Official Protocol Title:	A Multicenter, Double-Blind, Randomized, Comparator-Controlled Study to Evaluate the Safety, Tolerability, and Efficacy of Caspofungin Versus Amphotericin B Deoxycholate in the Treatment of Invasive Candidiasis in Neonates and Infants Less Than 3 Months of Age
NCT number:	NCT01945281
Document Date:	27-Aug-2013

THIS PROTOCOL AMENDMENT AND ALL OF THE INFORMATION RELATING TO IT ARE CONFIDENTIAL AND PROPRIETARY PROPERTY OF MERCK SHARP & DOHME CORP., A SUBSIDIARY OF MERCK & CO., INC., WHITEHOUSE STATION, NJ, U.S.A.

THIS PROTOCOL AMENDMENT IS APPLICABLE ONLY TO BRAZIL.

SPONSOR:

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. (hereafter referred to as the **SPONSOR** or **Merck**)
One Merck Drive
P.O. Box 100
Whitehouse Station, NJ, 08889-0100, U.S.A.

Protocol-specific Sponsor Contact information can be found in the Administrative Binder.

TITLE:

A Multicenter, Double-Blind, Randomized, Comparator-Controlled Study to Evaluate the Safety, Tolerability, and Efficacy of Caspofungin Versus Amphotericin B Deoxycholate in the Treatment of Invasive Candidiasis in Neonates and Infants Less Than 3 Months of Age

INVESTIGATOR:

PRIMARY:

CLINICAL PHASE: IIA

US IND NUMBER: 48,484

SITE:

INSTITUTIONAL REVIEW BOARD/ETHICS REVIEW COMMITTEE:

TABLE OF CONTENTS

SUMMARY OF CHANGES

PRIMARY REASON(S) FOR THIS AMENDMENT

Section Num-ber(s)	Section Title(s)	Description of Change(s)
1.7 2.2 3.1.4 3.2.3.1.2 3.2.3.1.3 3.2.3.8 6.4 7.	Study Flow Chart Inclusion Criterion #4: removed 2nd and 3rd sentences Rationale for Future Biomedical Research Consent and Collection of Specimens for Future Biomedical Research Future Biomedical Research Withdrawal From Future Biomedical Research Collection and Management of Specimens for Future Biomedical Research Attachments: Pharmacogenomics Informational Brochure for IRBs/IECs & Investigational Site Staff	Removal of Future Biomedical Research sample collection and any associated protocol language

ADDITIONAL CHANGE(S) FOR THIS AMENDMENT

Section Num-bers	Section Titles	Description of Change
		There are no additional changes.

1. SUMMARY

1.1 TITLE

A Multicenter, Double-blind, Randomized, Comparator-Controlled Study to Evaluate the Safety, Tolerability, and Efficacy of Caspofungin Verses Amphotericin B Deoxycholate in the Treatment of Invasive Candidiasis in Neonates and Infants Less Than 3 Months of Age

1.2 INDICATION

A prior clinical study has evaluated the pharmacokinetics and tolerability of single- and multiple-dose therapy with caspofungin in the neonatal and infant population (i.e., children <3 months of age). The current study will investigate the safety, tolerability, and efficacy of caspofungin versus amphotericin B deoxycholate for the treatment of invasive candidiasis in this same pediatric patient population.

1.3 SUMMARY OF RATIONALE

Caspofungin acetate (MK-0991, CANCIDAS™; herein referred to as caspofungin) is a parenteral echinocandin antifungal agent that has received approval in the United States, the European Union (EU), and over 80 other countries for the treatment of adult patients (≥18 years of age) for one or more of the following: (1) invasive aspergillosis in patients who are refractory to or intolerant of other therapies (i.e., amphotericin B deoxycholate, lipid formulations of amphotericin B, and/or itraconazole); (2) esophageal candidiasis; (3) candidemia and other *Candida* infections, including intra-abdominal abscesses, peritonitis, and pleural space infection; and (4) empirical therapy of suspected invasive fungal infections in febrile, neutropenic patients [1-2]. Furthermore, caspofungin has been approved for use in pediatric patients (≥3 months of age) in over 60 countries worldwide for the same indications as in adults.

In the neonatal and infant population, candidemia and other forms of invasive candidiasis are a major medical concern and are associated with excess mortality, increased length of hospital stay and health-care costs [3, 4]. *Candida* species represent the second most common pathogen among all nosocomial blood stream infections and the most common fungal infection in infants less than 1 year of age [5]. Furthermore, in the United States in 2003, the overall incidence of invasive candidiasis among neonates was 15 cases per 10,000 neonatal admissions [3]. However incidence has been shown to vary widely between clinical centers [4, 6-7]. Notably, the current antifungal regimens administered in the neonatal population are associated with significant toxicity, multiple drug-drug interactions, or limitations in spectrum of activity. With caspofungin approved for use as primary treatment of older pediatric patients (3 months to 17 years of age), the use of this agent in the neonatal population will be further investigated in this study.

The pharmacokinetics and safety of caspofungin in the neonatal patient population were evaluated in a prospective pharmacokinetic trial (Protocol 058). In this study, the pharmacokinetics in 18 neonates and infants receiving single or multiple once-daily caspofungin doses of 25 mg/m^2 were generally similar to that in adults receiving a 50-mg

once-daily maintenance dose. Caspofungin was well tolerated in the 18 patients included in this study; in fact, no drug-related adverse experiences were noted in any of the 18 caspofungin recipients [8]. However, measurements of height are not routinely performed in the neonatal/infant population, so a dosing regimen based on body surface area (BSA) is not preferred in this patient population. Simulations for weight-based dosing, using a 2 mg/kg dose, performed for the 12 patients who received multiple doses of caspofungin in Protocol 058 showed similar C_{1hr} and C_{24hr} values to the 25 mg/m^2 daily dose. Based on this analysis, a weight-based dose of 2 mg/kg of caspofungin is deemed roughly equivalent to 25 mg/m^2.

The efficacy of caspofungin in the treatment of invasive candidiasis and other *Candida* infections in neonates and infants was recently demonstrated in a randomized, double-blind, prospective clinical trial in 32 patients comparing caspofungin to amphotericin B deoxycholate [9]. In this study conducted at a single site in Saudi Arabia, newborn infants received either caspofungin (2 mg/kg/day, n=15) or amphotericin B deoxycholate (1 mg/kg/day, n=17). A favorable response at the end of intravenous therapy, the primary timepoint for efficacy, was observed at a greater rate in patients who received caspofungin (86.7%) than those who received amphotericin B deoxycholate (41.7%) (p=0.04). Importantly, caspofungin was effective in all sites of *Candida* infection, including all 3 cases with *Candida* meningitis and 4 of 5 patients with *Candida* endocarditis.

Furthermore, published data from several case series in neonates with invasive candidiasis (two from Costa Rica, one from Italy, and one from the United States) provide additional evidence of efficacy in this age group [10-13]. In these studies, caspofungin therapy was begun only after initial therapy with conventional antifungals (amphotericin B deoxycholate, fluconazole, and/or flucytosine) had failed; in other words, the *Candida* infection was resistant to, or the patient was intolerant of, the initial therapy. Collectively, 53 of 75 neonates received either a caspofungin dose of 2 mg/kg or 25 mg/m^2 and the favorable response rate across these series was in excess of 80%. Caspofungin was well tolerated, with few drug-related adverse events reported.

With the approval of the use of caspofungin in many countries in children and adolescents between the ages of 3 months to 17 years, this study will prospectively evaluate the safety and efficacy of caspofungin in the treatment of invasive candidiasis in the youngest pediatric group, the neonatal and infant population less than 3 months of age. The recommended dose for caspofungin for this study is 2 mg/kg daily. This dose is based on the published data referenced above as well as the simulated results from the prior pharmacokinetic and safety study for caspofungin in neonates and infants <3 months of age (Protocol 058).

1.4 SUMMARY OF STUDY DESIGN

This is a double-blind, randomized, comparative study to evaluate the safety, tolerability, and efficacy of caspofungin versus amphotericin B deoxycholate in the treatment of neonatal candidiasis. Neonates and infants less than 3 months of age will be eligible for enrollment provided they have documented (culture-confirmed) invasive *Candida* infections within the 96 hours prior to study entry. Diagnosis of invasive candidiasis in a

symptomatic or at-risk patient would require either (a) a positive culture for *Candida* spp. from a normally sterile body fluid, or (b) a positive culture for *Candida* spp. from a newly-placed drain at a normally sterile body site. For this study, patients with a *Candida* urinary tract infection (UTI) are considered to have invasive candidiasis, as such infections are associated with high mortality (~30%) and morbidity in the neonatal patient population [14-16]; these patients are eligible for enrollment, provided there is a positive urine culture of >10,000 colony-forming units (CFUs) per milliliter of a *Candida* spp. from a newly placed urinary catheter. Patients with a positive culture from sputum or nonsterile sites are not eligible for enrollment.

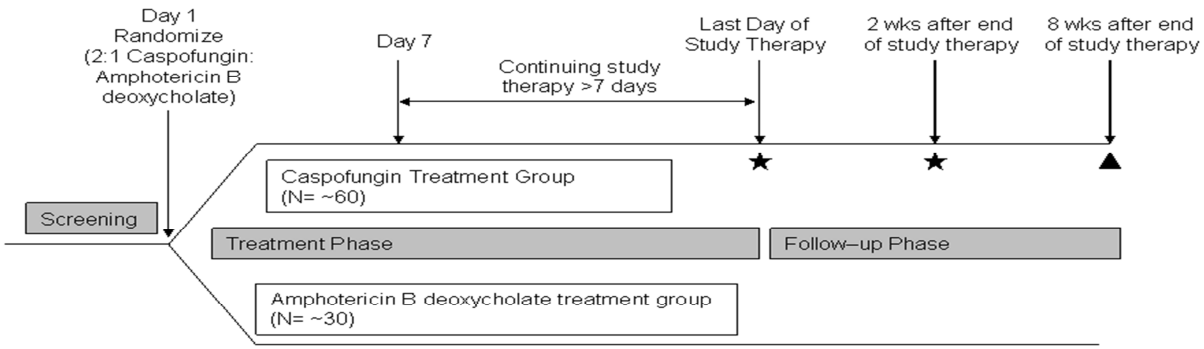
A detailed description and evaluation of the *Candida* infection will be performed at screening, daily while on study therapy, on the last day of study therapy, and at the 2-week and 8-week posttherapy follow-up visits. Resolution or progression of the *Candida* infection will be documented by assessment of signs and symptoms, radiographic studies (when clinically indicated), and follow-up blood cultures or, as appropriate, other follow-up cultures (including urine or cerebrospinal fluid [CSF]). Based on available data, an efficacy assessment will be made at the end of study therapy and at the 2-week posttherapy follow-up visit. The efficacy endpoint will be based on fungal-free survival (i.e., patient survival in the setting of documented microbiological eradication of *Candida* sp. from follow-up cultures). Although fungal-free survival will be assessed at 2 different time points, the primary efficacy time point will be at the 2-week posttherapy follow-up visit.

All patients who receive 1 or more doses of study therapy will be evaluated for the presence of adverse experiences while on study therapy and through the 2-week posttherapy follow-up visit.

The overall design of the study is in Figure 1-1.

Figure 1-1

MK-0991 Protocol 064 Trial Design



Note:
1) Timepoints in the figure are applicable to both the caspofungin and amphotercin B deoxycholate treatment groups.
2) Please refer to the Section 1.7 (Study Flow Chart) and Section 3.2.3 for complete descriptions of study procedures.
3) Patients will be monitored for adverse events while on study therapy and through the 2-week posttherapy follow-up visit.
4) Study therapy begins on Day 1 and should not exceed 90 days
★ = The primary efficacy assessment is fungal-free survival at the end of study therapy (secondary timepoint) and 2-week posttherapy follow-up visit (primary timepoint).
▲ = An exploratory efficacy assessment is development of complicated candidiasis at the 8-week posttherapy follow-up visit.

1.5 SAMPLE

Approximately 90 patients with documented invasive candidiasis will be randomized in a 2:1 ratio (caspofungin: amphotericin B deoxycholate), as specified in Table 1-1 below. All doses of study drug will be administered intravenously as a single once-daily dose.

Table 1-1

Protocol 064 Treatment Groups

Treatment Group	Regimen	Number of Patients
Group 1	Caspofungin at 2 mg/kg (per body weight) once daily	~60
Group 2	Amphotericin B deoxycholate at 1 mg/kg (per body weight) once daily	~30

In an effort to strive for adequate representation of patients from different weight groups (reflective of patient gestational age) in both treatment arms, randomization will be stratified into 3 weight categories (based on weight at study entry): <1000 grams, 1000 to 1500 grams, and >1500 grams. Patients will be stratified into each of the weight categories in a manner consistent with the 2:1 randomization of caspofungin to amphotericin B deoxycholate.

1.6 DOSAGE/DOSAGE FORM, ROUTE, AND DOSE REGIMEN

Caspofungin will be administered at 2 mg/kg once daily (with no loading dose).

Amphotericin B deoxycholate will be administered at 1 mg/kg once daily.

Initial dosing with the study medications will be based on the patient's actual body weight (in kg) at the time of study entry. The patient is to be weighed at least weekly during the treatment period. The study medication dose (mg) should be adjusted as the patient's weight increases to maintain the mg/kg dose of the assigned treatment throughout the study treatment period.

Caspofungin and amphotericin B deoxycholate will both be administered intravenously over approximately 2 hours. As these 2 products differ in color, opaque masking will be used over the infusion materials (e.g., infusion syringe and tubing) to ensure adequate blinding of the treatment group.

The duration of study therapy with caspofungin or amphotericin B deoxycholate is variable and dependent on a variety of factors, including (1) the rapidity of a patient's clinical and microbiological response, (2) the patient's general medical condition, and (3)

the underlying site of *Candida* infection. In general, patients should be treated with study therapy for a minimum of 14 days following the time of documented negative cultures from the site of infection and improvement of any clinical signs and symptoms of invasive candidiasis. Certain sites of infection, including *Candida* endocarditis, meningitis, osteomyelitis/septic arthritis, and endophthalmitis, may warrant a longer treatment course based on the consideration of a variety of relevant factors (see Table 2-1 in Section 2.4.2, Treatment Plan).

1.7 STUDY FLOW CHART

	Screening	Study Therapy[a]									Follow-up Assessments	
Activity	**Prestudy**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**	**Continuing Study Therapy Past Day 7**	**Last Day of Study Therapy**	**2 Weeks after the End of Study Therapy**	**8 Weeks after the End of Study Therapy**
Informed Consent from Parent/Guardian	X											
Provide Participant Identification Card	X											
Review Inclusion/Exclusion Criteria	X											
Medical History	X											
Chest X-ray[b]	X											
Assessment of signs and symptoms pertaining to *Candida* infection	X	X	X	X	X	X	X	X	Daily	X	X	X
Vital signs	X	X	X	X	X	X	X	X	Daily	X	X	X
Physical examination	X				X			X	Twice weekly	X	X	X
Weight	X				X[c]			X[c]	Weekly			
Blood culture	X[d, e]	X[d]							X[d]	X[d]	X[f]	X[f]
Other cultures or biopsies	X[e]	X[f]							X[f]	X[f]	X[f]	X[f]
Other radiographic studies	X[g]	X[h]							X[h]	X[h]	X[h]	X[h]
Administer study therapy		X	X	X	X	X	X	X	Once daily	X		
Blood for safety	X				X[i]			X	Twice weekly	X	X	
Plasma (and CSF, if available) for drug level					X[j]			X[j]				
Monitor for adverse experiences	X	X	X	X	X	X	X	X	Daily	X	X	
Efficacy assessment (fungal-free survival)										X	X	
Efficacy assessment (development of complicated candidiasis)												X

a Duration of study therapy should be according to criteria specified in Table 2-1 of the protocol. In general, patients should be treated with study therapy for a minimum of 14 days following the time of documented negative cultures from the site of infection and improvement of any clinical signs and symptoms of invasive candidiasis.
b Prior chest X-ray may be used, provided the chest X-ray was performed within 10 days prior to initiation of study therapy.
c In addition to at least weekly measurements of weight, weight is to be measured on either Day 4 or Day 7 based on the assigned day of PK blood sampling (see Section 3.3.2).
d Two sets of blood cultures must be obtained at screening in all patients. Patients with candidemia should have periodic blood cultures collected while on therapy until cultures are negative for *Candida* (on at least 2 consecutive occasions).
e The blood cultures or cultures from the non-blood site(s), which confirm the evidence of invasive *Candida* infection during the screening phase, must be obtained within 96 hours prior to study entry.
f Follow-up culture samples to be collected from the site(s) of *Candida* infection, as clinically indicated (see Section 3.2, Study Procedures). Specifically, follow-up CSF cultures should be collected until negative follow-up CSF cultures are documented.
g When appropriate, a radiographic study from the site of infection (e.g., echocardiogram, chest/abdominal ultrasound) should be performed within 96 hours prior to study entry.
h Follow-up radiographs are to be performed from the site(s) of infection (e.g., echocardiogram, chest/abdominal ultrasound, CT, MRI) as clinically indicated, based on the site of infection (see Section 3.2, Study Procedures). If a radiographic study that helped confirm the diagnosis of invasive candidiasis is deemed necessary to assess the outcome of study therapy, a follow-up radiographic study must be obtained within 72 hours (3 days) prior to completion of study therapy.
i The first laboratory safety sample following initiation of study therapy should be performed on Day 4. If collection of a Day 4 sample is not possible, the laboratory sample may be obtained on Day 3 or Day 5 of study therapy. The selected chemistry and hematology laboratory tests for safety are included in Appendix 6.1.
j Three blood samples (350 µL each) are to be collected on either Day 4 or Day 7 (according to the assigned schedule as described in Section 3.3.2). Plasma will be separated from blood and sent to a central laboratory for pharmacokinetic testing. If sampling cannot be performed on the assigned day, blood samples can be drawn at comparable timepoints on the following day. If a patient undergoes any procedure at baseline or during study therapy that involves collecting CSF, a CSF sample (350 µL) should be retained at each timepoint and sent to a central laboratory for pharmacokinetic testing.

2. CORE PROTOCOL

2.1 OBJECTIVES AND HYPOTHESES

2.1.1 Primary Objective

Efficacy: To compare caspofungin to amphotericin B deoxycholate with respect to the efficacy endpoint of fungal-free survival at the 2-week posttherapy follow-up visit (i.e., the proportion of patients who survived through the 2-week posttherapy follow-up period and had documented microbiological eradication of *Candida* sp. from follow-up cultures collected after the initiation of study therapy).

Hypothesis: In neonates and infants with invasive candidiasis, caspofungin will be superior to amphotericin B deoxycholate, with regard to the proportion of patients with fungal-free survival at the 2-week posttherapy follow-up visit.

2.1.2 Secondary Objectives

2.1.2.1 Efficacy

To assess in neonates and infants who are treated with caspofungin or amphotericin B deoxycholate for documented invasive candidiasis, fungal-free survival at the end of study therapy (i.e., the proportion of patients who survived through the end of study therapy visit period and had documented microbiological eradication of *Candida* sp. from follow-up cultures collected after the initiation of study therapy).

2.1.2.2 Safety

To assess the safety in neonates and infants who are treated with caspofungin or amphotericin B deoxycholate for documented invasive candidiasis.

2.1.3 Exploratory Objectives

[redacted]

[redacted]

2.2 SUBJECT/PATIENT INCLUSION CRITERIA

1. Patient is <3 months (90 days) of age on day of informed consent.

   NOTE*:* Age is based on chronological assessment from the time of birth.

2. Patient (either symptomatic or at-risk) has a documented (culture-confirmed), invasive *Candida* infection, as defined by the presence of (a) a positive culture for *Candida* spp. collected from a normally sterile body fluid within 96 hours of study entry or (b) a positive culture for *Candida* spp. collected within 96 hours of study entry from a newly-placed drain inserted into a normally sterile body site. "At-risk" is defined by the presence of one or more of the risk factors included in Appendix 6.2.

   NOTE: A symptomatic or at-risk patient with a *Candida* UTI, as defined by a positive urine culture of >10,000 colony-forming units (CFUs) per milliliter of *Candida* spp. from a newly placed catheter, will also be eligible for enrollment.

