cancidas® may not result in hyperbilirubinemia to the extent that a higher dose is expected to. Because there are reports of a clear ethnic relationship to the distribution of this transporter, the occurrence of hyperbilirubinemia and hepatitis in this young Asian male is of interest. Furthermore, the occurrence of hepatitis with cyclosporine noted in previous studies in adults is another indicator of a possible relationship of the transported with Cancidas®, as both drugs may compete for the cellular transporter in the hepatocyte.*

3. **WAES 0211AUT00005**

The third case of hepatic failure also documents treatment failure of Cancidas® for mucormycosis. A 17 year-old female with chylomicronemia syndrome, underwent surgical resection for necrotizing pancreatitis, developed multiorgan failure and mucoromycosis in the laparotomy wound (Rhizopus species). Therapy with liposomal amphotericin B and amphotericin B (for daily local lavages) and subsequently Cancidas®, 50 mg daily (duration not reported), was initiated. On day 28, the patient developed hypotension and liver failure, and died of multi-organ failure. The physician reported that the liposomal amphotericin B and Cancidas® were well tolerated, but that the Cancidas® did not reduce the fungal burden and did not modify the clinical course of the disease.

MO comment: *The timing of liver failure in relation to Cancidas® treatment and development of hypotension is not described in detail in this report and the reviewing MO is unable to exclude a relationship with Cancidas® treatment. Cancidas® has no in vitro activity against mucormycosis at clinically relevant concentrations is known to cause hepatic damage and sits off label use for mucormycosis cannot be justified if it causes undue harm without benefit.*

Possible Allergic Reactions Reported in the Pediatric Population

To assess possible allergic reaction in pediatric patients, the sponsor selected adverse event terms that could represent an allergic reaction. The following terms that might indicate an allergic reaction were selected: anaphylactic reaction, chills, dyspnea, erythema, erythema multiforme, hypersensitivity, hypotension, periorbital edema, pruritus, rash, rash macular, rash maculopapular, rash pruritic, skin exfoliation and Stevens-Johnson syndrome. The sponsor identified 153 pediatric patients with allergic reactions based on this aggregate term. The sponsor then reviewed these reports and excluded reaction they considered attributable to an underlying disease process or an alternate etiology (confounder), thus excluding most reports except for ten (10) reports with 16 allergic adverse experiences (9 serious) in pediatric patients. Of the 10 reports, 5 (50%) were in adolescents between 12-17 years of age, 4 (40%) were in children between 2 to 11 years of age and 1 (10%) was in a child of unknown age. No possible allergic reactions were identified in infants and toddlers between birth and 23 months of age.

Table 81 Possible Allergic Reactions in Pediatric Patients Treated with Cancidas®14-Dec-2000 to 31-Aug -2007 (Sponsor's Table 5)

System Organ Class	Listed Number of Reports				Breakdown by Age			
	Listed Unknown	Total	Serious 0-27 days		28 days to 23months	2 to 11 years	12 to 17 years	
Anaphylactic reaction	Yes	1	1	0	0	0	1	0
Chills	Yes	1	0	0	0	0	1	0
Dyspnea	Yes	1	1	0	0	0	1	0
Erythema	No	1	0	0	0	1	0	0
Hypotension	No	1	0	0	0	0	0	1
Erythema multiforme	**No**	1	0	0	0	0	1	0
Hypersensitivity	Yes	1	1	0	0	0	1	0
Periorbital edema	No	1	1	0	0	1	0	0
Pruritus	Yes	2	2	0	0	1	1	0
Rash	Yes	1	1	0	0	1	0	0
Rash macular	Yes	1	0	0	0	1	0	0
Rash maculopapular	Yes	1	1	0	0	1	0	0
Rash pruritic	Yes	1	0	0	0	1	0	0
Skin exfoliation	No	1	0	0	0	1	0	0
Stevens-Johnson syndrome	**No**	1	1	0	0	0	1	0
Total Number Experiences		**16**	**9**	**0**	**0**	**8**	**7**	**1**
Total Number of Reports†		**10**	**5**	**0**	**0**	**4**	**5**	**1**

† Although a report may have had two or more of these adverse experiences listed it was counted only once in the total number of reports or serious reports.

Of the 10 reports of allergy, outcome was ascertained in 8, of which half (4 patients) had recovered (a positive dechallenge) whereas half (4 patients) had not recovered. Five (5) reports contained serious, unlisted adverse experiences: hypotension (WAES 0603NLD00001); erythema, skin exfoliation (WAES 0702COL00004); periorbital edema with maculopapular rash (WAES 0301USA02731); erythema multiforme (WAES 0511GBR00072); and Stevens-Johnson syndrome (WAES 0411USA00750). These 5 reports are discussed below.

