

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
50-740/SE8-001

MEDICAL REVIEW

**A RANDOMIZED, DOUBLE-BLIND COMPARATIVE TRIAL OF
AMBISOME® VERSUS ABELCET® IN THE EMPIRICAL
TREATMENT OF FEBRILE NEUTROPENIA**

Medical Officer Review

NDA 50-740, SE 8, Serial # 001:

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Drug Name: AmBisome®

Generic Name: amphotericin B liposome for injection

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Indication: Empirical Treatment of Febrile Neutropenia

Protocol Number: 97-0-034

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1. Rationale and Objective

It has been estimated that as many as one-third of neutropenic patients who remain febrile despite 1 week of antibacterial therapy will have a systemic fungal infection. Currently, the two most common invasive fungal infections in neutropenic patients are candidiasis and aspergillosis. Empirical systemic antifungal therapy is commonly administered after 4 or more days of febrile neutropenia. While amphotericin B has demonstrated efficacy against both *Candida* and *Aspergillus*, and has been the standard of care for febrile neutropenic patients unresponsive to broad-spectrum antibiotic therapy, its traditional formulation has a less than optimum safety profile and its therapeutic efficacy can be limited by toxicity-associated dosing constraints.

AmBisome[®] is a dosage form of amphotericin B that consists of unilamellar bilayer liposomes with amphotericin B intercalated within the membrane. AmBisome was approved by the Food and Drug Administration in August 1997 for the following indications:

- 1) Empirical therapy for presumed fungal infection in febrile, neutropenic patients, at a dosage of 3 mg/kg/day.
- 2) Treatment of patients with *Aspergillus* species, *Candida* species and/or *Cryptococcus* species infections refractory to amphotericin B deoxycholate, or in patients where renal impairment or unacceptable toxicity precludes the use of amphotericin B deoxycholate, at a dosage of 3-5 mg/kg/day.

- 3) Treatment of visceral leishmaniasis at the following dosage:

Immunocompetent patients 3 mg/kg/day on days 1-5 and days 14, 21
Immunocompromised patients 4 mg/kg/day on days 1-5 and 4 mg/kg/day
on days 10, 17, 24, 31, 38

Abelcet[®] is a lipid complex formulation of amphotericin B that was approved by the FDA in November 1995 at a dosage of 5 mg/kg/day for the treatment of invasive fungal infections in patients who are refractory to or intolerant of conventional amphotericin B therapy. Comparative trial and historical data comparisons show the incidence of nephrotoxicity (as measured by the doubling of the baseline serum creatinine concentration) with Abelcet is lower compared with traditional amphotericin. The present study directly compared the incidence of adverse events (particularly chills/rigors and other infusion-related reactions) and the incidence of nephrotoxicity in febrile neutropenic patients administered Abelcet or AmBisome for the empirical treatment of fungal infections.

The objectives of this safety study were:

- 1) To compare the safety, primarily chills/rigors on Day 1 [primary endpoint of this study], of 5 mg/kg/day Abelcet to an equivalent dose of AmBisome (liposomal amphotericin B) as well as to a lower yet efficacious dose of AmBisome (3 mg/kg/day).
- 2) To compare the incidence of other safety variables such as nephrotoxicity [secondary endpoint], other infusion-related reactions on Day 1, all adverse events, hepatotoxicity, hypokalemia, anemia and drug tolerance among the treatment groups.
- 3) To evaluate the efficacy among the treatment groups. Efficacy endpoints included overall success rate; incidence of treatment-emergent probable or proven fungal infections; incidence of fever resolution during the neutropenic period (absolute neutrophil count $<500/\text{mm}^3$); incidence of improvement/cure for patients with a proven baseline fungal infection; incidence of mortality from fungal infections (as a primary or contributing factor) on study or within 7 days of last dose of study drug; incidence of discontinuation of study drug due to toxicity; and the incidence of treatment with an alternative systemic antifungal agent for a probable or proven fungal infection.

Reviewer's comments: An FDA memorandum dated August 8, 1997 and written by Jeffrey Murray, M. D., used data available at that time to compare the safety profiles of Abelcet and AmBisome. Those data were collected from animal toxicity studies and from human trials comparing amphotericin B with Abelcet and AmBisome separately. There were no data comparing the latter 2 drugs directly. The conclusion was that AmBisome was clinically superior to AmBisome with respect to safety. The memorandum served to establish that the 2 products are not the same drug under 21CFR § 316.3(b)(13)(ii). In this present trial, the 2 drugs are being compared for multiple endpoints, which increases the chances of having a statistically significant difference in one or more endpoint outcomes when there actually is no difference. It is more appropriate to compare the 2 drugs just for chills/rigors and nephrotoxicity to minimize this effect. These 2 side effects are the ones most frequently encountered and the most frequent reasons for discontinuation of therapy with amphotericin B. Moreover, the study was not powered to detect a significant difference in efficacy.