3. Parent (or guardian) understands the study procedures, alternative treatments available, and risks involved with the study and voluntarily agree to the patient's participation by giving written informed consent.

4. Parent (or guardian) provides written informed consent for the trial.

2.3 SUBJECT/PATIENT EXCLUSION CRITERIA

1. Patient is ≥3 months (≥90 days) of age at the time of informed consent.

2. Patient has *Candida* disease limited to the oropharynx, esophagus, or other mucosal or superficial skin surfaces (e.g., vagina or other genitalia, colonic tract, skin folds, nail beds, etc.).

3. Patient has evidence of infection limited to a positive culture for *Candida* spp. from the sputum, broncho-alveolar lavage (BAL), catheter tip, or previously placed indwelling non-vascular catheters/drains.

   NOTE: Patients with a positive *Candida* culture sample obtained at the time of the sterile placement of a non-vascular catheter or drain are eligible.

4. Patient has a prosthetic device (e.g., prosthetic heart valve) at a suspected site of *Candida* infection.

   NOTE: Patients may be eligible for enrollment if the device is surgically removed at study entry or within 72 hours after randomization.

5. Patient is actively co-infected with a non-*Candida* fungal organism.

6. Patient has received more than 48 hours of systemic (IV or oral) antifungal treatment since the time the positive *Candida* index culture was collected *as therapy for this episode of invasive candidiasis*.

   NOTE: Prior antifungal prophylaxis with a triazole [e.g., fluconazole] is permitted.

7. Patient has failed prior systemic (IV or oral) antifungal therapy for this episode of invasive candidiasis.

8. Patient has exclusionary laboratory values (obtained within 48 hours of study therapy initiation) as listed below:

   - Aspartate aminotransferase (AST, also referred to as SGOT) >3 times the upper limit of normal, for age.
   - Alanine aminotransferase (ALT, also referred to as SGPT) >3 times the upper limit of normal, for age.

   NOTE: Patients with screening values/findings outside the ranges described may, at the discretion of the investigator, have one repeat determination performed and if the repeat value satisfies the criterion, the investigator may continue in the screening process for this particular patient. Only the specific out of range values/findings should be repeated (not the entire panel).

9. Patient is not expected to survive at least 5 days.

10. Patient has a diagnosis of acute hepatitis or cirrhosis due to any cause.

11. Patient is currently participating or has participated in a study with an investigational compound or device.

12. Patient has previously participated in this study.

13. Patient is scheduled or anticipated to receive rifampin or other systemic (IV or oral) antifungal therapy (i.e., an intravenous or oral formulation of the member of the polyene, triazole, or echinocandin class) while on study therapy.

    NOTE: Patients who were on rifampin or other systemic antifungal therapy prior to study entry are eligible for enrollment, provided these are discontinued prior to the initiation of study therapy.

14. Patient has known renal insufficiency, which, in the investigator's assessment, has the potential to worsen as a result of subsequent study therapy with amphotericin B deoxycholate.

15. Patient or the patient's mother has a history of allergy, hypersensitivity, or any serious reaction to caspofungin or another member of the echinocandin class (e.g., micafungin, anidulafungin, or aminocandin).

16. Patient or the patient's mother has a history of allergy, hypersensitivity, or any serious reaction to amphotericin B deoxycholate or other members of the polyene class (e.g., amphotericin B lipid complex, liposomal amphotericin B, or amphotericin B colloidal dispersion).

17. Patient has a severe congenital disorder known to lower immune response.

18. Patient has a history or current evidence of any condition, therapy, lab abnormality or other circumstance that might confound the results of the study, or interfere with the patient's participation for the full duration of the study, such that it is not in the best interest of the patient to participate.

2.4 STUDY DESIGN AND DURATION

2.4.1 Summary of Study Design

This is a multicenter, double-blind, randomized, comparative study to evaluate the safety, tolerability, and efficacy of caspofungin versus amphotericin B deoxycholate in the treatment of neonatal candidiasis. Approximately 90 neonates and infants less than 3 months of age with documented (culture-confirmed) invasive *Candida* infections within 96 hours prior to study entry will be enrolled and randomized in a 2:1 ratio to receive intravenous caspofungin 2 mg/kg (per body weight) once daily (~60 patients) or intravenous amphotericin B deoxycholate 1 mg/kg (per body weight) once daily (~30 patients).

The duration of study therapy with caspofungin or amphotericin B deoxycholate is variable and dependent on a variety of factors, including (1) the rapidity of a patient's clinical and microbiological response, (2) the patient's general medical condition, and (3) the underlying site of *Candida* infection. In general, patients should be treated with study therapy for a minimum of 14 days following the time of documented negative cultures from the site of infection and improvement of any clinical signs and symptoms of invasive candidiasis (see Section 2.4.2, Treatment Plan).

Patients will be monitored for adverse experiences while on study therapy and during the 2-week posttherapy follow-up period. Selected laboratory safety tests will be performed from blood collected at screening, on Day 4 (or Day 3 or Day 5) and Day 7 of study therapy, twice weekly thereafter while on study therapy, on the last day of study therapy, and at the 2-week posttherapy follow-up visit. A physical examination will be performed at prestudy, twice weekly throughout the study therapy period (including Day 4 and Day 7), on the last day of study therapy, and at each of the 2 posttherapy follow-up visits (2 and 8 weeks posttherapy).

A detailed description and evaluation of the *Candida* infection will be performed at screening, daily while on study therapy, on the last day of study therapy, and at the 2- and 8-week posttherapy follow-up visits. Resolution or progression of the *Candida* infection should be documented by assessment of signs and symptoms, radiographic studies (when clinically indicated), and follow-up blood cultures or, as appropriate, other follow-up cultures (including urine or CSF). Based on all available data, an efficacy assessment will be made at the end of study therapy and at the 2-week posttherapy follow-up visit.

2.4.2 Treatment Plan

Neonates and infants <3 months of age with documented (culture-confirmed) *Candida* infections will be randomized in a 2:1 ratio to receive caspofungin (~60 patients) or amphotericin B deoxycholate (~30 patients).

In an effort to strive for adequate representation of patients from different weight groups (reflective of patient gestational age) in both treatment arms, randomization will be stratified into 3 weight categories (based on weight at study entry): <1000 grams, 1000 to 1500 grams, and >1500 grams. Patients will be stratified into each of the weight categories in a manner consistent with the 2:1 randomization of caspofungin to amphotericin B deoxycholate.

Study Drug Preparation

Caspofungin will be administered at 2 mg/kg once daily (with no loading dose). Dosing with caspofungin will be based on the patient's actual weight at the time of study entry.

Caspofungin will be reconstituted/prepared by an unblinded study pharmacist. Appropriate quantities of caspofungin will be diluted with normal (0.9%) saline to achieve a final concentration not to exceed 0.5 mg/mL. For example, for a 1-kg neonate, the daily caspofungin dose is 2 mg, and should be diluted in at least 4 mL. **NOTE: Dilution of caspofungin in dextrose-containing solutions is contraindicated.** The final total volume of infusate is at the discretion of the unblinded pharmacist and should be based on the patient's ability to tolerate the fluid load. However, the final caspofungin concentration should **not** exceed 0.5 mg/mL. Full guidelines for the preparation of caspofungin study therapy for infusion are provided in the Pharmacy Binder.

Amphotericin B deoxycholate will be administered at 1 mg/kg (per body weight) once daily. Amphotericin B deoxycholate will be reconstituted/prepared by an unblinded study pharmacist. Dosing with amphotericin B deoxycholate will be based on the patient's actual weight at the time of study entry. The amphotericin preparation will also be administered as a single daily infusion. Full guidelines for the preparation of amphotericin B deoxycholate study therapy for infusion are provided in the Pharmacy Binder.

In order to verify the patient is receiving the correct dose of either caspofungin or amphotericin B deoxycholate, weight should be measured at least once weekly while the patient is on study therapy, and the dose of caspofungin or amphotericin B deoxycholate should be adjusted accordingly.

All study therapy (caspofungin or amphotericin B deoxycholate) will be administered intravenously as a single daily dose. Each infusion should be administered over approximately 2 hours. The IV line should be flushed thoroughly after each study therapy infusion. Infusion of study therapy may be given through either a pediatric syringe pump or ambulatory pump if this will help ensure that the patient receives the complete dose.

As these 2 products differ in color, opaque masking will be used over the infusion materials (e.g., infusion syringe and tubing) to ensure adequate blinding of the treatment

group. The unblinded pharmacist will be responsible to cover the materials (e.g., infusion syringe and tubing) with opaque masking. Importantly, the unblinded pharmacist will be uninvolved in any of the postinfusion evaluations for the patient. All study personnel involved with the postinfusion evaluations of safety and efficacy outcomes, including the study coordinator(s), investigator, or subinvestigator(s), must have no access to the treatment group assignment or the preparation of the study infusion.

Duration of Study Therapy

The duration of study therapy with caspofungin or amphotericin B deoxycholate is variable and dependent on a variety of factors, including (1) the rapidity of a patient's clinical and microbiological response, (2) the patient's general medical condition, and (3) the underlying site of *Candida* infection. In general, patients should be treated with intravenous study therapy for a minimum of 14 days following the time of documented negative cultures from the site of infection and improvement of any clinical signs and symptoms of invasive candidiasis. Certain sites of infection, including *Candida* endocarditis, meningitis, osteomyelitis/septic arthritis, and endophthalmitis, may warrant a longer treatment course based on the consideration of a variety of relevant factors (see Table 2-1).

The maximum duration of study therapy permitted is 90 days. If longer duration of therapy is warranted, a written request for continuation of therapy, including a written summary of the case, should be provided to the SPONSOR Clinical Monitor (or designee) before Day 85 of therapy.

Table 2-1

General Guidelines for the Duration of Total Antifungal Therapy[a] for Various Non-fungemic Forms of Invasive Candidiasis

***Candida* Infection**	**Recommended Duration of Therapy**	**Other Considerations or Guidelines for Management[b]**
Peritonitis	2 to 4 weeks of therapy (minimum of at least 14 days following both clinical resolution and microbiological eradication)	• *Patients on peritoneal dialysis*: Removal of peritoneal dialysate catheter likely required • *Surgical patients*: Surgical repair and drainage of perforation or leak likely required.
Abscess involving intraabdominal cavity or organ	2 to 4 weeks of therapy (minimum of at least 14 days following both clinical resolution and microbiological eradication)	• Surgical drainage or aspiration drainage of abscess collection likely required • Follow-up radiography (ultrasound, CT, or MRI) should be used to gauge response and determine treatment duration
Abscess involving other cavity or organ	2 to 4 weeks of therapy (minimum of at least 14 days following both clinical resolution and microbiological eradication)	• Surgical drainage or aspiration drainage of abscess collection likely required • Follow-up radiography (ultrasound, CT, or MRI) should be used to gauge response and determine treatment duration
Pleural space infection (empyema)	2 to 4 weeks of therapy (minimum of at least 14 days following both clinical resolution and microbiological eradication)	• Ongoing chest tube drainage likely required • Follow-up radiography (chest ultrasound, x-ray, or CT) should be used to gauge response and determine treatment duration
Pneumonia	2 to 4 weeks of therapy (minimum of at least 14 days following both clinical resolution and microbiological eradication)	• Follow-up radiography (chest ultrasound, x-ray, or CT) should gauge response and determine treatment duration • In general, consider 2 weeks of therapy for non-necrotizing pneumonia and 4 weeks of therapy for necrotizing pneumonia
Endophthalmitis	Generally 6 to 12 weeks of therapy (until complete resolution of lesions or stabilization)	Not Applicable

General Guidelines for the Duration of Total Antifungal Therapy[a] for Various Non-fungemic Forms of Invasive Candidiasis (Cont.)

Candida Infection	Recommended Duration of Therapy	Other Considerations or Guidelines for Management[b]
Osteomyelitis	At least 4 weeks of therapy	• Initial surgical debridement may be required. • Repeat follow-up debridements may also be necessary, based on response (follow-up cultures encouraged during repeated debridements) • Follow-up radiography should be used to gauge response and determine treatment duration
Septic arthritis	At least 4 weeks of therapy	• Initial, adequate drainage of joint fluid may be required. • Repeated drainage (with assessments of fluid cell count and repeat culture) may also be necessary, based on response
Meningitis	3 to 6 weeks of therapy	• Meningitis associated with neurosurgical procedures: Consideration for removal of any prosthetic material and shunts Consider 3 weeks of therapy for patients with meningitis without associated abscess • Consider 6 weeks of therapy (or longer) for complicated meningitis. In such cases consider continuation of treatment until normalization of all CSF analyses (including negative follow-up CSF cultures), normalization of radiologic findings, and stabilization of neurological function
Endocarditis	At least 6 weeks of therapy	• Combined medical and surgical treatment may be needed. Removal of all infected valves and debridement of abscessed cardiac/pericardial tissue may be required • Document follow-up blood cultures are negative for *Candida* species • Careful follow-up of cardiac function to assure no relapse of infection

[a] These general guidelines for treatment duration are based, in part, on Infectious Diseases Society of America (IDSA) Treatment Guidelines for the treatment of invasive candidiasis. As there are no dedicated guidelines for neonatal candidiasis, most of the dosing duration recommendations are based on adult experience, and, hence, may require some modification in the neonatal/infant population on a case-by-case basis.

[b] The general IDSA guidelines for treatment management of each site of *Candida* infection are included in Appendix 6.3.

2.5 LIST OF EFFICACY MEASUREMENTS

Based on all available data, an efficacy assessment will be made at the end of study therapy and at the 2-week posttherapy follow-up visit. The efficacy endpoint will be based on fungal-free survival (i.e., the proportion of patients who survived at the timepoint of interest and had documented microbiological eradication of *Candida sp.* from follow-up cultures collected after the initiation of study therapy). Microbiological eradication denotes negative follow-up cultures for *Candida* sp. from the site of infection at the time of evaluation. If a culture is not obtained on the day of assessment, then the last culture after study entry may be used to assist in the assessment of microbiological eradication. If the last culture is negative for *Candida* sp., then microbiologic eradication would be considered achieved. Although fungal-free survival will be assessed at 2 different time points (end of study therapy and the 2-week posttherapy follow-up visit), the primary efficacy time point will be at the 2-week posttherapy follow-up visit. **NOTE:** Fungal-free survival assumes no additional antifungal therapy is required for the treatment of the underlying *Candida* infection once study therapy has ended; however, once study therapy has ended, prophylaxis with an antifungal agent (e.g., fluconazole) may be administered, if this is deemed appropriate by the investigator.

[redacted]

Finally, the efficacy with caspofungin in neonates and infants (less than 3 months of age) enrolled in this study will be compared descriptively to the efficacy in caspofungin-treated patients enrolled with invasive candidiasis in the prior Phase II pediatric documented infection study (Protocol 043, children and adolescents [3 months to 17 years]) and prior Phase III adult studies (Protocols 014 and 801).

2.6 LIST OF SAFETY MEASUREMENTS

All patients who receive one or more doses of study therapy will be evaluated for the presence of adverse experiences while on study therapy and through the 2-week posttherapy follow-up visit. To assist with these safety assessments, a physical examination will be performed at prestudy, twice weekly throughout the study therapy period (including Day 4 and Day 7), on the last day of study therapy, and at each of the 2 posttherapy follow-up visits (2 and 8 weeks posttherapy). In addition, selected laboratory safety tests will be performed at screening, on Day 4 (or Day 3 or Day 5) and Day 7 of study therapy, twice weekly thereafter while on study therapy, on the last day of study therapy, and at the 2-week posttherapy follow-up visit (see Appendix 6.1).

To address the secondary safety objective, the following safety endpoints will be evaluated: (1) the development of adverse experience(s) during the study therapy period or during the 2-week posttherapy follow-up period; (2) the development of drug-related adverse experience(s) during the study therapy period or during the 2-week posttherapy follow-up period; (3) the development of serious adverse experience(s) during study therapy period or during the 2-week posttherapy follow-up period; (4) the development of drug-related, serious adverse experience(s) during study therapy period or during the 2-week posttherapy follow-up period; (5) the development of adverse experiences that necessitate discontinuation of study therapy; and (6) the development of drug-related adverse experiences that necessitate discontinuation of study therapy.

2.7 PHARMACOKINETIC MEASUREMENTS

Three blood samples (each 350 µL) for pharmacokinetic assessments will be collected from all patients. Each patient will be randomly assigned to one of 8 sampling schedules; all 3 samples are to be taken on the same study day. Half of the patients will have samples taken on Study Day 4 and the other half will have samples taken on Study Day 7. If it is not possible to take samples on the assigned Study Day, it is recommended that samples be taken on the following Study Day.

Blood samples will be collected from all patients at the time of peak concentration (within 5 minutes after the end of study therapy infusion) and time of trough concentration (approximately 24 hours after the start of study therapy infusion but prior to the next day's dose). In addition, a blood sample will be collected at an intermediate time between peak and trough times as shown in Table 3-4, in Section 3.3.2.

Weight should be measured within 12 hours prior to the infusion of study therapy on the assigned day of pharmacokinetic blood sampling, and the study therapy dose given on the pharmacokinetic sample day should be adjusted to reflect the most recently measured weight.

If a patient undergoes any procedure that involves collecting CSF while on study therapy, approximately 350-µL of CSF should be retained for pharmacokinetic assessments. If available, a baseline (or prestudy) CSF sample should also be retained.

Plasma will be separated from blood and sent to a central laboratory for pharmacokinetic testing. The CSF will also be sent to a central laboratory for pharmacokinetic testing. Procedures for collection, processing, storage, and shipment of pharmacokinetic samples from blood (plasma) and CSF are included in the Administrative Binder.

2.8 STATISTICAL ANALYSIS PLAN SUMMARY

Key elements of the statistical analysis plan are summarized below; the comprehensive plan is provided in Section 3.5 of the protocol details.

2.8.1 Efficacy Analyses

The primary and secondary endpoints, primary analysis population, and statistical methods that will be employed for the efficacy analyses are presented in Table 2-2.

The primary hypothesis will be evaluated by comparing the caspofungin treatment group to the amphotericin B deoxycholate treatment group with respect to the proportion of patients with fungal-free survival at the 2-week posttherapy follow-up visit.

All efficacy evaluations will use a full analysis set (FAS) patient population, which includes those patients who receive at least one dose of study therapy and have a documented (culture-confirmed) diagnosis of invasive candidiasis (see Section 2.2, Inclusion Criteria). All patients, irrespective of body weight at study entry, will be grouped together for the primary evaluation. Subgroup evaluation based on the 3 body weight categories at study entry (<1000 grams, 1000-1500 grams, >1500 grams) will also be displayed. Of note, a per-protocol population will also be evaluated for the primary and secondary efficacy endpoints (see Section 3.5.5.1, Efficacy Analysis Populations).

The treatment comparisons for the primary and secondary efficacy analyses will be made using the difference in response rates between the 2 treatment groups and its 95% confidence interval. The confidence interval for the difference in response rates will be calculated using a methodology proposed by Miettinen and Nurminen [17].

Table 2-2

Analysis Strategy for Key Efficacy Variables

Endpoint/Variable (Description, Time Point)	Primary vs. Supportive Approach[a]	Statistical Method	Analysis Population	Missing Data Approach
Primary				
Proportion of patients with fungal-free survival through the 2-week posttherapy period	P	Miettinen and Nurminen method	FAS	A patient with missing data will be considered a failure.
Proportion of patients with fungal-free survival through the 2-week posttherapy period	S	Miettinen and Nurminen method	PP	Observed data
Secondary				
Proportion of patients reporting fungal-free survival at the end of study therapy	P	Miettinen and Nurminen method	FAS	A patient with missing data will be considered a failure.
Proportion of patients reporting fungal-free survival at the end of study therapy	S	Miettinen and Nurminen method	PP	Observed data
[redacted]				

[a] P=Primary approach; S=Secondary approach.

2.8.2 Safety Analyses

All safety tabulations will use an all-patients-as-treated (APaT) population, which includes all patients who receive at least one dose of study therapy. There are no safety parameters that rise to the level of formal statistical testing in this study (i.e., no Tier 1 events).