1. **WAES 0603NLD00001**

This report concerned a child (age not reported; 60 kilograms in weight) who was placed on therapy with Cancidas® 70 mg, 30 minutes into the one hour infusion, (01-Feb-2006), the patient experienced hypotension. Infusion rate was immediately reduced to over 4 hours, resulting in recovery from hypotension.

MO Comment: *The report does not describe any signs/symptoms suggestive of histamine release which is a labeled adverse drug reaction. The timing of the reaction makes it difficult to exclude a relationship to Cancidas® although it is unknown if the event was noted following the initial dose of Cancidas®.*

2. **WAES 0702COL00004**

A 6 year-old Mestizo boy with sepsis, VATER syndrome, renal failure, secondary hypertension, and colostomy (due to imperforate anus) was placed on therapy with Cancidas® for the treatment of sepsis and fungal peritonitis (dose not reported) on 05-Feb- 2007. He was concurrently receiving vancomycin, meropenem, acetaminophen, omeprazole, folic acid, epoetin, calcium carbonate, metoprolol, lorazepam, and nitrendipine. On 06-Feb-2007, erythema, macules, and desquamation were reported on his thorax, face, and extremities; assessed by a dermatologist as a drug reaction for which Cancidas® was discontinued (07-Feb-2007) and an antihistamine was initiated. Ten days later, when the patient was considered stable, the report notes that all other therapies were discontinued (17-Feb-2007). The sponsor notes that the report indicates that the adverse experiences were not related to therapy with Cancidas®.

MO Comment: *Although the patient was on several concomitant medications (meropenem, vancomycin and omeprazole) for which desquamating skin reactions have been reported these medications were not discontinued until after the patient was reported to have stabilized. A relationship to Cancidas® cannot be excluded and ---------- ----------*

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3. **WAES 0301USA02731**
A 9 year-old boy with non-lymphocytic leukemia, fever and neutropenia, and Staphylococcus aureus necrotizing cellulitis of the scalp received 40 mg Cancidas® on 26-Jan-2003 and by 25 mg on 27-Jan-2003 for suspected pulmonary aspergillosis. The patient developed periorbital edema one hour after the first dose of Cancidas® and a rash within 24 hours after the second dose of Cancidas®. Cancidas® was discontinued, voriconazole was started. Duration of periorbital edema and rash is not described. Despite the onset of periorbital edema an hour after Cancidas® initiation and prior to initiation of voriconazole, the submission indicates that "the reporting physician is unable to determine if unclear if the rash was temporally associated with Cancidas® or if it was due to voriconazole and that periorbital edema could be secondary to invasive aspergillosis."

MO Comment: *We are unable to exclude a relationship to Cancidas® due to the temporal association of rash and periorbital edema with Cancidas® infusion.*

4. **WAES 0511GBR00072**
This scanty report indicates that a 17 year-old female with AML developed erythema multiforme a day (09-Nov-2005) following therapy initiation (08-Nov-2005) with Cancidas® 35 mg. No other clinical detail is provided save that the reporter felt that the erythema multiforme was not related to therapy with Cancidas®, but more likely to be related to concomitant therapy with vancomycin.

MO Comment: *In the absence of detail we are unable to exclude a relationship to Cancidas® due to the temporal association of Erythema multiforme with Cancidas® treatment initiation.*

5. **WAES 0411USA00750**
A 17 year-old hospitalized male was placed on therapy with Cancidas® for febrile neutropenia experienced Stevens-Johnson syndrome. Concomitant medication included meropenem. Therapy with Cancidas® was discontinued and the patient recovered from Stevens- Johnson syndrome.

MO Comment: *Although confounding medication could account for the reaction, the positive dechallenge with Cancidas® makes a causal association more likely.*

Renal Adverse Reactions Reported in the Pediatric Population
As in the experience in adult patients, isolated cases of renal failure were also reported in the postmarketing experience for pediatric patients. As this infrequent adverse event is currently labeled, no additional modification is suggested.

CONCLUSION:
The following adverse events identified in postmarketing need to be added to the postmarketing section of the label: pancreatitis, erythema multiforme, ---------- , Steven's Johnson, skin exfoliation, ---------- edema. Additionally, the precautions and adverse events section should give prominence to the following adverse events: hepatic failure, hepatitis.

9 Appendices

9.1 References

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9.2 Labeling Recommendations

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