2. Study Design

This Phase 4, randomized, double-blind multicenter study was conducted at 18 study centers in the United States. The principal investigator at each center was a licensed practitioner with experience in the treatment of neutropenic patients with suspected fungal infections. The study was designed to evaluate the safety of AmBisome and Abelcet when administered to neutropenic patients at least 2 years of age who remained febrile after at least 72 hours of broad-spectrum antibacterial therapy. Based on an estimated 50% incidence of Day 1 chills/rigors in the Abelcet group, and the desire to detect a treatment difference of 25%, planned enrollment was at least 80 patients per treatment group. Study drug (Abelcet 5 mg/kg per day or AmBisome 5 mg/kg per day or

AmBisome 3 mg/kg per day) was administered once daily via a 120-minute intravenous infusion.

The duration of therapy was dependent on the patient's clinical response (i.e., neutrophil recovery defined as an absolute neutrophil count [ANC] of at least 500/mm³) but was not to exceed 42 days of treatment. Vital signs were obtained at baseline and for the first 5 days of therapy. On each of the first 5 days of therapy, vital signs were determined prior to and 60 and 120 minutes after the start of each study drug administration. Throughout the period of study drug therapy and up to 24 hours after discontinuing study drug, temperature was determined every 4 - 6 hours while the patient was awake.

Adverse events were recorded through the 7-day posttreatment follow-up visit.

Medications for the prevention of infusion-related reactions were not permitted on the first day of study drug administration. Clinical laboratory profile was determined at baseline and, as clinically appropriate, through the 7-day posttreatment follow-up visit; however, serum creatinine was to be measured at least 3 times per week during study drug administration and ANC was to be documented daily during neutropenia. Blood was collected for the determination of serum amphotericin B concentrations from patients at seven investigative centers on Days 3 and 4.

The primary endpoint in this safety study was the incidence of chills/rigors on Day 1. The secondary endpoint was the incidence of nephrotoxicity. Other safety assessments included the incidence of other infusion-related reactions on Day 1, all adverse events, hepatotoxicity, hypokalemia, anemia, and drug tolerance. In addition to safety assessments, the comparative efficacy of AmBisome and Abelcet was also evaluated. Fungal infection status was assessed weekly through the 7-day posttreatment follow-up visit. At the 7-day posttreatment follow-up visit, the physician evaluated the treatment as either being a success (became afebrile [$\leq 38^{\circ}\text{C}$ or 100.4°F] while neutropenic and remained afebrile for 24 hours; did not meet any failure criterion) or a failure (persistent fever; progression or persistence of a proven baseline infection such as a persistent positive blood culture or other determinations; treatment emergent development of a probable or proven systemic fungal infection; a requirement for treatment with an alternative systemic antifungal agent for a presumed, probable, or proven fungal infection; discontinuation of study drug due to toxicity; or death with fungal infection as a primary or contributing factor).

Abelcet was administered in the study at the recommended dosage (5 mg/kg per day) for secondary treatment of fungal infections since it is not indicated for empirical therapy and thus no approved dose has been established. AmBisome was administered at a dosage equivalent to that of Abelcet (5 mg/kg per day) and at a lower dosage (3 mg/kg per day) which has been previously demonstrated to be effective and approved for the empirical treatment of febrile neutropenic patients. Because of a suggestion of a differential toxicological profile with AmBisome compared with Abelcet, the primary and secondary endpoints for this study were chills/rigors on Day 1 and nephrotoxicity, respectively. A randomized, parallel group, double-blind design was used. This trial was multicenter to provide a good basis for generalization of its findings as well as to ensure patient accrual within a reasonable time frame. Patients were stratified at each center based on the use of immunosuppressants (i.e., tacrolimus or cyclosporine) in order to ensure a similar mixture of high risk and low risk patients in each treatment group.

Reviewer's comments: *The randomized, double-blind design is the preferred design for such a trial comparing 2 drugs for a safety parameter as a primary endpoint. The minimum duration of therapy (72 hours) with antibacterial agents before administration of an antifungal agent is shorter than what most authorities would recommend, i.e. 4 to 7 days of antibacterial therapy, but this is not expected to affect the incidence of adverse reactions. AmBisome was used according to the approved dosing regimen, and although it is recommended at 3 mg/kg/d for febrile neutropenia, the inclusion of a group at a higher dose (5 mg/kg/d) would provide for a more complete and fair comparison with Abelcet used at the same dose. Although Abelcet is not approved for the empirical treatment of febrile neutropenic patients, the choice of a dosage of 5 mg/kg/d is appropriate given that the rationale behind treating those patients is to treat an invasive fungal infection before it has disseminated. The safety of the 2 drugs in the pediatric population has been previously demonstrated and both drugs are approved for use in children. The definition of neutropenia that is used ($ANC < 500/mm^3$) is the one widely accepted.*

3. Protocol

3.1 Population and Procedures

At baseline, patients had their demographic information, height, weight, medical history and current medical status recorded. Selected medical treatments administered within 14 days prior to the first dose of study drug were recorded. Women with childbearing potential underwent a serum or urine pregnancy test within 14 days prior to the first dose of study drug. Within 72 hours prior to the first dose of study drug, patients underwent a physical examination, chest X-ray, laboratory evaluation and had their fungal infection status assessed.