2.8.3 Power and Sample Size

This study will enroll approximately 60 patients in the caspofungin treatment group and 30 patients in the amphotericin B deoxycholate treatment group, to achieve 80% power (2-sided, α=0.05) to demonstrate the primary efficacy hypothesis that caspofungin is superior to amphotericin B deoxycholate with regard to the proportion of patients with fungal-free survival at the 2-week posttherapy follow-up visit. The minimum criterion for success is that the lower bound of the 95% CI for the difference between the 2 treatment groups (caspofungin minus amphotericin B deoxycholate) in the primary efficacy endpoint is >0.

The sample size is based on an underlying response rate of 50% for the amphotericin B deoxycholate treatment group from the recently published comparative study in 32 neonates and infants with invasive candidiasis where a favorable response was observed in 86.7% of caspofungin-treated patients and 41.7% of amphotericin B deoxycholate-treated patients [9]. The study is designed to have 80% power to demonstrate the superiority of caspofungin over amphotericin B deoxycholate at an overall two-sided, 5% alpha-level, if the underlying treatment difference in fungal-free survival at the 2-week posttherapy visit is ~30 percentage points (or larger).

3. PROTOCOL DETAILS

3.1 RATIONALE

Caspofungin is a parenteral echinocandin antifungal agent that has received approval in the United States, the European Union (EU), and over 80 other countries for the treatment of adult patients (≥18 years of age) for one or more of the following: (1) invasive aspergillosis in patients who are refractory to or intolerant of other therapies (i.e., amphotericin B deoxycholate, lipid formulations of amphotericin B, and/or itraconazole); (2) esophageal candidiasis; (3) candidemia and other *Candida* infections, including intra-abdominal abscesses, peritonitis, and pleural space infection; and (4) empirical therapy of suspected invasive fungal infections in febrile, neutropenic patients [1, 2]. Furthermore, caspofungin has been approved for use in pediatric patients (≥3 months of age) in over 60 countries worldwide for the same indications as in adults.

As of 11-Jan-2012, a total of 2036 adult and pediatric subjects/patients have received at least one dose of caspofungin in the global registration studies. In these studies, caspofungin was administered for up to 196 days at daily doses ranging between 5 mg and 210 mg. Integrated safety data has been summarized across 1951 of these 2036 subjects. Of the 1951 subjects, 42% experienced at least one drug-related adverse experience during caspofungin therapy or within the 14-day posttherapy follow-up period. The most common drug-related adverse experiences were pyrexia (9.3%), increased ALT (6.5%), increased AST (6.0%), increased alkaline phosphatase (5.2%), chills (5.2%), and headache (4.6%). Across all studies, caspofungin has a favorable safety profile, with few serious, drug-related adverse experiences and few discontinuations due to drug-related adverse experiences. The incidence of drug-drug-interactions with caspofungin has also been relatively infrequent. Additional details regarding the pharmacokinetics, safety, and efficacy of caspofungin in adult patients are further described in the Investigator's Brochure (IB).

3.1.1 Rationale for This Study

Fungal Infections in Pediatric Patients, including Neonates and Infants

The epidemiological rise in invasive fungal infections (IFI) in pediatric patients rivals the increases seen in the adult population. As in adults, IFI are commonly seen in pediatric patients with childhood malignancies or those pediatric patients undergoing hematopoietic stem cell transplantation or pediatric surgery [14]. *Candida* remains the most common cause of IFI in children. In 2000 alone, candidemia was diagnosed in an estimated 1,118 hospital admissions of all pediatric patients (≤20 years of age) in the United States. This yielded a frequency of 43 cases per 100,000 pediatric admissions (95% CI, 35-52 cases per 100,000 pediatric admissions). In comparison, candidemia was seen in 30 cases per 100,000 adult admissions (95% CI, 26-34 cases per 100,000 adult admissions). The estimated annual incidence of candidemia among all pediatric and adult admissions is 0.043% and 0.03%, respectively [15].

In the neonatal and infant population, candidemia and other forms of invasive candidiasis are a major medical concern. *Candida* species represent the second most common pathogen among nosocomial blood stream infections and the most common fungal infection in infants less than 1 year of age [5]. Furthermore, in the United States in 2003, the overall incidence of invasive candidiasis among neonates was 15 cases per 10,000 neonatal admissions (95% CI, 13-16 case per 10,000 neonatal admissions) [3]. However, incidence has been shown to vary widely between clinical centers [4, 6-7]. *C. albicans* is the most frequently isolated species, and *C. parapsilosis* is the most frequently isolated non-*C. albicans* species [4, 7, 18-22].

Invasive candidiasis is an opportunistic infection resulting from either the immaturity of the immune system, a depleted immune response in a critically ill neonate, an increased colonization rate, or invasive intensive-care procedures. The risks associated with infection include a young gestational age and a very low birth weight [4, 14]. In a study published from Israel, the incidence of acquired fungal sepsis in neonates ranged from 0.4 to 2 cases per 1000 live-births; fungal sepsis was seen in 1.1% of all neonatal intensive care unit (NICU) admissions. The incidence of invasive candidiasis in this population is inversely related to the weight of the infant, with cumulative incidence rates of 0.26%, 3.1%, and 5.5% in infants with birth weights ≥2500g, very low birth weights (VLBW, <1500g), or extremely low birth weights (ELBW, <1000g), respectively [16]. Notably, the current antifungal regimens administered in the neonatal population are associated with significant toxicity, multiple drug-drug interactions, or limitations in spectrum of activity.

To date, four clinical studies (Protocols 033, 042, 043, 044) have been conducted to evaluate caspofungin in pediatric patients 3 months to 17 years of age. Two pharmacokinetic studies (Protocols 033 and 042) have demonstrated that caspofungin, administered at a 50 mg/m^2 once-daily maintenance dose in pediatric patients (3 months to 17 years of age), resulted in plasma pharmacokinetic parameters commensurate with those achieved in adults receiving the 50-mg once-daily maintenance dosing regimen. The results of the other 2 studies confirm that the efficacy and safety of caspofungin at the 50-mg/m^2 daily maintenance dose is comparable to that seen in caspofungin-treated adults. Additional details regarding the pharmacokinetics, safety, and efficacy of caspofungin in pediatric patients (3 months to 17 years of age) are further detailed in the IB.

Based on these studies, caspofungin has been approved for use in pediatric patients ≥3 months of age in over 60 countries worldwide for the same indications as in adults. Importantly, the indications and age range for use vary by country [1, 2].

Caspofungin Use in Neonates and Infants Less than 3 Months of Age

The pharmacokinetics and safety of caspofungin in the neonatal patient population were evaluated in a prospective pharmacokinetic trial (Protocol 058). Protocol 058 was an open-label, noncomparative study to investigate the safety, tolerability, and pharmacokinetics of caspofungin in neonates and infants <3 months of age. In this study, the pharmacokinetics in 18 neonates and infants receiving single or multiple once-daily doses of 25-mg/m^2 were generally similar to that in adults receiving a 50-mg once-daily

maintenance dose. Caspofungin was well tolerated in the 18 patients included in this study; in fact, no drug-related adverse experiences were noted in any of the 18 caspofungin recipients [8]. Efficacy in the neonatal population can also be anticipated based on the efficacy of caspofungin against invasive candidiasis in pediatric patients 3 months to 17 years of age enrolled in the documented infection study (Protocol 043). The data from Protocol 043 demonstrated an 80% success rate in children and adolescents with invasive candidiasis (including a 73% response rate in children <6 years of age) [23].

The efficacy of caspofungin in the treatment of invasive candidiasis and other *Candida* infections in neonates and infants was recently demonstrated in a randomized, double-blind, prospective clinical trial in 32 neonates comparing caspofungin to amphotericin B deoxycholate (see Table 3-1) [9]. In this study conducted at a single site in Saudi Arabia, newborn infants received either caspofungin (2 mg/kg/day, n=15) or amphotericin B deoxycholate (1 mg/kg/day, n=17). A favorable response at the end of intravenous therapy, the primary timepoint for efficacy, was observed at a greater rate in patients who received caspofungin (86.7%) than those who received amphotericin B deoxycholate (41.7%) ($p=0.04$). Importantly, caspofungin was effective in all sites of *Candida* infection, including all 3 cases with *Candida* meningitis and 4 of 5 patients with *Candida* endocarditis. The proportion of patients who experienced at least 1 drug-related laboratory adverse event was significantly lower in neonates who received caspofungin compared to those who received amphotericin B deoxycholate ($p<0.05$).

Table 3-1

Randomized, Comparative Trial of Caspofungin vs. Amphotericin B Deoxycholate in Neonates

Lead Author	Study Design	Treatment N Daily Dose	Age[a] (Mean ± SD, Days)	*Candida* Species (n)	Site of Infection (n)	Response Rate[b] % (n/N)	Safety Endpoints % (n/N)
Mohamed WA and Ismail M[9]	Single-center, prospective, randomized, controlled trial	Caspofungin 15 2 mg/kg	21.1 ± 3.1	*C. albicans* (11) *C. parapsilosis* (3) *C. tropicalis* (1)	Meningitis (3) Ventriculitis (1) Endocarditis (5) Endophthalmitis (2) Urinary candidiasis (3) Osteomyelitis (1)	86.7% (13/15)	Clinical AE: 26.7% (4/15) Laboratory AE: 33.3% (5/13) Discontinuation due to AE: 0% (0/15)
		Amphotericin B deoxycholate 17 1 mg/kg	22.3 ± 2.4	*C. albicans* (13) *C. parapsilosis* (2) *C. tropicalis* (2)	Meningitis (4) Ventriculitis (1) Endocarditis (4) Endophthalmitis (3) Urinary candidiasis (4) Osteomyelitis (1)	41.7% (5/12[c])	Clinical AE: 64.7% (11/17) Laboratory AE: 76.4% (13/17) Discontinuation due to AE: 29.4% (5/17)

[a] Age at onset of *Candida* infection
[b] Favorable response at the end of intravenous therapy, the primary time point for determination of efficacy in the study
[c] Five patients in the amphotericin B deoxycholate group withdrew due to drug-related adverse events and were not included in the calculation of the response rate.
N = Overall sample size for each treatment group
n = Number of patients in each subcategory within a specific treatment group.

Published data from several case series in neonates with invasive candidiasis (two from Costa Rica, one from Italy, and one from Detroit, Michigan, United States) provide additional evidence of efficacy in this age group (see Table 3-2) [10-13]. In these studies, caspofungin therapy was begun only after initial therapy with conventional antifungals (amphotericin B deoxycholate, fluconazole, and/or flucytosine) had failed; in other words, the *Candida* infection was resistant to, or the patient was intolerant of, the initial therapy. In 29 of 75 cases, caspofungin treatment was added to a conventional antifungal regimen, while caspofungin monotherapy was given in the remaining 46 cases. Collectively, 53 of 75 neonates received either a caspofungin dose of 2 mg/kg or 25 mg/m^2, and the favorable response rate across these series was in excess of 80%. Importantly, caspofungin was effective in all sites of *Candida* infection, including all 6 patients with *Candida* meningitis in these 4 case series. Caspofungin was well tolerated, with few drug-related adverse events reported. The drug-related adverse events were consistent with those reported in older children and adults.

Table 3-2

Case Series Documenting Caspofungin Use in Neonates

Publication	Country	Number of Patients	Findings
Mondello I et al. [10]	Italy	16	• All infants or neonates (15 very low birth weight and 1 full term) • Caspofungin added to conventional therapy: 25 mg/m^2 (11), 50 mg/m^2 (4), and 1 dose unspecified • Favorable response estimated to be >81% (13/16) • No adverse event (AE) attributed to caspofungin; reported AEs (n) included: ➢ Transient mild hypokalemia (4) ➢ Thrombocytopenia (1) ➢ Deaths (4): severe intraventricular hemorrhage (1), ICI (3, all dosed at 25 mg/m^2)
Natarajan G et al. [11]	United States	13	• All infants or neonates (12 preterm and 1 term) • All caspofungin use at 1 mg/kg daily (5 patients had 1.5 mg/kg loading dose) • All as combination salvage therapy with lipid amphotericin B, amphotericin B deoxycholate, fluconazole, or 5-FC • Success in 11 (85%) of 13 patients • No serious drug-related AEs • Reported AEs (n) included: ➢ Thrombophlebitis on initial dose; further doses tolerated with increased dilution & infusion duration (1) ➢ Transaminase elevation (4) ➢ Hypokalemia (2) ➢ Isolated direct hyperbilirubinemia (1) ➢ 2 deaths not related to caspofungin
Odio CM et al. [12]	Costa Rica	10	• All infants or neonates • Caspofungin mostly at 2 mg/kg daily • All caspofungin as salvage monotherapy following initial amphotericin B deoxycholate use • Success in 10 (100%) of 10 patients • No demonstrable toxicity
Odio CM et al. [13]	Costa Rica	36	• All infants or neonates • Caspofungin at 2 mg/kg daily or 3 mg/kg for meningitis (3 patients) • All caspofungin as salvage monotherapy following initial amphotericin B deoxycholate use • 100% favorable response (36/36 pts with sterilized blood/cerebrospinal fluid [CSF]) ➢ All 3 patients with Candida meningitis had sterile follow-up CSF cultures ➢ 1 patient relapsed and was successfully treated with a second course of caspofungin • No demonstrable toxicity

With the approval of the use of caspofungin in many countries in children and adolescents between the ages of 3 months to 17 years, and with the availability of preclinical data in juvenile rodent model and pharmacokinetic data in infants and neonates (Protocol 058), this study will prospectively evaluate the safety and efficacy of caspofungin in the treatment of invasive candidiasis in the youngest pediatric group, the neonatal and infant population less than 3 months of age.

Amphotericin B Use in Neonates and Infants Less than 3 Months of Age

The IDSA clinical practice guideline for the management of candidiasis [29] recommends amphotericin B deoxycholate as the first-line treatment for invasive candidiasis in neonates/young infants at a dose of 1 mg/kg/day. Publications describing prospective, randomized, comparator-controlled trials of amphotericin B deoxycholate in neonatal candidiasis are predominantly limited to three studies, each enrolling less than 60 patients in total and less than 35 in the amphotericin B deoxycholate treatment groups, as shown in Table 3-3. Measurements of treatment success, which varied among these studies, ranged from 41.7% to 67.6% for the amphotericin B deoxycholate group. Although limited in population sizes, two of these studies showed that patients treated with amphotericin B deoxycholate had more findings of hepatotoxicity, namely elevated alkaline phosphatase and total serum bilirubin, than comparators [9, 24]. As noted comparator-controlled trial of caspofungin versus amphotericin B deoxycholate, greater rates of drug-related laboratory abnormalities were also observed in patients who received amphotericin B deoxycholate than those who received caspofungin (see Table 3-1) [9]. Nephrotoxicity is generally the most concerning side effect for neonates [27]; however, it has been reported that nephrotoxicity associated with amphotericin B deoxycholate use in infants and children is generally less severe than in adults, likely due to the more rapid clearance in children [25]. In addition, evidence suggests that amphotericin B deoxycholate is generally well tolerated in premature infants [26, 27]. For this reason, liposomal preparations are not generally used in this patient population.

Table 3-3

Clinical Trials of Amphotericin B Deoxycholate in the Neonatal Population

Publication	Study Description (Year Conducted)	Dose of Amphotericin B Deoxycholate	Findings
Mohamed WA and Ismail M [9]	Caspofungin vs. amphotericin B deoxycholate (October 2008 to September 2010)	1 mg/kg/day	• See Table 3-1 • Nephrotoxicity was seen in 11.8% (2/17 patients) in the amphotericin B deoxycholate group and 0% in caspofungin group
Dreissen M, et al. [24]	Fluconazole vs. amphotericin B deoxycholate (June 1992 to June 1993)	1 mg/kg/day	• Neonates <3 months of age were eligible for enrollment • In total, 24 neonates were enrolled, with 11 patients receiving amphotericin B deoxycholate • Survival rate of 55% (6/11) in amphotericin B deoxycholate group and 67% (8/12) patients in the fluconazole group • Amphotericin B deoxycholate group demonstrated more signs of hepatotoxicity, specifically elevated alkaline phosphatase and total and direct serum bilirubin.
Linder N, et al [26]	Amphotericin B deoxycholate vs. two different amphotericin B lipid formulations (January 1996 to December 2000)	1 mg/kg/day	• Mean gestational age of patients was 29.3 (± 4.2) weeks • In total, 56 neonates were enrolled, with 34 patients receiving amphotericin B deoxycholate • Sterilization of blood was observed in 67.6% of patients treated with amphotericin B deoxycholate monotherapy, and 100% of patients with addition of a second antifungal agent • No immediate local or systemic adverse events were reported • No renal function deterioration was reported

3.1.2 Rationale for Dose and Regimen

The recommended dose for caspofungin for this study is 2 mg/kg daily. This dose is based on the published data referenced above as well as the simulated results from the prior pharmacokinetic and safety study for caspofungin in neonates and infants <3 months of age (Protocol 058).

In Protocol 058, neonates and infants with documented or highly suspected *Candida* infections received a single or multiple doses of caspofungin at 25 mg/m^2 once daily. The duration of caspofungin treatment in patients receiving multiple doses was a minimum of 4 days and a maximum of 28 days. Blood for plasma pharmacokinetic (PK) sampling was collected predose (at screening), at 1 hour and 24 hours post-caspofungin infusion on Day 1, and at 1 hour and 24 hours post-caspofungin infusion on Day 4 (corresponding to presumed steady-state peak and trough concentrations, respectively). Caspofungin was generally safe and well tolerated in this study population. On Day 1, the geometric mean ratios (90% CIs) for the neonates and infants relative to adults receiving the standard adult dose were 1.07 (0.89, 1.30) and 1.36 (1.04, 1.78), at 1 and 24 hours post-dose, respectively. On Day 4, the geometric mean ratios (90% CIs) for the neonates and infants relative to adults receiving the standard adult dose were 1.18 (0.95, 1.46) and 1.21 (0.90, 1.63), at 1 and 24 hours post-dose, respectively. Overall, these pharmacokinetic results suggest that the pharmacokinetics in neonates and infants <3 months of age receiving single or multiple, once-daily caspofungin doses of 25 mg/m^2 are fairly similar to those of adults receiving caspofungin at 50 mg once daily and the peak concentrations observed in neonates/infants did not exceed the range of clinical experience in adults. Based on these results, it was also determined that a loading dose is likely not required in this pediatric age group.

Measurements of height are not routinely performed in the neonatal/infant population; therefore, a dosing regimen based on body surface area is not preferred in this patient population. As a result, simulations for weight-based dosing were performed for the 12 patients who received multiple doses of caspofungin in Protocol 058. After calculating the actual dose received (in milligrams) based on each patient's BSA and adjusting by each patient's weight, the 25 mg/m^2 dose equated to a mean daily dose of ~2.1 mg/kg and median of ~2.0 mg/kg. Actual Day 4 C_{1hr} and C_{24hr} data were adjusted based on the dose the patient would have received had a 2 mg/kg dose been administered. Depending on the relative weight to BSA ratio of a given patient, estimated caspofungin concentrations were increased or decreased using a weight-based dosing scheme compared to BSA-based. However, the mean C_{1hr} and C_{24hr} values were nearly unchanged, and a decrease in variability was noted. Therefore, based on this analysis, a weight-based dose of 2 mg/kg of caspofungin is deemed roughly equivalent to 25 mg/m^2.

The proposed 2 mg/kg daily dose for caspofungin to be evaluated in this study is also consistent with the caspofungin dose evaluated in a prospective, randomized, double-blind study of the efficacy, safety, and tolerability of caspofungin compared to amphotericin B deoxycholate in 32 neonates [9]. As shown in Table 3-1, a favorable response at the end of intravenous therapy, the primary timepoint for efficacy in this study, was observed at a greater rate in patients who received caspofungin (86.7%) than those who received amphotericin B deoxycholate (41.7%) (p=0.04). Furthermore, as outlined in Table 3-2, a proposed 2 mg/kg daily dose for caspofungin in this study is supported by efficacy and safety observations from 4 case series in neonates from Costa Rica, Italy, and the US [10-13] where 53 of 75 neonates received either a reported 2 mg/kg dose or 25 mg/m^2 dose and the favorable response rate across these series was in excess of 80%. No loading dose was used in these various studies, thereby further confirming its limited value in this patient population.

Finally, a preclinical study in the juvenile rodent model also provides useful information for the use of caspofungin in disseminated (including CNS) candidiasis [28], which is a complication commonly seen in the neonatal population. This study confirmed that either a 1 or 2 mg/kg once-daily dosing regimen of caspofungin would be associated with efficacy in the treatment of candidiasis in both CNS and other tissues.

In summary, a 25 mg/m^2 or 2 mg/kg daily dose of caspofungin appears to demonstrate desirable pharmacokinetics in neonates and infants <3 months of age; the peak concentrations were not elevated beyond the clinical range of peak concentrations that have been observed to be well-tolerated in adults, and the trough concentrations in this age group were not reduced from those observed in adults at the 50 mg daily dose. In addition, the 2 mg/kg dose (without a loading dose) has been demonstrated to be safe and effective in a prospective, randomized, controlled clinical trial and other smaller efficacy studies. Therefore, a daily dose of 2 mg/kg (without a loading dose) has been selected for evaluation in this clinical trial. Importantly, the recommended daily maintenance dose for caspofungin in infants/toddlers over the age of 3 months is 50 mg/m^2. However, for the purposes of this study, the daily maintenance dose of 2 mg/kg is to be used throughout the treatment duration, even for patients who reach 3 months of age while on study therapy.

The daily dose for amphotericin B deoxycholate (1 mg/kg per body weight) was chosen based on the recommended standard dose in the IDSA guidelines for use in the neonatal population with invasive candidiasis [14, 24, 29]. Additionally, in the three studies listed in Table 3-3, patients in the amphotericin B deoxycholate treatment groups received a 1-mg/kg daily dose. Furthermore, although there is a relationship between total dose administered and tissue concentrations for amphotericin B deoxycholate, there is no conclusive clinical evidence that doses higher than 1 mg/kg/day are necessary for successful therapy in the pediatric population [25].

3.1.3 Rationale for Study Design

The current trial has been designed as a randomized, multicenter, comparator-controlled study to collect prospective data for caspofungin (relative to the current standard, amphotericin B deoxycholate) in the treatment of neonatal candidiasis. A double-blind approach has been instituted to ensure an unbiased evaluation of the efficacy, safety, and tolerability data for caspofungin (relative to amphotericin B deoxycholate) in this relatively frail population. A 2:1 randomization scheme of caspofungin to amphotericin B deoxycholate has been implemented to maximize the available efficacy and safety data for caspofungin in this indication, which is further supported by the comparative efficacy and safety study of caspofungin versus amphotericin B deoxycholate (see Table 3-1) [9].

There are currently no standard approved criteria for the evaluation of efficacy in infants and neonates with invasive candidiasis. The primary efficacy endpoint chosen for this study (i.e., fungal-free survival at 2 weeks following the completion of study therapy) is deemed an appropriate parameter as it incorporates 2 objective parameters: survival at least 2 weeks after study therapy and the requirement of *Candida* eradication from follow-up cultures following the onset of study therapy. [redacted]

[redacted]

The power and sample size are based on an underlying response rate of 50% for the amphotericin B deoxycholate treatment group from the recently published comparative study in 32 neonates and infants with invasive candidiasis where a favorable response was observed in 86.7% of caspofungin-treated patients and 41.7% of amphotericin B deoxycholate-treated patients [9]. The study is designed to have 80% power to demonstrate the superiority of caspofungin over amphotericin B deoxycholate at an overall two-sided, 5% alpha-level, if the underlying treatment difference in fungal-free survival at the 2-week posttherapy visit is ~30 percentage points (or larger). The SPONSOR believes the chosen sample size should allow for a reasonable evaluation of the efficacy of caspofungin against amphotericin B deoxycholate (both as an active comparator in this study and from historical data from the literature).

3.2 STUDY PROCEDURES

3.2.1 Concomitant Medication(s)/Treatment(s)

Drugs specifically excluded in the exclusion criteria must not be administered. Medications not permitted at any time during course of study therapy include rifampin and any systemic antifungal agent (oral or IV) other than the study therapy.

Should there be a clinical indication for any additional medication during the course of the study, the name of the drug, dosage (if required), and date(s) of administration must be recorded on the appropriate electronic case report form (eCRF).

3.2.2 Diet/Activity/Other

There are no dietary restrictions for this study.

3.2.3 Procedures

Study procedures should be conducted as summarized in the Study Flow Chart in Section 1.7. The following subsections provide additional details for each of the study procedures.

3.2.3.1 Informed Consent

3.2.3.1.1 General Informed Consent

General Informed Consent

The investigator or designated study personnel must obtain written informed consent from the parent (or guardian) of each potential patient prior to the initiation of any study-related procedures. Consent must be documented with dated signatures on the consent form from both the parent (or guardian) of the patient and the study personnel conducting the consent discussion. A copy of the signed informed consent will be given to the patient's parent (or guardian).

3.2.3.2 Assignment of Baseline Number

After informed consent has been obtained, the patient will be assigned a unique baseline number. The baseline number identifies the patient for all study-related procedures that occur prior to randomization to a treatment group (at which time an allocation number will be assigned). Baseline numbers will be 9-digit numbers containing the 4-digit, SPONSOR-assigned investigator site number followed by a sequential 5-digit patient number (e.g., site number = 0017; sequential patient number = 00001; Baseline Number = 001700001).

Each baseline number will be assigned only once and baseline numbers should not be reassigned for any reason. A single patient will not be assigned more than one baseline number. If a patient needs to be rescreened for any reason, the same baseline number should be used.

3.2.3.3 Screening Procedures

Once consent has been obtained and a baseline number has been assigned, the patient will undergo preliminary prestudy evaluations which will include the following procedures (also refer to the Screening Visit on the Study Flow Chart, Section 1.7):

- Complete documentation of medical history: This should include a description of all relevant underlying medical history and risk factors for *Candida* infection. Specific risks for *Candida* infection in this patient population are outlined in Appendix 6.2. All relevant underlying medical history and risk factors will be recorded on the appropriate eCRF. In addition, both the chronological and gestational age of the patient should be recorded on the appropriate eCRF.
- Chest X-ray: A chest X-ray does not need to be repeated if a prior chest X-ray was performed within 10 days prior to the initiation of study therapy. The results should be recorded on the appropriate eCRF.
- Complete evaluation of the diagnosis of invasive candidiasis: A detailed description of all symptoms and signs of the *Candida* infection at screening should be performed. These symptoms and signs of infection should be recorded on the appropriate eCRF. In addition, documentation of all tests confirming the diagnosis of invasive candidiasis (i.e., radiographs, histopathology, cultures, and any detailed descriptions of sterile invasive procedures) should also be collected. Importantly, as noted below, cultures and histopathology positive for *Candida* infection must have been obtained from sites of infection within 96 hours prior to study entry.
- Vital signs (including weight): Measurements of the patient's weight and vital signs (pulse, respiratory rate, blood pressure, and temperature) are required. The vital sign findings should be recorded on the appropriate eCRF.
- Physical examination: A physical examination, including a detailed description of the nature and extent of the invasive *Candida* infection, is required for study entry. Any abnormal findings should be recorded on the appropriate eCRF.
- Blood cultures: The blood cultures which confirm the evidence of invasive *Candida* infection during the screening phase must have been obtained within 96 hours prior to

study entry. These results should be recorded on the appropriate eCRF. Isolates from blood cultures obtained at the time of diagnosis and at study entry, if available, must be saved and sent to the fungal isolate central laboratory for identification and antifungal susceptibility testing.

Importantly, two sets of blood cultures must be obtained at screening in all patients. All blood culture results should be recorded on the appropriate eCRF. **NOTE:** Although 2 sets of blood cultures are collected from all patients, patients with candidemia must only have 1 positive *Candida* culture for study entry.

For those patients enrolled with candidemia, specific management of arterial and venous catheters is also indicated:

(a) Where feasible, all peripheral intravenous or arterial catheters in place at the time a positive blood culture for *Candida* is identified should be removed. If removal or replacement of a catheter is not feasible, the investigator should consult with the SPONSOR Clinical Monitor (or designee) as to whether the patient should be allowed to enroll in the study.

(b) Where feasible, all central venous catheters in place at the time a positive blood culture for *Candida* is identified should be removed. If removal or replacement of a central venous catheter is not feasible, the investigator should consult with the SPONSOR Clinical Monitor (or designee) as to whether the patient should be allowed to enroll in the study.

- Non-blood culture samples: For non-fungemic infections, cultures (or biopsies) from non-blood site(s) which confirm the presence of invasive *Candida* infection must be collected within 96 hours prior to study entry. All results should be recorded on the appropriate eCRF. The isolates from cultures obtained at the time of diagnosis and at study entry, if available, must be saved and sent to the fungal isolate central laboratory for identification and antifungal susceptibility testing.
- Other radiographic studies: Where appropriate, radiographic studies from the site(s) of *Candida* infection (i.e., echocardiogram, chest/abdominal ultrasound, CT, MRI) should also be obtained within 96 hours of study entry. All results should be recorded on the appropriate eCRF.

  In general, in patients with invasive *Candida* abscesses, consideration should be given to have the abscess drained and/or removed via percutaneous puncture or open surgery prior to study entry **OR** within the first 72 hours following study entry. Special considerations for other specific non-blood sites are included below:

  (a) *Candida* endocarditis: A transthoracic (or transesophageal) echocardiograph should be performed within 96 hours prior to study entry.

  (b) *Candida* meningoencephalitis: All patients should have a positive culture for *Candida* from a cerebrospinal fluid (CSF) sample collected via a lumbar/cisternal puncture within 96 hours prior to study entry. Additional CSF for glucose, protein, and cell count (i.e., RBC, WBC, cell differential) assessments should also

be collected at the time CSF culture was obtained (within 96 hours prior to study entry).

(c) *Candida* septic arthritis or osteomyelitis: Patients with bone infections should have a positive culture for *Candida* from either the intraarticular joint (i.e., synovial) fluid or from a bony tissue sample collected via a sterile procedure within 96 hours prior to study entry. In patients with septic arthritis or osteomyelitis abutting an intraarticular joint, synovial fluid for glucose, protein, cell count (i.e., RBC, WBC, cell differential), and cast/crystal assessment should also be collected at the time a joint fluid culture was obtained (within 96 hours prior to study entry). For patients with osteomyelitis, consideration should also be given to performing an appropriate radiograph (including X-ray, CT, or MRI) of the involved bone within the 96 hours prior to study entry.

- Blood for laboratory safety tests: Selected hematology and blood chemistry tests from blood will be performed at screening. The selected laboratory tests for safety evaluation are outlined in Appendix 6.1. The results, which will be tested locally, should be recorded on the appropriate eCRF.
- CSF for pharmacokinetic evaluation: If a patient undergoes any procedure in the prestudy (screening) period that involves collecting CSF, approximately 350 μL of CSF should be retained to serve as a baseline sample for measurement of caspofungin concentration. The CSF will be sent to a central laboratory for pharmacokinetic testing. The exact time of CSF sampling should be recorded on the appropriate eCRF.

3.2.3.4 Randomization and Stratification

After written consent has been obtained, all screening procedures have been completed, and all inclusion/exclusion criteria have been met, the patient will be assigned an allocation number. Once an allocation number is assigned, it cannot be re-assigned to another patient.

In an effort to strive for adequate representation of patients from different weight groups (reflective of patient gestational age) in both treatment arms, randomization will be stratified into 3 weight categories (based on weight at study entry): <1000 grams, 1000 to 1500 grams, and >1500 grams. Patients will be stratified into each of the weight categories in a manner consistent with the 2:1 randomization of caspofungin to amphotericin B deoxycholate.

A single patient/subject cannot be assigned more than 1 allocation number.

3.2.3.5 Treatment Evaluation/Follow-Up

3.2.3.5.1 Procedures Performed During the Treatment Phase

While on study therapy, the patient will undergo the following procedures (also refer to the Study Therapy Visit on the Study Flow Chart, Section 1.7):

- Assessment of symptoms and signs of the invasive *Candida* infection: An assessment of symptoms and signs of the *Candida* infection should be performed daily while on study therapy and on the last day of study therapy. These findings should be recorded on the source documents and the appropriate eCRF.
- Vital signs (including weight): Certain vital signs (pulse, respiratory rate, blood pressure, and temperature) should be performed at least once daily while on study therapy and on the last day of study therapy. It is preferred that the method for obtaining temperatures (e.g., oral or tympanic) is consistent throughout the course of study therapy. The most abnormal vital sign findings within the previous 24 hours should be recorded on the appropriate eCRF. Weight should also be collected at least once weekly while on study therapy as a standard procedure when evaluating vital signs and to ensure the appropriate dose of study therapy is being maintained. Weight should also be collected on the day of pharmacokinetic assessment (Day 4 or Day 7). The weekly weight result should also be recorded on the appropriate eCRF.
- Physical examination: A physical examination, including a detailed description of the nature and extent of the invasive *Candida* infection, should be performed on Day 4 and Day 7 of study therapy, twice weekly thereafter (while on study therapy), and on the last day of study therapy. Any abnormal findings should be recorded on the appropriate eCRF.
- Follow-up blood cultures: For patients with candidemia, follow-up blood cultures should be collected periodically while on study therapy until cultures are negative for *Candida* (on at least 2 separate occasions). All results should be recorded on the appropriate eCRF. The general IDSA guidelines for treatment management of candidemia are included in Appendix 6.3.
- Follow-up cultures from non-blood samples: Patients with non-blood sites of invasive candidiasis should have follow-up cultures collected from the non-blood site of *Candida* infection, as clinically indicated by the patient's signs and symptoms of infection and radiographic abnormalities. All results should be recorded on the appropriate eCRF. Specifically, patients with known meningoencephalitis should have follow-up CSF cultures performed on a periodic basis while on study therapy until negative follow-up CSF cultures are documented. The general IDSA guidelines for treatment management of non-fungemic sites of infection are included in Appendix 6.3.
- Follow-up radiographs: Follow-up radiographs should be performed from the site(s) of infection (e.g., echocardiogram, chest/abdominal ultrasound, CT, or MRI) as clinically indicated, based on the site of infection. If a radiographic study that helped confirm the diagnosis of invasive candidiasis is deemed necessary to assess the outcome the outcome of study therapy, the follow-up radiographic study must be obtained within 72 hours (3 days) prior to the completion of study therapy. All results should be recorded on the appropriate eCRF. The general IDSA guidelines for treatment management of the various sites of invasive *Candida* infection are included in Appendix 6.3.

- Study therapy administration: During the study therapy period, the study drug (either caspofungin or amphotericin B deoxycholate) will be prepared by the unblinded pharmacist as outlined in Section 2.4.2 (Treatment Plan). All study therapy (caspofungin or amphotericin B deoxycholate) will be administered intravenously as a single once-daily dose. Each infusion should be administered over approximately 2 hours. The IV line should be flushed thoroughly after each study therapy infusion. Infusion of study therapy may be given through either a pediatric syringe pump or ambulatory pump if this will help ensure that the patient receives the complete dose. As these 2 products differ in color, opaque masking of the infusion materials (e.g., infusion syringe and tubing) will be used to ensure adequate blinding of the treatment group. The unblinded pharmacist will be responsible to cover the infusion materials with opaque masking. Importantly, the unblinded pharmacist will not be involved in any of the postinfusion evaluations for the patient. All study personnel involved with the postinfusion evaluations of safety and efficacy outcomes, including the study coordinator(s), investigator, or subinvestigator(s), must have no access to the treatment group assignment or the preparation of the study infusion. Additional details on study therapy preparation are included in the Pharmacy Binder.

  Of note, total parenteral nutrition (TPN) can be administered to patients enrolled in this study. However, it is preferred that TPN is not infused through the same intravenous line as the study therapy. For those patients with catheters containing multiple lumens, study therapy should be administered via a separate lumen than the lumen used for TPN infusion. For patients with single lumen catheters as the only intravenous access site, TPN should be held during the 2-hour infusion of study therapy. In this case, the IV line should be flushed thoroughly prior to and following study therapy infusion.

- Blood for laboratory safety tests: Selected hematology and blood chemistry tests from blood will be performed on Day 4 (± 1 day) and Day 7 of study therapy, twice weekly thereafter (while on study therapy), and on the last day of study therapy. The selected laboratory tests for safety evaluation are outlined in Appendix 6.1. The results, which will be tested locally, should be recorded on the appropriate eCRF.

- Blood (plasma) for pharmacokinetic evaluation: Three blood samples (each 350 µL) should be collected from all patients. Each patient will be randomly assigned to one of 8 sampling schedules; all 3 samples are to be taken on the same study day. Half of the patients will have samples taken on Study Day 4 and the other half will have samples taken on Study Day 7. If it is not possible to take samples on the assigned Study Day, it is recommended that samples be taken on the following Study Day.

  Blood samples will be collected from all patients at the time of peak concentration (immediately after the end of study therapy infusion) and time of trough concentration (approximately 24 hours after the start of study therapy infusion but prior to the next day's dose). In addition, a sample will be collected at an intermediate time between peak and trough times as shown in Table 3-4, in Section 3.3.2. Plasma will be separated from blood and sent to a central laboratory for pharmacokinetic testing. The exact time and date of blood sampling should be recorded on the appropriate eCRF.

Weight should be measured within 12 hours prior to the infusion of study therapy on the assigned day of pharmacokinetic blood sampling, and the study therapy dose given on the pharmacokinetic sample day should be adjusted to reflect the most recently measured weight.

- CSF for pharmacokinetic evaluation: If a patient undergoes any procedure that involves collecting CSF while on study therapy, approximately 350 µL of CSF should be retained for pharmacokinetic assessments. The CSF will also be sent to a central laboratory for pharmacokinetic testing. The exact time and date of CSF sampling should be recorded on the appropriate eCRF.
- Monitoring for adverse experiences: Patient will be monitored daily for adverse experiences while on study therapy. Any findings consistent with an adverse experience should be recorded on the appropriate eCRF. Please refer to Section 3.4 (Safety Measurements) for further details.
- Efficacy evaluation: Resolution or progression of disease should be documented by assessment of symptoms and signs, follow-up culture results, and follow-up radiographic studies, as appropriate. An efficacy evaluation for fungal-free survival will be performed on the last day of study therapy. This evaluation will be recorded on the appropriate eCRF. Please refer to Section 3.3 (Efficacy Measurements) for further details.

3.2.3.5.2 Procedures Performed During the Posttherapy Follow-up Visits

At the 2- and 8-week posttherapy follow-up visits, the patient will undergo the following procedures (also refer to the Follow-up Assessment Visit on the Study Flow Chart, Section 1.7):

- Assessment of symptoms and signs for invasive *Candida* infection: Potential symptoms and signs of the patient's *Candida* infection will be assessed at the 2-week and 8-week posttherapy follow-up visits. Any findings should be recorded on the source documents and the appropriate eCRF.
- Vital signs: Assessments of specific vital signs (pulse, respiratory rate, blood pressure, and temperature) should be performed at the 2-week and 8-week posttherapy follow-up visits. These findings should be recorded on the appropriate eCRF.
- Physical examination: A physical examination, including a detailed description of the nature and extent of the *Candida* infection, should be performed at the 2-week and 8-week posttherapy follow-up visits. Any abnormal findings should be recorded on the appropriate eCRF.
- Follow-up blood or non-blood samples: Patients should have follow-up blood (or pertinent non-blood) cultures collected, as clinically indicated, by the patient's signs and symptoms of infection and radiographic abnormalities through the 8-week posttherapy follow-up visit. All results should be recorded on the appropriate eCRF.
- Follow-up radiographs: Follow-up radiographs should be performed from the site(s) of infection (e.g., echocardiogram, chest/abdominal ultrasound, CT, or MRI) as

clinically indicated based on the site of infection, through the 8-week posttherapy follow-up visit. All results should be recorded on the appropriate eCRF.

- Blood for laboratory safety tests: Selected hematology and blood chemistry tests from blood will be performed at the 2-week posttherapy follow-up visit. The selected laboratory tests for safety evaluation are outlined in Appendix 6.1. The results, which will be tested locally, should be recorded on the appropriate eCRF.
- Monitoring for adverse experiences: After the completion of study therapy, patient will be monitored for adverse experiences through the 2-week posttherapy follow-up visit. Any findings consistent with an adverse experience should be recorded on the appropriate eCRF. Please refer to Section 3.4 (Safety Measurements) for further details.
- Efficacy evaluation: Resolution or progression of disease should be documented by assessment of symptoms and signs, follow-up culture results, and follow-up radiographic studies, as appropriate. An efficacy evaluation for fungal-free survival will be performed at the 2-week posttherapy follow-up visit. An efficacy evaluation for the development of complicated candidiasis will be performed through the 8-week posttherapy follow-up visit. These evaluations will be recorded on the appropriate eCRFs. Please refer to Section 3.3 (Efficacy Measurements) for further details.

3.2.3.6 Blinding/Unblinding

This is a double-blind study in which the patients, the investigator (and site staff, with the exception of the unblinded pharmacists who will not be involved in patient assessment), and members of the SPONSOR staff (or designee) directly involved with the conduct of the study will remain blinded to the treatment administered to all patients.

In the event that an individual patient becomes unblinded to treatment group (either accidental unblinding or emergency unblinding for a serious adverse experience), the investigator must do the following:

- Immediately notify the SPONSOR Clinical Monitor or Clinical Scientist (CS), or respective designees;
- Promptly document the circumstances in the patient's chart;
- Document the unblinding on the Patient Unblinding Log located in the Administrative Binder.

Every effort should be made to contact the Clinical Monitor or CS (or their respective designees) prior to performing an emergency unblinding of any patient.

3.2.3.7 Discontinuation/Withdrawal from Study

Subjects/patients may withdraw at any time or be dropped from the study at the discretion of the investigator should any untoward effects occur. In addition, a subject/patient may be withdrawn by the investigator or the SPONSOR if he/she violates the study plan or for administrative and/or other safety reasons. The investigator or study coordinator must notify the SPONSOR immediately when a subject/patient has been discontinued/ withdrawn due to an adverse experience (telephone or FAX). When a subject/patient

discontinues/withdraws prior to study completion, all applicable activities scheduled for the final study visit should be performed at the time of discontinuation. Any adverse experiences which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 3.4 SAFETY MEASUREMENTS - DETAILS.

3.2.3.7.1 Discontinuation/Withdrawal Criteria

Discontinuation from study therapy should be done for the following reason(s):

- The patient's parent (or guardian) refuses further treatment or follow-up and withdraws consent.
- Continuation is not in the best interest of the patient, in the judgment of the investigator.
- Failure to demonstrate or sustain clinical improvement after a course of study therapy. In general, patients who do not have some clinical evidence of improvement by Day 7 of therapy should be discontinued.
- Significant progression of invasive candidiasis after at least 72 hours of study therapy.
- The need to increase the dose of the antifungal study therapy or to give another systemic antifungal drug in addition to the antifungal study therapy.
- Development of signs or symptoms of a rapidly progressive underlying disease that would preclude evaluation of therapy, or that would render continuation in the study inadvisable, in the judgment of the investigator.
- Development of concomitant fungal infection with an organism that is not susceptible to the antifungal study therapy.
- Instances in which pretherapy or follow-up microbiologic studies indicate that the etiologic pathogen(s) of the index infection is/are not susceptible to amphotericin B deoxycholate and/or caspofungin.
- Development of a serious adverse experience related to study therapy or the occurrence of an adverse clinical experience or clinically significant laboratory change or abnormality that, in the judgment of the investigator, warrants withdrawal of the patient from the antifungal study therapy.
- An elevated AST or ALT lab value that is greater than or equal to 3 X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2 X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2 X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing. **NOTE:** Patients will be discontinued from study therapy but followed for safety until the abnormal value(s) has/have normalized, stabilized, or returned to baseline.
- Development of nephrotoxicity, which in the opinion of the investigator, warrants discontinuation of study therapy.

- Requirement for treatment with an investigational drug.

If a patient discontinues from study therapy for any reason, evaluations (e.g., cultures, radiographic studies) should be performed as clinically indicated at that time. An efficacy assessment of response to study therapy should be documented at the time of study therapy discontinuation. Unless the patient is also withdrawing from the study, the patient should be followed for safety and for the efficacy endpoint through the end of the follow-up period.

Withdrawal from study should be considered for the following reason(s):

- The patient's parent (or guardian) refuses further treatment or follow-up and withdraws consent.

If a patient discontinues/withdraws from the study for any reason, an efficacy assessment of response to study should be documented at the time of study discontinuation/withdrawal.

3.3 EFFICACY/PHARMACOKINETIC MEASUREMENTS

3.3.1 Clinical and Laboratory Measurements for Efficacy

A detailed description and evaluation of the *Candida* infection will be performed at screening, daily while on study therapy, on the last day of study therapy, and at the 2-week and 8-week posttherapy follow-up visits. Resolution or progression of the *Candida* infection should be documented by assessment of signs and symptoms, radiographic studies (when clinically indicated), and follow-up blood cultures or, as appropriate, other follow-up cultures (including urine or CSF).

Based on all available data, an efficacy assessment will be made at the end of study therapy and at the 2-week posttherapy follow-up visit. The efficacy endpoint will be based on fungal-free survival (i.e., the proportion of patients who survived at the timepoint of interest and had documented microbiological eradication of *Candida* sp. from follow-up cultures collected after the initiation of study therapy). Microbiological eradication denotes negative follow-up cultures for *Candida* sp. from the site of infection at the time of evaluation. If a culture is not obtained on the day of assessment, then the last culture after study entry may be used to assist in the assessment of microbiological eradication. If the last culture is negative for *Candida* sp., then microbiologic eradication would be considered achieved. Although fungal-free survival will be assessed at 2 different time points (end of study therapy and the 2-week posttherapy follow-up visit), the primary efficacy time point will be at the 2-week posttherapy follow-up visit. **NOTE:** Fungal-free survival assumes no additional antifungal therapy is required for the treatment of the underlying *Candida* infection once study therapy has ended; however, once study therapy has ended, prophylaxis with an antifungal agent (e.g., fluconazole) may be administered, if this is deemed appropriate by the investigator.

[redacted]

[redacted]

The efficacy with caspofungin in neonates and infants enrolled in this study will be compared descriptively to the efficacy in caspofungin-treated patients enrolled with invasive candidiasis in the prior Phase II pediatric documented infection study (Protocol 043, children and adolescents [3 months to 17 years]) and prior Phase III adult studies (Protocols 014 and 801).

3.3.2 Measurements for Pharmacokinetics

Three blood samples (each 350 µL) should be collected from all patients. Each patient will be randomly assigned to one of 8 sampling schedules; all 3 samples are to be taken on the same study day. Half of the patients will have samples taken on Study Day 4 and the other half will have samples taken on Study Day 7. If it is not possible to take samples on the assigned Study Day, it is recommended that samples be taken on the following Study Day.

Blood samples will be collected from all patients at the time of peak concentration (immediately after the end of study therapy infusion) and time of trough concentration (approximately 24 hours after the start of study therapy infusion but prior to the next day's dose). In addition, a sample will be collected at an intermediate time between peak and trough times as shown in Table 3-4. Plasma will be separated from blood and sent to a central laboratory for pharmacokinetic testing. The exact time and date of blood sampling should be recorded on the appropriate eCRF.

Table 3-4
Pharmacokinetic Sample Schedule

Sample Schedule	Number of Patients	Study Days	Peak (Sample 1)	Interim (Sample 2)	Trough (Sample 3)
1	12	Day 4	Within 5 minutes after the end of the 1-hr infusion	Between 2 and 4 hr postdose	Within 15 minutes prior to Day 5 dose
2	11			Between 6 and 8 hr postdose	
3	11			Between 10 and 12 hr postdose	
4	11			Between 14 and 16 hr postdose	
5	12	Day 7	Within 5 minutes after the end of the 1-hr infusion	Between 2 and 4 hr postdose	Within 15 minutes prior to Day 8 dose
6	11			Between 6 and 8 hr postdose	
7	11			Between 10 and 12 hr postdose	
8	11			Between 14 and 16 hr postdose	
Volume of blood drawn for each PK sample:			350 µL	350 µL	350 µL

Weight should be measured within 12 hours prior to the infusion of study therapy on the assigned day of pharmacokinetic blood sampling, and the study therapy dose given on the pharmacokinetic sample day should be adjusted to reflect the most recently measured weight.

If a patient undergoes any procedure that involves collecting CSF while on study therapy, approximately 350 µL of CSF should be retained for pharmacokinetic assessments. If available, a baseline (or prestudy) CSF sample should also be retained.

Plasma will be separated from blood and sent to a central laboratory for pharmacokinetic testing. The CSF will also be sent to a central laboratory for pharmacokinetic testing. Procedures for collection, processing, storage, and shipment of pharmacokinetic samples from blood (plasma) and CSF are included in the Administrative Binder.

3.3.3 Microbiological Measurements

In addition to local microbiological testing, identification and susceptibility testing will be performed at a central laboratory contracted by Merck on the following isolates: (a) *Candida* isolates collected at study entry, (b) at any time subsequent fungal isolates are obtained, and (c) at any time that there is clinical or laboratory evidence of persistence or progression of the infectious process. The investigator should ensure that the *Candida* isolate(s) obtained from the invasive site of infection at these time points are saved and sent to the fungal isolate central laboratory.

Procedures for collection, processing, storage, and shipment of microbiological samples from blood (plasma) and other non-blood sites of *Candida* infection are included in the Administrative Binder.

3.3.4 Data Monitoring Committee

The Data Monitoring Committee (DMC) is a group with pertinent expertise that reviews on a regular basis accumulating safety data during the study to assess the effects of the study drug. With the exception of a non-voting SPONSOR (or designee) statistician, the members of the committee are independent of the SPONSOR and clinical investigators participating in the trial, and will not have any other involvement in the study, nor will they have any relation to the study participants. The statistician role may alternatively be filled by an individual external to the SPONSOR (or its designee).

To guarantee the unbiased performance of its task, the DMC will initially receive blinded study data from the designated statistician. If required to address a safety concern, unblinded safety data may be requested by and provided to the DMC.

Prior to scheduled meetings, the DMC will be provided with the following reports, which are cumulative and generated from a current data file:

- Patient enrollment status, including counts of patients enrolled by study site
- Blinded counts tables of all adverse events (AEs), drug-related AEs, serious AEs, drug-related serious AEs, and AEs leading to discontinuation
- Blinded counts tables of clinically significant laboratory AEs

The need for additional reports will be assessed once the DMC members have been appointed and the study is initiated. Unblinded data may be provided to the DMC by the SPONSOR (or its designee) upon request.

Based upon review of the accumulating safety data, the DMC will recommend if the study should continue, be modified, or terminated for safety reasons. The DMC may also recommend steps needed to ensure the safety of study participants and integrity of the trial or trial data. Guidelines for making such recommendations will be developed by the SPONSOR (or its designee) and DMC in advance of the evaluation of study data by the DMC. Following each meeting, the DMC Chairperson will be responsible for reporting post-meeting decisions and/or recommendations (e.g., discontinuation of study due to a major safety concern) to a steering committee comprised of Merck Senior Management members (Merck Senior Management Committee, or MSMC). It will be the responsibility of the MSMC to carefully consider and appropriately implement the recommendations of the DMC and to ensure the investigators and the respective Institutional Review Boards (IRBs)/Independent Ethical Committees (IECs) are properly notified. The MSMC will inform the protocol team of any modifications to the protocol. The investigator, study site staff, and blinded SPONSOR personnel will remain strictly blinded to specific patient treatment group assignments until the study has ended.

Further details regarding the DMC and its functions will be described in the DMC Charter.

3.4 SAFETY MEASUREMENTS

3.4.1 Clinical and Laboratory Measurements for Safety

All patients who receive one or more doses of study therapy will be evaluated for the presence of adverse experiences while on study therapy and through the 2-week posttherapy follow-up visit. To assist with these safety assessments, a physical examination will be performed at prestudy, twice weekly throughout the study therapy period (including Day 4 and Day 7), on the last day of study therapy, and at the 2- and 8-week posttherapy follow-up visits. In addition, selected laboratory safety tests will be performed at screening, on Day 4 (or Day 3 or Day 5) and Day 7 of study therapy, twice weekly thereafter while on study therapy, on the last day of study therapy, and at the 2-week posttherapy follow-up visit (see Appendix 6.1).

To address the secondary safety objective, the following safety endpoints will be evaluated: (1) the development of adverse experience(s) during the study therapy period or during the 2-week posttherapy follow-up period; (2) the development of drug-related adverse experience(s) during the study therapy period or during the 2-week posttherapy follow-up period; (3) the development of serious adverse experience(s) during study therapy period or during the 2-week posttherapy follow-up period; (4) the development of drug-related, serious adverse experience(s) during study therapy period or during the 2-week posttherapy follow-up period; (5) the development of adverse experiences that necessitate discontinuation of study therapy; and (6) the development of drug-related adverse experiences that necessitate discontinuation of study therapy.

3.4.2 Management of Adverse Events

Patients will be monitored for any evident adverse experiences at all study visits (through the 2-week posttherapy follow-up visit), and the information will be recorded on the appropriate eCRF. Decisions to temporarily withhold study therapy because of an adverse experience will be reviewed on a case-by-case basis by the investigator. Guidelines for managing certain adverse experiences are presented below. The investigator will use discretion in the application of these guidelines.

For those circumstances not described below that require a hold on administration of study therapy, it may be possible to reinitiate study therapy upon resolution of the laboratory abnormality or clinical adverse experience. Individual cases should be discussed with the investigator and SPONSOR Clinical Monitor (or designee).

Liver Enzyme Abnormalities

Safety assessments of injury or damage to the liver will be performed by monitoring of liver function tests during and at the end of study therapy. Laboratory tests should be repeated if AST or ALT increase to ≥2 times the baseline value. If on repeated measures, the laboratory test elevated at study entry continues to rise (and reaches 6 times the upper limit of normal), study therapy should be discontinued as described in Section 3.2.3.7.1. However, if the enzyme elevations are clearly due to another etiology, the case may be discussed with the SPONSOR Clinical Monitor (or designee) prior to discontinuing the patient from study therapy. If liver enzymes return to normal, rechallenge with the study therapy may be allowed. The decision will be made by the investigator in consultation with the SPONSOR Clinical Monitor (or designee).

Any elevated AST or ALT lab value that is greater than or equal to 3 X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2 X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2 X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing will be evaluated. The trial site guidance for assessment and follow up of these criteria can be found in the Administrative Binder.

Other Adverse Experiences

While receiving study therapy, patients who develop any adverse experience that is felt to possibly be related to the study drug, and for which interruption of therapy is clinically indicated, should have their study therapy stopped.

3.4.3 Recording Adverse Experiences

An adverse experience is defined as any unfavorable and unintended change in the structure, function, or chemistry of the body temporally associated with the use of the SPONSOR's product, whether or not considered related to the use of the product. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition which is temporally associated with the use of the SPONSOR's product, is also an adverse experience.

Changes resulting from normal growth and development which do not vary significantly in frequency or severity from expected levels are not to be considered adverse experiences. Examples of this may include, but are not limited to, teething, typical crying in infants and children, and onset of menses or menopause occurring at a physiologically appropriate time.

Adverse experiences may occur in the course of the use of a Merck product in clinical studies or within the follow-up period specified by the protocol, or prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse, and from withdrawal.

Adverse experiences may also occur in screened subjects/patients during any preallocation baseline period as a result of a protocol-specified intervention including washout or discontinuation of usual therapy, diet, placebo treatment, or a procedure.

Such events will be recorded at each examination on the Adverse Experience Case Report Forms/Worksheets.

3.4.4 Definition of an Overdose for This Protocol

Any overdose, whether or not associated with an adverse experience, must be reported within 24 hours to the SPONSOR (or its designee).

For this protocol, an overdose is defined as any daily dose that exceeds 2 times the prescribed dose in a 12-hour period.

3.4.4.1 Reporting of Overdose to SPONSOR

If an adverse experience(s) is associated with ("results from") the overdose of test drug or vaccine, the adverse experience(s) is reported as a serious adverse experience, even if no other criteria for serious are met.

If a dose of test drug or vaccine meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as a non-serious Event of Clinical Interest (ECI), using the terminology "accidental or intentional overdose without adverse effect."

All reports of overdose with and without an adverse experience must be reported within 24 hours to one of the individuals listed on the sponsor contact information page found in the Administrative Binder.

3.4.5 Immediate Reporting of Adverse Experiences to the SPONSOR

3.4.5.1 Serious Adverse Experiences

Any serious adverse experience, including death due to any cause, which occurs to any subject/patient entered into this study or within 14 days following cessation of treatment or within the established off therapy follow-up period for safety described in the protocol,

whether or not related to the investigational product, must be reported within 24 hours to one of the individual(s) listed on the contact information page.

Additionally, any serious adverse experience considered by an investigator who is a qualified physician to be possibly, probably, or definitely related to the investigational product that is brought to the attention of the investigator at any time outside of the time period specified in the previous paragraph also must be reported immediately to one of the individuals listed on the sponsor contact information page found in the administrative binder.

All subjects/patients with serious adverse experiences must be followed up for outcome.

3.4.5.2 Selected Nonserious Adverse Experiences

Events of clinical interest for this trial include:

An elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

***NOTE**: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The trial site guidance for assessment and follow up of these criteria can be found in the Administrative Binder.

3.4.6 Evaluating Adverse Experiences

Refer to Table 3-5 for instructions in evaluating adverse experiences.

Table 3-5

An investigator who is a qualified physician, will evaluate all adverse experiences as to:

Maximum Intensity	**Mild**	awareness of sign or symptom, but easily tolerated (for pediatric studies, awareness of symptom, but easily tolerated)
	Moderate	discomfort enough to cause interference with usual activity (for pediatric studies, definitely acting like something is wrong)
	Severe	incapacitating with inability to work or do usual activity (for pediatric studies, extremely distressed or unable to do usual activities)
Seriousness	A serious adverse experience is any adverse experience occurring at any dose that:	
	†**Results in death; or**	
	†**Is life threatening; or** places the subject/patient, in the view of the investigator, at immediate risk of death from the experience as it occurred [Note: This does not include an adverse experience that, had it occurred in a more severe form, might have caused death.]; or	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation). (Note: Hospitalization [including hospitalization for an elective procedure] for a preexisting condition which has not worsened does not constitute a serious adverse experience.); or	
	†**Is a congenital anomaly/birth defect** (in offspring of subject/patient taking the product regardless of time to diagnosis); or	
	Is a cancer; or	
	Is an overdose (Whether accidental or intentional.) Any overdose whether or not associated with an adverse experience must be reported within 24 hours.	
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse experience when, based upon appropriate medical judgment, the event may jeopardize the subject/patient and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	
Duration	Record the start and stop dates of the adverse experience. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse experience cause the test drug to be discontinued?	
Relationship to test drug	Did the test drug cause the adverse experience? The determination of the likelihood that the test drug caused the adverse experience will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet, that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse experience based upon the available information. **The following components are to be used to assess the relationship between the test drug and the AE;** the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the test drug caused the adverse experience (AE):	
	Exposure	Is there evidence that the subject/patient was actually exposed to the test drug such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
	Time Course	Did the AE follow in a reasonable temporal sequence from administration of the test drug? Is the time of onset of the AE compatible with a drug-induced effect?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors

Relationship to test drug (continued)	**The following components are to be used to assess the relationship between the test drug and the AE: (continued)**	
	Dechallenge	Was the dose of test drug discontinued or reduced? If yes, did the AE resolve or improve? If yes, this is a positive dechallenge. If no, this is a negative dechallenge. (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the test drug; or (3) the study is a single-dose drug study.)
	Rechallenge	Was the subject/patient reexposed to the test drug in this study? If yes, did the AE recur or worsen? If yes, this is a positive rechallenge. If no, this is a negative rechallenge. (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the study is a single-dose drug study.) NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY THE TEST DRUG, OR IF REEXPOSURE TO THE TEST DRUG POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE SUBJECT/PATIENT, THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE U.S. CLINICAL MONITOR AND THE INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE.
	Consistency with Study Drug Profile	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the test drug or drug class pharmacology or toxicology?
The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.		
Record one of the following:		**Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a drug relationship).**
Yes, there is a reasonable possibility of drug relationship.		There is evidence of exposure to the test drug. The temporal sequence of the AE onset relative to the administration of the test drug is reasonable. The AE is more likely explained by the test drug than by another cause. **Depending on data collection method employed, drug relationship may be further graded as follows:**
	Definitely related	There is evidence of exposure to the test drug. The temporal sequence of the AE onset relative to administration of the test drug is reasonable. The AE is more likely explained by the test drug than by another cause. Dechallenge is positive. Rechallenge (if feasible) is positive. The AE shows a pattern consistent with previous knowledge of the test drug or test drug class.
	Probably related	There is evidence of exposure to the test drug. The temporal sequence of the AE onset relative to administration of the test drug is reasonable. The AE is more likely explained by the test drug than by another cause. Dechallenge (if performed) is positive.
	Possibly related	There is evidence of exposure to the test drug. The temporal sequence of the AE onset relative to administration of the test drug is reasonable. The AE could have been due to another equally likely cause. Dechallenge (if performed) is positive.
No, there is not a reasonable possibility of drug relationship		Subject did not receive the test drug OR temporal sequence of the AE onset relative to administration of the test drug is not reasonable OR there is another obvious cause of the AE. (Also entered for a subject with overdose without an associated AE.) **Depending on data collection method employed, drug relationship may be further graded as follows:**
	Probably not related	There is evidence of exposure to the test drug. There is another more likely cause of the AE. Dechallenge (if performed) is negative or ambiguous. Rechallenge (if performed) is negative or ambiguous.
	Definitely not related	The subject/patient did not receive the test drug. OR Temporal sequence of the AE onset relative to administration of the test drug is not reasonable. OR There is another obvious cause of the AE.

3.4.7 SPONSOR Responsibility for Reporting Adverse Experiences

All adverse experiences will be reported to regulatory agencies, IRB/IECs, and investigators in accordance with all applicable global laws and regulations.

3.5 STATISTICAL ANALYSIS PLAN (SAP)

3.5.1 Responsibility for Analysis

This section details the statistical analysis strategy and procedures for this study. If, after the study has begun, but prior to any unblinding, changes are made to the primary objective, or the statistical methods related to this objective, then the protocol will be amended (consistent with ICH Guideline E-9). Changes to secondary or [redacted] and/or statistical analyses made after the protocol has been finalized, along with an explanation as to when and why they occurred, will be listed in the Clinical Study Report (CSR) for the study. [redacted]

3.5.2 Responsibility for Analyses/In-House Blinding

The statistical analysis of the data obtained from this study will be the responsibility of the Clinical Biostatistics department of the SPONSOR (or its designee).

Because this is a double-blind with in-house blind study, the investigator, study participant, and SPONSOR personnel (or their designees) will remain blinded to the IV antifungal study therapy regimen. In order to maintain this blind, preparation and administration of the IV study therapy must be performed by someone other than the person(s) who will evaluate the patient for efficacy response and presence of adverse experiences. As these 2 products differ in color, opaque masking will be used over the infusion materials (e.g., infusion syringe and tubing) to ensure adequate blinding of the treatment group.

Unblinding of the data will not take place until medical/scientific review has been performed, protocol violators have been identified, and the data have been declared final and complete.

3.5.3 Hypotheses/Estimation

Objectives and hypotheses of the study are stated in Section 2.1 (Objectives and Hypotheses).

3.5.4 Analysis Endpoints

Efficacy and safety endpoints that will be evaluated for between-treatment differences are listed below.

3.5.4.1 Efficacy/Pharmacokinetic Endpoints

3.5.4.1.1 Pharmacokinetic Endpoints

Pharmacokinetic (PK) profile (C_{max} [peak], $C_{24\ hr}$ [trough]) of the administered dose of caspofungin will be determined for neonates and infants less than three months of age on

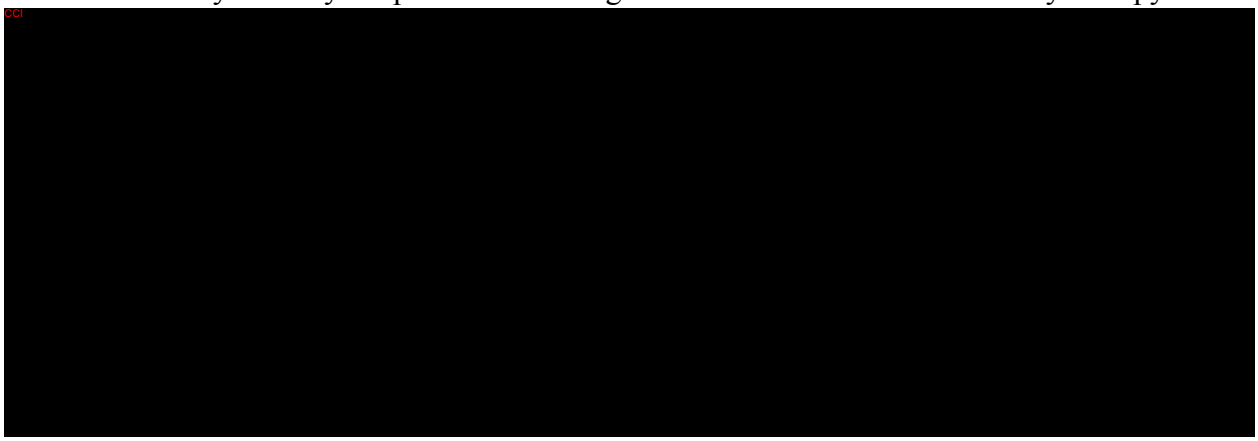
or around Days 4 and 7 of study therapy. Pharmacokinetic profiling will be the responsibility of the Drug Metabolism department of the SPONSOR (or its designee).

3.5.4.1.2 Efficacy Endpoints

An initial description of efficacy measurements is provided in Section 3.3.1.

The primary efficacy endpoint of interest will be fungal-free survival at two weeks posttherapy. Fungal-free survival is defined as those patients who survived at the time point of interest and had documented microbiological eradication of *Candida* sp. from follow-up cultures collected after the initiation of study therapy. Microbiological eradication denotes negative follow-up cultures for *Candida* sp. from the site of infection at the time of evaluation. If a culture is not obtained on the day of assessment, the last culture after study entry may be used to assist in the assessment of microbiological eradication. If the last culture is negative for *Candida* sp., then microbiological eradication would be considered achieved. Fungal-free survival also assumes no additional antifungal therapy is required for the treatment of the underlying *Candida* infection once study therapy has ended; however, once study therapy has ended, prophylaxis with an antifungal agent (e.g., fluconazole) may be administered, if this is deemed appropriate by the investigator.

The secondary efficacy endpoint will be fungal-free survival at the end of study therapy.



3.5.4.2 Safety Endpoints

There are no safety parameters that rise to the level of formal statistical testing for this study (i.e., no Tier 1 events).

To address the secondary safety objective, the following safety endpoints will be evaluated: (1) the development of adverse experience(s) during the study therapy period or during the 2-week posttherapy follow-up period; (2) the development of drug-related adverse experience(s) during the study therapy period or during the 2-week posttherapy follow-up period; (3) the development of serious adverse experience(s) during study therapy period or during the 2-week posttherapy follow-up period; (4) the development of drug-related, serious adverse experience(s) during study therapy period or during the 2-week posttherapy follow-up period; (5) the development of adverse experiences that

necessitate discontinuation of study therapy; and (6) the development of drug-related adverse experiences that necessitate discontinuation of study therapy.

3.5.5 Analysis Populations

3.5.5.1 Efficacy Analysis Populations

All efficacy evaluations will use the Full Analysis Set (FAS) patient population, which includes those patients who receive at least 1 full dose of study therapy and have a documented (culture-confirmed) diagnosis of invasive candidiasis. All patients, irrespective of body weight at study entry, will be grouped together for the primary evaluation. Subgroup evaluation based on the 3 body weight categories at study entry (<1000 grams, 1000-1500 grams, >1500 grams) will also be displayed.

A supportive analysis using the Per-Protocol population will be performed for the primary and secondary efficacy endpoints. The Per-Protocol population excludes patients due to important deviations from the protocol that may substantially affect the results of the primary and secondary efficacy endpoints. Inclusion within the per-protocol population mandates meeting all of the following:

- The patient must have a documented (culture-confirmed) diagnosis of invasive candidiasis.
- The patient must not receive >1 day of concomitant systemic antifungal therapy while on study therapy, if the total duration of study therapy is 3 weeks or less. For durations of study therapy exceeding 3 weeks, the patient must not receive concomitant systemic antifungal therapy while on study therapy, that amounts to more than 5% of the total duration of study therapy.
- The patient must have a 2-week posttherapy efficacy evaluation, including an appropriate microbiological assessment completed either at this visit or confirmed prior to that visit.
- The patient must receive at least 5 full days of study therapy.

The patient must not commit any protocol violations that interfere with the assessment of efficacy.

The final determination on protocol violations, and thereby the composition of the Per-Protocol population, will be made prior to the final unblinding of the database and will be documented in a separate memo. A patient who violates the protocol at randomization (e.g., certain inclusion or exclusion criteria, such as the use of prohibited prior treatment) will be excluded from the Per Protocol population. For patients who violate the protocol during the study (e.g., taking prohibited concomitant medication), data obtained subsequent to the violation will be excluded from analysis.

Patients who receive incorrect study medication for their entire treatment period will be counted in the treatment group for the treatment actually received. Otherwise, patients will be included in the treatment group to which they are randomized for the analysis of

efficacy data using both the FAS and Per-Protocol populations. In the event 3 or more patients receive the incorrect study medication for their entire treatment period, a sensitivity analysis will be performed with such patients included in the treatment group to which they were initially randomized for the analysis of efficacy data using both the FAS and Per-Protocol populations. Details on the approach to handling missing data are provided in Section 3.5.6 (Statistical Methods).

3.5.5.2 Safety Analysis Population

The All Patients as Treated (APaT) population will be used for the analysis of safety data in this study. The APaT population consists of all randomized patients who received at least one dose of study treatment. Patients will be included in the treatment group corresponding to the study treatment they actually received for the analysis of safety data using the APaT population. For most patients, this will be the treatment group to which they are randomized. Patients who take incorrect study treatment for the entire treatment period will be included in the treatment group corresponding to the study treatment actually received.

At least one laboratory or vital sign measurement obtained subsequent to at least one dose of study treatment is required for inclusion in the analysis of each specific parameter. To assess change from baseline, a baseline measurement is also required.

Details on the approach to handling missing data for safety analyses are provided in Section 3.5.6 (Statistical Methods).

3.5.6 Statistical Methods

Statistical testing and inference for safety analyses are described in 3.5.6.2. Efficacy results that will be considered to be statistically significant after consideration of the strategy for controlling the Type I error are described in Section 3.5.6.1 (Multiplicity). Nominal p-values may be (will be) computed for other efficacy analyses as a measure of strength of association between the endpoint and the treatment effect rather than formal tests of hypotheses. Unless otherwise stated, all statistical tests will be conducted at the α=0.05 (2-sided) level.

3.5.6.1 Statistical Methods for Efficacy Analyses

The primary efficacy analysis will compare the caspofungin treatment group to the amphotericin B deoxycholate treatment group with respect to the proportion of patients with fungal-free survival at the 2-week posttherapy period. The minimum criterion for success is that the lower bound of 95% CI for the difference between the 2 treatment groups (caspofungin minus amphotericin B deoxycholate) in the primary efficacy endpoint is >0.

CCI

[redacted]

[redacted]

The treatment comparisons for the primary and secondary efficacy analyses will be made using the difference in response rates between the 2 treatment groups and its 95% confidence interval. The confidence interval for the difference in response rates will be calculated using a methodology proposed by Miettinen and Nurminen [17].

Patients who have missing data for a given endpoint at the timepoint of interest will be counted as a failure for that endpoint at that timepoint.

[redacted]

Also, the caspofungin efficacy results from this study will be compared descriptively to the efficacy results for patients with invasive candidiasis in a prior Phase II pediatric documented infection study (Protocol 043, children and adolescents aged 3 months to 17 years) and prior Phase III adult studies (Protocols 014 and 801).

Table 3-6 summarizes the key efficacy analyses.

Table 3-6

Analysis Strategy for Key Efficacy Variables

Endpoint/Variable (Description, Time Point)	Primary vs. Supportive Approach[†]	Statistical Method	Analysis Population	Missing Data Approach
Primary				
Proportion of patients with fungal-free survival through the 2-week posttherapy period	P	Miettinen and Nurminen method	FAS	A patient with missing data will be considered a failure.
Proportion of patients with fungal-free survival through the 2-week posttherapy period	S	Miettinen and Nurminen method	PP	Observed data
Secondary				
Proportion of patients reporting fungal-free survival at the end of study therapy	P	Miettinen and Nurminen method	FAS	A patient with missing data will be considered a failure.
Proportion of patients reporting fungal-free survival at the end of study therapy	S	Miettinen and Nurminen method	PP	Observed data
[redacted]				

P=Primary approach; S=Secondary approach.

3.5.6.2 Statistical Methods for Safety Analyses

Safety and tolerability are assessed by clinical review of all safety parameters, including adverse experiences and laboratory values.

The analysis of safety results will follow a tiered approach (Table 3-7). The tiers differ with respect to the analyses that will be performed. Safety parameters or adverse experiences of special interest that are identified *a priori* constitute "Tier 1" safety endpoints that will be subject to inferential testing for statistical significance with p-values and 95% CI provided for between-group comparisons. Other safety parameters

will be considered Tier 2 or Tier 3. Tier 2 parameters will be assessed via point estimates with 95% CI provided for between-group comparisons; only point estimates by treatment group are provided for Tier 3 safety parameters.

Adverse experiences (specific terms as well as system organ class terms) that are not pre-specified as Tier-1 endpoints will be classified as belonging to "Tier 2" or "Tier 3", based on the number of events observed. Membership in Tier 2 requires that at least 4 patients in any treatment group exhibit the event; all other adverse experiences will belong to Tier 3.

The threshold of at least 4 events was chosen because the 95% confidence interval for the between-group difference in percent incidence will always include zero when treatment groups of equal size each have less than 4 events and thus would add little to the interpretation of potentially meaningful differences. Because many 95% confidence intervals may be provided without adjustment for multiplicity, the confidence intervals should be regarded as a helpful descriptive measure to be used in review, not a formal method for assessing the statistical significance of the between-group differences in adverse experiences and predefined limits of change.

Continuous measures such as changes from baseline in laboratory, vital signs, and ECG parameters that are not pre-specified as Tier-1 endpoints will be considered Tier 3 safety parameters. Summary statistics for baseline, on-treatment, and change from baseline values will be provided by treatment group in table format.

P-values (Tier 1 only) and 95% confidence intervals (Tier 1 and Tier 2) will be provided for between-treatment differences in the percentage of patients with events; these analyses will be performed using the Miettinen and Nurminen method (1985), an unconditional, asymptotic method. For this protocol, there are no Tier 1 events.

Table 3-7

Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoint[a]	p-Value	95% CI for Treatment Comparison	Descriptive Statistics
Tier 1	None	--	--	--
Tier 2	Any AE		X	X
	Any Serious AE		X	X
	Any Drug-Related AE		X	X
	Any Serious and Drug-Related AE		X	X
	Discontinuation due to AE		X	X
	Discontinuation due to a Drug-Related AE		X	X
	Specific AEs, SOCs, or PDLCs[b] (incidence ≥4 in one of the treatment groups)		X	X
Tier 3	Specific AEs, SOCs or PDLCs[b] (incidence <4 in all of the treatment groups)			X
	Change from Baseline Results (Labs, ECGs, Vital Signs)			X

[a] Adverse Experience references refer to both Clinical and Laboratory AEs.
[b] Includes only those endpoints not pre-specified as Tier 1 or not already pre-specified as Tier-2 endpoints.
Note: SOC=System Organ Class; PDLC=Pre-Defined Limit of Change; X = results will be provided.

3.5.6.3 Summaries of Baseline Characteristics and Demographics

The comparability of the treatment groups with respect to baseline characteristics will focus on clinical (rather than statistical) equivalence of the treatment groups. No statistical hypothesis tests will be performed on these characteristics. Mean, median, standard deviation, and range will be tabulated for characteristics which are continuous. Characteristics which are categorical, such as gender and race, will be summarized by count and percent.

3.5.7 Multiplicity

No multiplicity adjustments are planned for any of the evaluations in this study.

3.5.8 Sample Size and Power Calculations

3.5.8.1 Sample Size and Power for Efficacy

This study will randomize approximately 90 patients at a 2:1 ratio into either the caspofungin treatment group (N = 60) or the amphotericin B deoxycholate treatment group (N = 30) and has 80% power to demonstrate the superiority of caspofungin over amphotericin B deoxycholate at an overall two-sided, 5% alpha-level, if the underlying treatment difference in fungal-free survival at 2 weeks posttherapy is approximately 30 percentage points (or larger). Randomization of approximately 90 patients should

yield approximately 84 FAS evaluable patients, assuming an approximate 5% drop-out rate. The power and sample size are based on an underlying response rate of 50% for the amphotericin B deoxycholate treatment group, based on a review of the available data in the literature, including the recent comparative efficacy and safety study of caspofungin versus amphotericin B deoxycholate in which a favorable response was observed in 41.7% of amphotericin B deoxycholate-treated patients (see Table 3-1) [9]. On balance, the literature suggests most currently available antifungal agents are associated with successful outcomes in 40-80% of the patients [9, 24, 26, 30-36]; however, the efficacy with amphotericin B deoxycholate from the recent analysis was on the lower end (~40%) [9]. The caspofungin data from retrospective analyses and the recent comparative study demonstrated a relatively high success rate (80-100%) [9-13]. The minimum criterion for success is that the lower bound of 95% CI for the difference between the 2 treatment groups (caspofungin minus amphotericin B deoxycholate) in the primary efficacy endpoint is >0. Given the assumed response rate in the amphotericin B deoxycholate treatment group, this may occur when the observed difference between treatment groups is approximately 30 percentage points (or larger).

Assuming the same 2:1 randomization ratio and superiority hypothesis with 80% power, Table 3-8 displays sample size requirements for a few favorable response rate combinations, along with the difference and 95% CI for the difference.

Table 3-8

Superiority Sample Size Projections
Based on 80% Power and 2:1 (Caspofungin:Amphotericin B Deoxycholate) Allocation Ratio

Percent Favorable Caspofungin Response (A)	Percent Favorable Amphotericin B Deoxycholate Response (B)	Sample Size Projection Total (A:B)	Difference and 2-Sided 95% Confidence Interval for the Difference[a] (A – B)
70	40	93 (62:31)	30 (7.9, 48.1)
65	40	137 (92:45)	25 (7.5, 41.4)
60	40	218 (146:72)	20 (5.9, 33.2)
80	50	84 (56:28)	30 (9.3, 50.3)
75	50	127 (85:42)	25 (7.7, 42.2)
70	50	206 (137:69)	20 (5.3, 33.1)
90	60	66 (44:22)	30 (11.0, 53.6)
85	60	105 (70:35)	25 (8.3, 43.8)
80	60	177 (118:59)	20 (5.6, 33.9)

[a] Calculated using the Miettinen and Nurminen method.

3.5.8.2 Sample Size and Power for Safety

In a previous pediatric study (Protocol 043) in which 38 patients (aged 6 months to 17 years, mean 8 years) with invasive candidiasis were treated with caspofungin, the

proportion of patients with one or more drug-related adverse experiences was 23.7%. With this figure as a guide and the assumption that experience in neonates/infants is similar to that of the pediatric patients, a drug-related adverse experience rate of 23.7 ± 10.8% (95% CI calculated using the binomial distribution) is projected for 60 patients in the caspofungin treatment group.

While the above is the projected drug-related adverse experiences rate based on a previous study rate, it does not address possible study outcomes based on an observed number of adverse experiences within each treatment group. Given anticipated sample sizes of 60 patients on caspofungin and 30 patients on amphotericin B deoxycholate, Table 3-9 summarizes the difference (caspofungin – amphotericin B deoxycholate) and 95% CI for the difference for possible drug-related adverse experience outcome combinations.

Table 3-9

Difference (Caspofungin – Amphotericin B Deoxycholate) and 95% Confidence Interval for the Differences [a] for Possible Drug-Related Adverse Experience Outcome Combinations

Caspofungin Therapy (N = 60)	Amphotericin B Deoxycholate Therapy (N = 30)					
N Events (%)	**3 (10.0)**	**6 (20.0)**	**9 (30.0)**	**12 (40.0)**	**15 (50.0)**	**18 (60.0)**
3 (5.0)	-5.0 (-21.2, 5.9)	-15.0 (-32.9, -1.8)	-25.0 (-43.5, -9.7)	-35.0 (-53.4, -18.0)	-45.0 (-62.6, -26.8)	-55.0 (-71.2, -36.1)
6 (10.0)	0.0 (-16.7, 12.4)	-10.0 (-28.4, 4.6)	-20.0 (-39.1, -3.5)	-30.0 (-49.0, -11.9)	-40.0 (-58.2, -20.8)	-50.0 (-67.0, -30.2)
9 (15.0)	5.0 (-12.1, 18.4)	-5.0 (-23.9, 10.5)	-15.0 (-34.6, 2.4)	-25.0 (-44.5, -6.2)	-35.0 (-53.8, -15.1)	-45.0 (-62.6, -24.5)
12 (20.0)	10.0 (-7.6, 24.1)	0.0 (-19.4, 16.2)	-10.0 (-30.1, 8.0)	-20.0 (-40.0, -0.6)	-30.0 (-49.4, -9.6)	-40.0 (-58.2, -19.0)
15 (25.0)	15.0 (-3.0, 29.6)	5.0 (-14.8, 21.7)	-5.0 (-25.5, 13.4)	-15.0 (-35.5, 4.8)	-25.0 (-44.9, -4.2)	-35.0 (-53.7, -13.7)
18 (30.0)	20.0 (1.7, 34.9)	10.0 (-10.2, 27.0)	0.0 (-20.9, 18.7)	-10.0 (-30.8, 10.1)	-20.0 (-40.3, 1.1)	-30.0 (-49.2, -8.4)
21 (35.0)	25.0 (6.4, 40.0)	15.0 (-5.5, 32.1)	5.0 (-16.2, 23.9)	-5.0 (-26.2, 15.3)	-15.0 (-35.6, 6.3)	-25 (-44.6, -3.2)

[a] Calculated using the Miettinen and Nurminen method.

3.5.8.3 Subgroup Analysis

No formal subgroup evaluations will be performed and 95% CIs will not be displayed. Only counts and percents will be displayed. For the main efficacy endpoint, the results will be displayed by gender and race. Subgroup evaluation by weight stratification categories (<1000g, 1000-1500g, >1500g) and use of prestudy systemic (oral or IV) antifungal prophylaxis, will also be displayed. Other subgroup evaluations, based on site of *Candida* infection, underlying demographics, or region, may also be performed.

3.5.9 Interim Analyses

While no formal interim analysis is planned for this study, an external DMC will periodically evaluate the blinded safety data (see Section 3.3.4).

3.5.10 Compliance (Medication Adherence)

Study medication will be administered in a supervised clinical setting and missed or incorrect dosing will be uncommon. Patients who miss a dose or receive an incorrect dose will be described in the CSR as to why the dose was missed or incorrect.

3.5.11 Extent of Exposure

The extent of exposure (dose and duration) to caspofungin will be summarized by the number of patients exposed to caspofungin for defined periods of time. Dose is defined as the daily dose, expressed as mg/kg. The main table will display the number of days on caspofungin irrespective of dose. There will also be a dose by duration table displaying the actual mgs/day of caspofungin received by the patients.

3.6 LABELING, PACKAGING, STORAGE, DISPENSING, AND RETURN OF CLINICAL SUPPLIES

3.6.1 Product Descriptions

Investigational materials will be provided by the SPONSOR as summarized in Table 3-10.

Table 3-10

Product Descriptions

Product Name & Potency	Dosage Form
Caspofungin acetate 50 mg/vial (CANCIDAS™, MK-0991)	Intravenous
Amphotericin B deoxycholate 50 mg/vial	Intravenous

3.6.2 Primary Packaging

Supplies will be affixed with a clinical label in accordance with regulatory requirements. The clinical supplies will be open-labeled and each vial will contain a component

identification (CID) number for management of the supplies through an Interactive Voice Response System (IVRS) (see Section 3.6.6).

Patients will receive the IV study therapy following preparation by an unblinded pharmacist, for a minimum of 14 days and maximum of 90 days. A patient's parent (or guardian) will remain blinded to the IV study therapy that the patient receives. Importantly, the unblinded pharmacist will be uninvolved in any of the postinfusion evaluations for the patient. All study personnel involved with the postinfusion evaluations of safety and efficacy outcomes, including the study coordinator(s), investigator, or subinvestigator(s), must have no access to the treatment group assignment or the preparation of the study infusion.

3.6.3 Clinical Supplies Disclosure

The IVRS should be used in order to unblind subjects/patients and to unmask drug identity. The SPONSOR (or its designee) will not provide disclosure envelope with the clinical supplies. Drug identification information is to be unmasked ONLY if necessary for the welfare of the subject/patient. Every effort should be made not to unblind the subject/patient unless necessary. Prior to unblinding, the investigator will attempt to contact the SPONSOR's Clinical Research Associate (CRA) or designee. Any unblinding that occurs at the site must be documented.

3.6.4 Storage and Handling Requirements

The storage conditions will be indicated on the label.

Vials of study drug (caspofungin and amphotericin B deoxycholate) will be shipped to the sites to be stored at 2°C to 8°C (35.6°F to 46.4°F). Upon receipt at the investigational site, the vials should be removed from the outer secondary shipping box and placed immediately into the refrigerator. The temperature monitoring device must be deactivated upon receipt of the shipment. Directions for inactivation are specified in the *Instructions to Site*, which are enclosed with each shipment. The temperature monitoring device will indicate whether the shipment has remained within the specified temperatures. Return the temperature monitoring device according to instructions accompanying the shipment. **Notify the SPONSOR CRA (or designee) immediately if the temperature monitoring device is in alarm. Store and hold product until instructed otherwise.**

The clinical supplies storage area at the site must be monitored by the site staff for temperature consistency with the acceptable storage temperature range specified in this protocol or in the product label attached to the protocol. Documentation of temperature monitoring should be maintained. Supplies should be stored in the original nested box with the lid closed to minimize exposure to light. **If the refrigerator in which the study supplies are stored deviates from the 2°C to 8°C (35.6°F to 46.4°F) range, study supplies should be suspended and the SPONSOR's CRA (or designee) be contacted immediately. The study supplies must NOT be frozen.**

It is strongly recommended that a non-frost free laboratory grade refrigerator is used to store the study drug supplies. This type of refrigerator is less likely to have wide

temperature fluctuations, so it will be more likely to stay within the 2°C to 8°C (35.6°F to 46.4°F) temperature range. A daily refrigerator temperature log must be maintained at the site. The refrigerator must be equipped with an appropriately calibrated min/max thermometer and/or circular chart temperature recorder. The temperature log will be reviewed by the SPONSOR (or designee) throughout the study. An appropriate back-up system (i.e. alarm, generator) and study site personnel telephone numbers should be in place in the event of a refrigerator failure.

3.6.5 Standard Policies / Return of Clinical Supplies

As the clinical supplies (vials) will be provided as unblinded supplies, investigational clinical supplies must be received by a designated person (e.g., unblinded pharmacist) at the study site, handled and stored safely and properly, and kept in a secured location. Clinical supplies are to be dispensed only in accordance with the protocol. The unblinded pharmacist is responsible for keeping accurate records of the clinical supplies received from the SPONSOR (or its designee), the amount dispensed to and returned by the subjects/patients, and the amount remaining at the conclusion of the study. The SPONSOR's CRA (or designee) should be contacted with any questions concerning investigational products where special or protective handling is indicated. At the end of the study, all clinical supplies including partial and empty containers must be returned as indicated on the Contact Information page(s).

U.S. sites should follow instructions for the Clinical Supplies Return Form and contact your SPONSOR representative (or designee) for review of shipment and form before shipping.

For sites outside of the United States, the local country SPONSOR personnel (or its designees) will provide appropriate documentation that needs to be completed for drug accountability.

3.6.6 Distributing to Sites and Dispensing to Subjects/Patients

Designated study personnel (e.g., unblinded pharmacist) will have access to IVRS to allocate patients, to assign drug to subjects/patients, and to manage the distribution of clinical supplies. Each person accessing the IVRS system must be assigned an individual unique PIN. They must use only their assigned PIN to access the system and they must not share their assigned PIN with anyone.

3.7 DATA MANAGEMENT

The investigator or qualified designee is responsible for recording and verifying the accuracy of subject data. By signing this protocol, the investigator acknowledges that his/her electronic signature is the legally binding equivalent of a written signature. By entering his/her electronic signature, the investigator confirms that all recorded data have been verified as accurate.

Information regarding Data Management procedures for this protocol will be provided by the SPONSOR.

3.8 BIOLOGICAL SPECIMENS

Information regarding biological specimens for this protocol will be provided by the SPONSOR (or its designee).

4. ADMINISTRATIVE AND REGULATORY DETAILS

4.1 CONFIDENTIALITY

4.1.1 Confidentiality of Data

For Studies Conducted Under the U.S. IND

Particular attention is drawn to the regulations promulgated by the Food and Drug Administration under the Freedom of Information Act providing, in part, that information furnished to clinical investigators and Institutional Review Boards will be kept confidential by the Food and Drug Administration only if maintained in confidence by the clinical investigator and Institutional Review Board.

For All Studies

By signing this protocol, the investigator affirms to the SPONSOR that information furnished to the investigator by the SPONSOR will be maintained in confidence and such information will be divulged to the Institutional Review Board, Ethics Review Committee, or similar or expert committee; affiliated institution; and employees only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. Data generated by this study will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol.

4.1.2 Confidentiality of Subject/Patient Records

For All Studies

By signing this protocol, the investigator agrees that the SPONSOR (or SPONSOR representative), Institutional Review Board/Independent Ethics Committee (IRB/IEC), or Regulatory Agency representatives may consult and/or copy study documents in order to verify worksheet/case report form data. By signing the consent form, the subject/patient agrees to this process. If study documents will be photocopied during the process of verifying worksheet/case report form information, the subject/patient will be identified by unique code only; full names/initials will be masked prior to transmission to the SPONSOR.

For Studies Conducted Under the U.S. IND

By signing this protocol, the investigator agrees to treat all patient data used and disclosed in connection with this study in accordance with all applicable privacy laws, rules and regulations, including all applicable provisions of the Health Insurance Portability and Accountability Act and its implementing regulations, as amended from time to time ("HIPAA").

4.1.3 Confidentiality of Investigator Information

For All Studies

By signing this protocol, the investigator recognizes that certain personal identifying information with respect to the investigator, and all subinvestigators and study site

personnel, may be used and disclosed for study management purposes, as part of a regulatory submissions, and as required by law. This information may include:

- name, address, telephone number, and email address;
- hospital or clinic address and telephone number;
- curriculum vitae or other summary of qualifications and credentials; and
- other professional documentation.

Consistent with the purposes described above, this information may be transmitted to the SPONSOR, and subsidiaries, affiliates and agents of the SPONSOR, in your country and other countries, including countries that do not have laws protecting such information. Additionally, the investigator's name and business contact information may be included when reporting certain serious adverse events to regulatory agencies or to other investigators. By signing this protocol, the investigator expressly consents to these uses and disclosures.

For Multicenter Studies
In order to facilitate contact between investigators, the SPONSOR may share an investigator's name and contact information with other participating investigators upon request.

4.2 COMPLIANCE WITH LAW, AUDIT, AND DEBARMENT

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of Good Clinical Practice; and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical study.

The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored by Merck, is attached.

The investigator also agrees to allow monitoring, audits, Institutional Review Board/ Independent Ethics Committee review, and regulatory agency inspection of trial-related documents and procedures and provide for direct access to all study-related source data and documents.

The investigator agrees not to seek reimbursement from subjects/patients, their insurance providers, or from government programs for procedures included as part of the study reimbursed to the investigator by the SPONSOR.

The Investigator shall prepare and maintain complete and accurate study documentation in compliance with Good Clinical Practice standards and applicable federal, state, and local laws, rules and regulations; and, for each subject/patient participating in the study, provide all data, and upon completion or termination of the clinical study submit any

other reports to the SPONSOR as required by this protocol or as otherwise required pursuant to any agreement with the SPONSOR.

Study documentation will be promptly and fully disclosed to the SPONSOR by the investigator upon request and also shall be made available at the investigator's site upon request for inspection, copying, review, and audit at reasonable times by representatives of the SPONSOR or any regulatory agencies. The investigator agrees to promptly take any reasonable steps that are requested by the SPONSOR as a result of an audit to cure deficiencies in the study documentation and worksheets/case report forms.

International Conference of Harmonization Good Clinical Practice guidelines (Section 4.3.3) recommend that the investigator inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.

According to European legislation, a SPONSOR must designate a principal or coordinating investigator (CI) to review the report (summarizing the study results) and confirm that to the best of his/her knowledge the report accurately describes conduct and results of the study. The SPONSOR may consider one or more factors in the selection of the individual to serve as the CI (e.g., thorough understanding of clinical trial methods, appropriate enrollment of subject/patient cohort, timely achievement of study milestones, availability of the CI during the anticipated review process).

The investigator will promptly inform the SPONSOR of any regulatory agency inspection conducted for this study.

Persons debarred from conducting or working on clinical studies by any court or regulatory agency will not be allowed to conduct or work on this SPONSOR's studies. The investigator will immediately disclose in writing to the SPONSOR if any person who is involved in conducting the study is debarred, or if any proceeding for debarment is pending or, to the best of the investigator's knowledge, threatened.

In the event the SPONSOR prematurely terminates a particular trial site, the SPONSOR will promptly notify that site's IRB/IEC.

4.3 COMPLIANCE WITH FINANCIAL DISCLOSURE REQUIREMENTS

By signing this protocol, the investigator agrees to provide to the SPONSOR accurate financial information to allow the SPONSOR to submit complete and accurate certification and disclosure statements as required by U.S. Food and Drug Administration regulations (21 CFR Part 54). The investigator further agrees to provide this information on a Financial Disclosure/Certification Form that is provided by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. This requirement also extends to subinvestigators. The investigator also consents to the transmission of this information to Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

4.4 QUALITY CONTROL AND QUALITY ASSURANCE

By signing this protocol, the SPONSOR agrees to be responsible for implementing and maintaining quality control and quality assurance systems with written SOPs to ensure that trials are conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of Good Clinical Practice, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical study.

4.5 COMPLIANCE WITH INFORMATION PROGRAM ON CLINICAL TRIALS FOR SERIOUS OR LIFE THREATENING CONDITIONS

Under the terms of The Food and Drug Administration Modernization Act (FDAMA), the SPONSOR of the study is solely responsible for determining whether the study is subject to the requirements for submission to the Clinical Trials Data Bank, http://clinicaltrials.gov/. Merck, as SPONSOR of this study, will review this protocol and submit the information necessary to fulfill this requirement. Merck entries are not limited to FDAMA mandated trials. Merck's voluntary listings, beyond those mandated by FDAMA, will be in the same format as for treatments for serious or life-threatening illnesses. Information posted will allow patients to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate study locations and site contact information.

By signing this protocol, the investigator acknowledges that the statutory obligation under FDAMA is that of the SPONSOR and agrees not to submit any information about this study to the Clinical Trials Data Bank.

4.6 PUBLICATIONS

This study is intended for publication, even if terminated prematurely. Publication may include any or all of the following: posting of a synopsis online, abstract and/or presentation at a scientific conference, or publication of a full manuscript. The SPONSOR will work with the authors to submit a manuscript describing study results within 12 months after the last data become available, which may take up to several months after the last patient visit in some cases such as vaccine trials. However, manuscript submission timelines may be extended on OTC studies. For studies intended for pediatric-related regulatory filings, the investigator agrees to delay publication of the study results until the SPONSOR notifies the investigator that all relevant regulatory requirements on the study drug have been fulfilled with regard to pediatric-related regulatory filings. Merck will post a synopsis of study results for approved products on www.clinicalstudyresults.org and www.clinicaltrials.gov by 12 months after the last patient's last visit or within 7 days of product approval in any major markets (United States, Europe or Japan), whichever is later. These timelines may be extended for products that are not yet marketed, if additional time is needed for analysis, to protect intellectual property, or to comply with confidentiality agreements with other parties. Authors of the primary results manuscript will be provided the complete results from the Clinical Study Report, subject to the confidentiality agreement.

For multicenter studies, subsequent to the multicenter publication (or after public disclosure of the results online at www.clinicalstudyresults.org if a multicenter manuscript is not planned), an investigator and his/her colleagues may publish their data independently. In most cases, publication of individual site data does not add value to complete multicenter results, due to statistical concerns. In rare cases, publication of single site data prior to the main paper may be of value. Limitations of single site observations in a multicenter trial should always be described in such a manuscript.

Authorship credit should be based on 1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; and 3) final approval of the version to be published. Authors should meet conditions 1, 2, and 3. Significant contributions to study execution may also be taken into account to determine authorship, provided that contributions have also been made to all three of the preceding authorship criteria. Although publication planning may begin before conducting the study, final decisions on authorship and the order of authors' names will be made based on participation and actual contributions to the study and writing, as discussed above. The first author is responsible to defend the integrity of the data, method(s) of data analysis, and the scientific content of the manuscript.

The SPONSOR must have the opportunity to review all proposed abstracts, manuscripts, or presentations regarding this study 60 days prior to submission for publication/presentation. Any information identified by the SPONSOR as confidential must be deleted prior to submission. SPONSOR review can be expedited to meet publication timelines.

5. LIST OF REFERENCES

1. CANCIDAS™ (Caspofungin Acetate), European Summary of Product Characteristics, 2009.

2. CANCIDAS™ (Caspofungin Acetate), United States Product Circular, 2010.

3. Zaoutis TE, Heydon K, Localio R, Walsh TJ, Feudtner C. Outcomes attributable to neonatal candidiasis. *Clin Infect Dis*. 2007; 44:1187-93.

4. Benjamin DK, Stoll BJ, Gantz MG, Walsh MC, Sánchez PJ, Das A, et al. Neonatal candidiasis: epidemiology, risk factors, and clinical judgment. *Pediatrics.* 2010; 126(4):e865-73.

5. Wisplinghoff H, Seifert H, Tallent SM, Bischoff T, Wenzel RP, Edmond MB. Nosocomial bloodstream infections in pediatric patients in United States hospitals: epidemiology, clinical features and susceptibilities. *Pediatr Infect Dis J.* 2003; 22(8):686-91.

6. Benjamin DK, Jr., Stoll BJ, Fanaroff AA, McDonald SA, Oh W, Higgins RD, et al. Neonatal candidiasis among extremely low birth weight infants: Risk factors, mortality rates, and neurodevelopmental outcomes at 18 to 22 months. *Pediatrics.* 2006; 117(1):84-92.

7. Fridkin SK, Kaufman D, Edwards JR, Shetty S, Horan T, the National Nosocomial Infections Surveillance System Hospitals. Changing incidence of *Candida* bloodstream infections among NICU patients in the United States: 1995-2004. *Pediatrics.* 2006; 117(5):1680-7.

8. Saez-Llorens X, Macias M, Maiya P, et al. Pharmacokinetics and safety of caspofungin in neonates and infants less than 3 months of age. *Antimicrobial Agents and Chemotherapy,* 2009; 53:869-75.

9. Wahab Mohamed WA, Ismail M. A randomized, double-blind, prospective study of caspofungin vs. amphotericin B for the treatment of invasive Candidiasis in newborn infants. *J Trop Pediatr*. 2011; 10.1093/tropej/fmr025:[published online 25-Feb-2011]

10. Mondello I, Rossi A, Serrao G, Foti F, Timpani G, Manzoni P, et al. Preterm neonates in NICU treated with caspofungin: our experience [Abstract]. *Early Hum Dev*. 2009;85:S98.

11. Natarajan G, Lulic-Botica, M, Rongkavilit C, Pappas A, Bedard M. Experience with caspofungin in the treatment of persistent fungemia in neonates. *Journal of Perinatology*, 2005; 25:770-777.

12. Odio CM, Araya R, Pinto LE, et al. Caspofungin therapy of neonates with invasive candidiasis. *Pediatric. Infectious Diseases Journal*, 2004; 23:1093-7.

13. Odio CM, Castro CE, Vasques S, Lazo J, Herrera ML. Caspofungin Therapy for neonates with invasive candidiasis cared for at intensive care units. Presented at the 47h Annual ICAAC Meeting, Chicago, Illinois USA, September 2007.

14. Steinbach W, Walsh TJ. Mycoses in pediatric patients. *Infectious Disease Clinics of North America.* 2006; 20:663-78.

15. Zaoutis TE, Argon J, Chu J, et al. The epidemiology and attributable outcomes of candidemia in adults and children hospitalized in the United States: A propensity analysis. *Clinical Infectious Diseases*. 2005; 41:1232-9.

16. Makhoul IR, Kassis I, Smolkin T, et al. Review of 49 neonates with acquired fungal sepsis: further characterization. *Pediatrics*. 2001; 107:61-6.

17. Miettinen O, Nurminen M. Comparative analysis of two rates. *Stat Med*. 1985; 4:213-26.

18. Dotis J, Roilides E. Candidemia in the pediatric intensive care unit: what's different from candidemia in adults? *Curr Fungal Infect Rep*. 2011; 5:49-55.

19. Zaoutis T. Candidemia in children. *Curr Med Res Opin*. 2010; 26(7):1761-8.

20. Pfaller MA, Castanheira M, Messer SA, Moet GJ, Jones FN. Variation in *Candida* spp. distribution and antifungal resistance rates among bloodstream infection isolates by patient age: report from SENTRY Antimicrobial Surveillance Program (2008-2009). *Diagn Microbiol Infect Dis*. 2010; 68(3):278-83.

21. Zaoutis TE, Foraker E, McGowan KL, Mortensen J, Campos J, Walsh TJ, et al. Antifungal susceptibility of *Candida* spp. isolated from pediatric patients: a survey of 4 children's hospitals. *Diagn Microbiol Infect Dis*. 2005; 52:295-8.

22. Blyth CC, Chen SCA, Slavin MA, Serena C, Nguyen Q, Marriott D, et al. Not just little adults: candidemia epidemiology, molecular characterization, and antifungal susceptibility in neonatal and pediatric patients. *Pediatrics*. 2009; 123(5):1360-8.

23. Zaoutis T, Jafri H ,Huang LM, Locatelli F, Barzilai A, Ebell W, Steinbach W, Bradley J, Lieberman J,Hsiao CC, Seibel N, Laws HJ, Gamba M, Petrecz M, Taylor A, Strohmaier K, Chow J, Kartsonis N, Ngai A, A prospective, multicenter study of caspofungin for the treatment of documented *Candida* or *Aspergillus* infections in pediatric patients. *Pediatrics* 2009;123:877-884.

24. Driessen M, Ellis JB, Cooper PA, et al. Fluconazole versus amphotericin B for the treatment of neonatal fungal septicemia: a prospective, randomized trial. *Pediatr Infect Dis J*. 1996; 15:1107-12.

25. Zaoutis T, Benjamin D, Steinbach W. Antifungal treatment in pediatric patients. *Drug Resistance Updates.* 2005;8:235-245.

26. Linder N, Klinger G, Shalit I, et al. Treatment of candidemia in premature infants: comparison of 3 amphotericin B preparations. *J Antimicrob Chemother.* 2003; 4:663-7.

27. Tiffany K, Smith P, Benjamin D. Neonatal candidiasis: prophylaxis and treatment. *Expert Opin Pharmacother*. 2005; 6(10):1647-55.

28. Flattery A, Hickey E, Gill C, et al. Efficacy of caspofungin in a juvenile mouse model of central nervous system candidiasis. Poster M-1836. Presented in poster format at the 47h Annual ICAAC Meeting, Chicago, Illinois USA, September 2007.

29. Pappas PG, Kauffman CA, Andes D, Benjamin DK, Jr., Calandra TF, Edwards JE, Jr., et al. Clinical practice guidelines for the management of candidiasis: 2009 update by the Infectious Diseases Society of America. *Clin Infect Dis.* 2009;48:503-35.

30. Scarcella A, Pasquariello MB, Giugliano B, et al. Liposomal amphotericin B treatment for neonatal fungal infections. *Pediatr Infect Dis J*. 1998; 17:146-8.

31. Lopez Sastre JB, Coto Cotallo GD, Fernandez Colomer B. Neonatal invasive candidiasis: a prospective multicenter study of 118 cases. *Am J Perinatology* 2003; 20:153-63.

32. Adler-Shohet F, Waskin H, Lieberman JM. Amphotericin B lipid complex for neonatal invasive candidiasis. *Arch Dis Child Fetal Neonat.* 2001; 84:F131-3.

33. Juster-Reicher A, Flidel-Rimon O, Amitay M, et al. High-dose liposomal amphotericin B in the therapy of systemic candidiasis in neonates. *Eur J Clin Microbiol.* 2003; 22:603-7.

34. Huttova M, Hartmanova I, Kralinsky K, et al. *Candida* fungemia in neonates treated with fluconazole: report of 40 cases, including 8 with meningitis. *Pediatr Infect Dis J*. 1998; 17:1012-15.

35. Wainer S, Cooper PA, Gouws H, et al. Prospective study of fluconazole therapy in systemic neonatal fungal infection. *Pediatr Infect Dis J*. 1997; 167:763-7.

36. Smith PB, Steinbach WJ, Benjamin DK. Invasive *Candida* infections in the neonate. *Drug Res Updates*. 2005; 8:147-62.

6. APPENDICES

6.1 LABORATORY SAFETY STUDIES

Tests to be done at screening (baseline prestudy), on Day 4 (+/- 1 day) and Day 7 of study therapy, twice weekly thereafter on study therapy, on the last day of study therapy, and at the 2 weeks following the completion of study therapy.

Hematology Laboratory Test

White blood cell count (Total WBC)
White blood cell differential
Blood platelet count
Whole blood hematocrit
Blood hemoglobin test

Blood Chemistry Test

Serum alanine aminotransferase test
Serum aspartate aminotransferase test
Serum blood urea nitrogen test (or serum blood urea test)
Serum creatinine test
Serum potassium test
Direct serum bilirubin test
Total serum bilirubin test

6.2 RISK FACTORS OF INVASIVE CANDIDIASIS IN NEONATES AND INFANTS LESS THAN 3 MONTHS OF AGE

Risk factors	Comments
Classic risk (also described in adults)	
Use of multiple or broad spectrum antibiotics and/or prolonged use of antibiotics	The length of antibiotic treatment is as important as the spectrum of antibiotics used.
Central venous catheters or prolonged intravascular catheterization	
Parenteral hyperalimentation or intravenous fat emulsion	
Colonization with *Candida* and/or previous episode of mucocutaneous candidiasis	
Risk factors unique to this age group	
Prematurity/ very low birth weight	~90% of affected neonates are very low birth weight (<1500 gm)
Endotracheal tube or existing tracheostomy	Many neonates have some type of respiratory insufficiency
Congenital malformations, including GI malformations and congenital heart disease	Most frequently seen in infants >2,500 gm at birth with prolonged NICU hospitalization
Gastrointestinal tract diseases	Necrotizing enterocolitis and anatomical abnormalities requiring surgery

6.3 GENERAL GUIDELINES FOR THE MANAGEMENT OF INVASIVE *CANDIDA* INFECTIONS

The following guidelines, adapted from the Infectious Diseases Society of America (IDSA) Treatment Guidelines for the treatment of invasive candidiasis [29], should generally be implemented in the management of the patients enrolled in this study. However, as there are no dedicated guidelines for neonatal candidiasis, some of these guidelines may require some modification in the neonatal/infant population on a case-by-case basis.

***Candida* Infection**	**Guidelines for Management**
Candidemia	• Please indicate in the source documents if the initial & follow-up blood cultures were obtained through an indwelling IV catheter or by percutaneous venipuncture (via peripheral draw). Please also indicate if all IV catheters in place at time of positive culture were removed or changed. • Although blood cultures are often not considered final until Day 7, blood cultures should be drawn periodically until negative on 2 separate occasions. Additional blood cultures should be drawn if clinically indicated (e.g., persistent fever, persistent leukocytosis, clinical change such as hypotension, tachycardia). • If cultures become negative during study therapy, the microbiology response should be eradication even if a culture was not obtained on the last day of study therapy. • For a patient to be considered as having microbiological eradication, follow-up blood cultures while on study therapy must become negative for *Candida sp.* Assessment of microbiological eradication should be based on the last available blood culture performed while on study therapy.

Peritonitis	• *Patients who develop peritonitis while on peritoneal dialysis*:
	  • Removal of peritoneal dialysate catheter should be considered at study entry or within the first 72 hours following the onset of study therapy.
	  • Clinical findings (signs and symptoms) of infection should be followed daily while on study therapy.
	  • Follow-up peritoneal fluid cultures (and fluid assessment of cell count, protein, glucose) should be collected prior to the completion of study therapy to assure eradication.
	• *Surgical patients (or any other patients) who develop peritonitis*:
	  • Patients with an intraabdominal source of the peritonitis or with an unclear etiology should have a radiographic study (abdominal ultrasound, CT, or MRI) documented within 96 hours prior to study entry.
	  • Surgical repair or drainage of perforation, leak, or other abdominal abnormality should be considered prior to study entry or within the first 72 hours following study entry.
	  • Clinical findings (signs and symptoms) of infection should be followed daily while on study therapy.
	  • Follow-up radiographs (ultrasound, CT, or MRI) should be repeated prior to end of study therapy (within 72 hours) to verify the resolution.
	  • Follow-up peritoneal fluid cultures (including fluid assessment of cell count, protein, and/or glucose) should be collected prior to the completion of study therapy, as clinically indicated.

Candida Infection	Guidelines for Management
Abscess involving intraabdominal cavity or organ	• Surgical drainage or aspiration drainage of abscess collection should be considered at study entry or within the first 72 hours following the onset of study therapy. • Patients who develop an intraabdominal abscess as a result of prior surgery or other intra-abdominal pathology (e.g., GI cancer) should also have a radiographic study (e.g., abdominal ultrasound, CT, or MRI) performed within the 96 hours prior to study entry to document the extent of the infection. • Clinical findings (signs and symptoms) of infection should be followed daily while on study therapy. • Follow-up radiographs (e.g., ultrasound, CT, or MRI) should be repeated prior to the end of study therapy (within 72 hours) to verify the abscess process has resolved. • Follow-up cultures from the invasive site of infection should be collected prior to the completion of study therapy, as clinically indicated.
Abscess involving other cavity or organ	• Surgical drainage or aspiration drainage of abscess collection should be considered at study entry or within the first 72 hours following the onset of study therapy. • Patients who develop an abscess as a result of prior surgery or other organ pathology (e.g., cancer) should also have a radiographic study (e.g., ultrasound, CT, or MRI) performed within the 96 hours prior to study entry to document the extent of the infection. • Clinical findings (signs and symptoms) of infection should be followed daily while on study therapy. • Follow-up radiographs (e.g., ultrasound, CT, or MRI) should be repeated prior to the end of study therapy (within 72 hours) to verify the abscess process has resolved. • Follow-up cultures from the invasive site of infection should be collected prior to the completion of study therapy, as clinically indicated.
Pleural space infection (empyema)	• A radiographic study (e.g., chest x-ray or CT) should be performed within 96 hours prior to study entry in those patients who develop pleuritis to document the extent of infection. In patients who develop empyema following a recent surgery, efforts must be made to assure there is no active connection (i.e., fistula, etc.) with either the GI tract or the exterior. • Ongoing chest tube drainage of the pleural space is usually required in these patients. • Clinical findings (signs and symptoms) of infection should be followed daily while on study therapy. • Follow-up radiography (chest x-ray or CT) should be repeated prior to the end of study therapy (within 72 hours) to verify the infectious process has resolved. • Follow-up pleural fluid cultures (including fluid assessment of cell count, protein, and/or glucose) should be collected prior to the completion of study therapy, as clinically indicated.

Candida Infection	Guidelines for Management
Pneumonia	• A radiographic study (chest x-ray or, preferably, chest CT) should be performed within 96 hours prior to study entry in those patients who develop pneumonia to document the extent of infection. • Clinical findings (signs and symptoms) of infection should be followed daily while on study therapy. • Follow-up radiography (chest x-ray or, preferably, chest CT) should be repeated prior to the end of study therapy (within 72 hours) to verify the infectious process has resolved. • Follow-up lung tissue biopsy (for histopathology or culture) should be collected prior to the completion of study therapy, as clinically indicated.
Endophthalmitis	• Clinical findings (signs and symptoms) of infection should be followed daily while on study therapy. • Two sets of blood cultures should be collected periodically until cultures are negative for *Candida sp*. on 2 separate occasions. • A follow-up dilated eye examination should be performed by an ophthalmologist within 72 hours following the completion of study therapy.
Chronic disseminated candidiasis (hepatosplenic)	• All patients must have an appropriate abdominal radiograph (e.g., ultrasound, CT, or MRI) performed within the 96 hours prior to study entry to document the extent of the lesions. • Clinical findings (signs and symptoms) of infection should be followed daily while on study therapy. • Follow-up radiography (e.g., ultrasound, CT, or MRI) should be repeated prior to the end of study therapy (within 72 hours) to verify the infectious process has resolved or all lesions have fully calcified.

Several general points apply to all infections:

- If a culture is not obtained on last day of study therapy, then the last culture after study entry should be used to assist in the assessment of microbiological eradication. If the last culture is negative for *Candida sp.*, then microbiological eradication is deemed appropriate.
- If no follow-up cultures from a non-blood site of infection were obtained during the study therapy course to document eradication, then in order to consider the microbiologic evaluation as "presumptive" eradication, there must be resolution of clinical signs and symptoms and resolution of radiographic evidence of infection.

Please assure all symptoms and signs of infection (collected daily), all relevant radiographs or other diagnostic procedures (e.g., echocardiogram, CT, MRI), and all relevant cultures are recorded on the appropriate eCRFs. Similarly, please ensure all surgical procedures performed to alleviate the infection are recorded on the appropriate eCRFs.

7. ATTACHMENTS

Merck Code of Conduct for Clinical Trials

Merck*
Code of Conduct for Clinical Trials

I. Introduction

A. Purpose

Merck, through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, implementing, conducting, analyzing and reporting these trials in compliance with the highest ethical and scientific standards. Protection of subject safety is the overriding concern in the design of clinical trials. In all cases, Merck clinical trials will be conducted in compliance with local and/or national regulations and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

Such standards shall be endorsed for all clinical interventional investigations sponsored by Merck irrespective of the party (parties) employed for their execution (e.g., contract research organizations, collaborative research efforts). This Code is not intended to apply to trials which are observational in nature, or which are retrospective. Further, this Code does not apply to investigator-initiated trials which are not under the control of Merck.

II. Scientific Issues

A. Trial Conduct

1. Trial Design

Except for pilot or estimation trials, clinical trial protocols will be hypothesis-driven to assess safety, efficacy and/or pharmacokinetic or pharmacodynamic indices of Merck or comparator products. Alternatively, Merck may conduct outcomes research trials, trials to assess or validate various endpoint measures, or trials to determine subject preferences, etc.

The design (i.e., subject population, duration, statistical power) must be adequate to address the specific purpose of the trial. Research subjects must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

Merck selects investigative sites based on medical expertise, access to appropriate subjects, adequacy of facilities and staff, previous performance in Merck trials, as well as budgetary considerations. Prior to trial initiation, sites are evaluated by Merck personnel to assess the ability to successfully conduct the trial.

3. Site Monitoring/Scientific Integrity

Trial sites are monitored to assess compliance with the trial protocol and general principles of Good Clinical Practice. Merck reviews clinical data for accuracy, completeness and consistency. Data are verified versus source documentation according to standard operating procedures. Per Merck policies and procedures, if fraud, misconduct or serious GCP-non-Compliance are suspected, the issues are promptly investigated. When necessary, the clinical site will be closed, the responsible regulatory authorities and ethics review committees notified and data disclosed accordingly.

B. Publication and Authorship

To the extent scientifically appropriate, Merck seeks to publish the results of trials it conducts. Some early phase or pilot trials are intended to be hypothesis-generating rather than hypothesis testing. In such cases, publication of results may not be appropriate since the trial may be underpowered and the analyses complicated by statistical issues of multiplicity.

Merck's policy on authorship is consistent with the requirements outlined in the ICH-Good Clinical Practice guidelines. In summary, authorship should reflect significant contribution to the design and conduct of the trial, performance or interpretation of the analysis, and/or writing of the manuscript. All named authors must be able to defend the trial results and conclusions. Merck funding of a trial will be acknowledged in publications.

III. Subject Protection

A. IRB/ERC review

All clinical trials will be reviewed and approved by an independent IRB/ERC before being initiated at each site. Significant changes or revisions to the protocol will be approved by the IRB/ERC prior to implementation, except that changes required urgently to protect subject safety and well-being may be enacted in anticipation of IRB/ERC approval. For each site, the IRB/ERC and Merck will approve the subject informed consent form.

B. Safety

The guiding principle in decision-making in clinical trials is that subject welfare is of primary importance. Potential subjects will be informed of the risks and benefits of, as well as alternatives to, trial participation. At a minimum, trial designs will take into account the local standard of care. Subjects are never denied access to appropriate medical care based on participation in a Merck clinical trial.

All participation in Merck clinical trials is voluntary. Subjects are enrolled only after providing informed consent for participation. Subjects may withdraw from a Merck trial at any time, without any influence on their access to, or receipt of, medical care that may otherwise be available to them.

C. Confidentiality

Merck is committed to safeguarding subject confidentiality, to the greatest extent possible. Unless required by law, only the investigator, sponsor (or representative) and/or regulatory authorities will have access to confidential medical records that might identify the research subject by name.

D. Genomic Research

Genomic Research will only be conducted in accordance with informed consent and/or as specifically authorized by an Ethics Committee.

IV. Financial Considerations

A. Payments to Investigators

Clinical trials are time- and labor-intensive. It is Merck's policy to compensate investigators (or the sponsoring institution) in a fair manner for the work performed in support of Merck trials. Merck does not pay incentives to enroll subjects in its trials. However, when enrollment is particularly challenging, additional payments may be made to compensate for the time spent in extra recruiting efforts.

Merck does not pay for subject referrals. However, Merck may compensate referring physicians for time spent on chart review to identify potentially eligible subjects.

B. Clinical Research Funding

Informed consent forms will disclose that the trial is sponsored by Merck, and that the investigator or sponsoring institution is being paid or provided a grant for performing the trial. However, the local IRB/ERC may wish to alter the wording of the disclosure statement to be consistent with financial practices at that institution. As noted above, publications resulting from Merck trials will indicate Merck as a source of funding.

C. Funding for Travel and Other Requests

Funding of travel by investigators and support staff (e.g., to scientific meetings, investigator meetings, etc.) will be consistent with local guidelines and practices including, in the U.S., those established by the American Medical Association (AMA).

V. Investigator Commitment

Investigators will be expected to review Merck's Code of Conduct as an appendix to the trial protocol, and in signing the protocol, agree to support these ethical and scientific standards.

* In this document, "Merck" refers to Merck Sharp & Dohme Corp. and Schering Corporation, each of which is a subsidiary of Merck & Co., Inc. Merck is known as MSD outside of the United States and Canada. As warranted by context, Merck also includes affiliates and subsidiaries of Merck & Co., Inc."

8. SIGNATURES

8.1 SPONSOR'S REPRESENTATIVE

TYPED NAME	SIGNATURE	DATE

8.2 INVESTIGATOR

I agree to conduct this clinical study in accordance with the design outlined in this protocol and to abide by all provisions of this protocol (including other manuals and documents referenced from this protocol); deviations from the protocol are acceptable only with a mutually agreed upon protocol amendment. I agree to conduct the study in accordance with generally accepted standards of Good Clinical Practice. I also agree to report all information or data in accordance with the protocol and, in particular, I agree to report any serious adverse experiences as defined in the SAFETY MEASUREMENTS section of this protocol. I also agree to handle all clinical supplies provided by the SPONSOR and collect and handle all clinical specimens in accordance with the protocol. I understand that information that identifies me will be used and disclosed as described in the protocol, and that such information may be transferred to countries that do not have laws protecting such information. Since the information in this protocol and the referenced Investigator's brochure is confidential, I understand that its disclosure to any third parties, other than those involved in approval, supervision, or conduct of the study is prohibited. I will ensure that the necessary precautions are taken to protect such information from loss, inadvertent disclosure, or access by third parties.

TYPED NAME	SIGNATURE	DATE