Inclusion Criteria

Patients were eligible for the study if they fulfilled all of the following criteria:

- Informed consent of the patient and/or legally authorized representative was obtained prior to study entry
- Patient was ≥ 2 years of age
- Patient agreed to use adequate birth control measures for the duration of study therapy (males and females with childbearing potential); females with childbearing potential were required to have a negative pregnancy test (blood or urine) within 14 days prior to baseline evaluation
- Patient was neutropenic (absolute neutrophil count $< 500/mm^3$); including but not limited to cancer patients, bone marrow transplant patients, or patients undergoing peripheral stem cell transfusions
- Patient had a suspected fungal infection as demonstrated by fever after at least 72 hours of broad spectrum antibacterial therapy; fever for the purposes of study entry was defined as:
 - a) Two oral equivalent temperatures of $>38^\circ C$ or $100.4^\circ F$ taken at least 4 hours apart, with the second reading taken after at least 72 hours of broad spectrum antibacterial therapy; OR

b) A single oral equivalent temperature of $>38.5^{\circ}\text{C}$ or 101.3°F after at least 72 hours of broad spectrum antibacterial therapy.

- Patient had a venous catheter or sufficient venous access to permit administration of study drug and monitoring of safety variables

Exclusion Criteria

Fulfillment of any of the following criteria resulted in exclusion from the study:

- Patient was pregnant or nursing
- Patient had moderate or severe liver disease and an exception was not granted after a physician-medical monitor consultation; moderate or severe liver disease was defined as:
 - (a) Transaminase (SGOT/AST or SGPT/ALT) > 10 times upper limit of normal (ULN)
 - (b) Total bilirubin > 5 times ULN
 - (c) Alkaline phosphatase > 5 times ULN
- Patient had serum creatinine > 3.0 mg/dl
- Patient had a history of anaphylaxis attributed to amphotericin B
- Patient received more than two systemic doses of amphotericin B, or preparations containing amphotericin B, within 10 days prior to initiation of study drug administration
- There was clinical or other evidence indicating a deep or disseminated fungal infection prior to enrollment (Note: patients who were diagnosed as having had a fungal infection at baseline but who had already been randomized and received study drug when the culture results were available were eligible to continue in the study)
- The presence of known uncontrolled bacteremia (positive bacterial cultures despite broad spectrum antibacterial therapy).
- Presence of a concomitant condition that, in the opinion of the investigator and/or medical monitor, created a risk for the patient
- Anticipated survival was ≤ 2 weeks
- Patient received an investigational drug, other than one for cancer/leukemia treatment or supportive care, within 7 days prior to the initiation of study drug administration

Study Withdrawal Criteria

Patients were to be withdrawn from the study if any of the following occurred:

- Unacceptable toxicity developed
- The patient required an alternative systemic antifungal agent due to clinical or mycological evidence of worsening fungal infection
- The investigator decided it was in the patient's best interest to discontinue therapy
- The patient declined further study participation

Patients who prematurely discontinued therapy were evaluated at a 7-day posttreatment follow-up visit (5-10 days posttreatment).

Reviewer's comments: The inclusion of neutropenic patients with a variety of underlying conditions provides a good basis for generalization of the findings but also increases the chances of imbalance between the 3 arms in terms of underlying conditions. Fever was reasonably defined. Exclusion and withdrawal criteria were generally acceptable, but the exclusion of patients with renal or hepatic insufficiency prevents generalization of the findings to these subgroups.

Randomization

Patients were stratified at each investigative center based on the use ("high risk") or non-use ("low risk") of immunosuppressants (cyclosporine or tacrolimus) before being randomized (1:1:1 by study center) to a treatment group. The sponsor, investigator, patient and study coordinator(s) were blinded to the treatment administered.

Reviewer's comments: Stratification based on the use of immunosuppressants is appropriate given that patients receiving those drugs may have a higher incidence of nephrotoxicity and other side effects caused by their immunosuppressant regimen. They may also have different efficacy rates. After reconstitution, AmBisome is a translucent yellow solution and Abelcet is an opaque yellow solution. Blinding was ensured by providing blind-labeled bags/bottles for administration and wrapping those as well as the reservoir with a mask to prevent identification. The volume of the solution in the bag was the same for each study drug.

Treatments

Study drugs were intravenously administered under the supervision of study personnel and, therefore, treatment compliance was not an issue in this study.

On the first day of dosing, each patient was to receive a "test dose" of study drug consisting of 5 ml of the infusion solution (or 1/20th of the total volume for pediatric patients with small infusion volumes), administered intravenously over 5 minutes without any premedication. The purpose of the test dose was to determine whether a patient would have an acute reaction to the study drug that would preclude further administration [Note: several study centers did not use test doses.]

Abelcet was administered in the study at the recommended dosage for secondary treatment of fungal infections (5 mg/kg/day). AmBisome was administered at dosage equivalent to that of Abelcet (5 mg/kg/day) and, in a third treatment group, at a lower dosage (3 mg/kg/day) which has been previously demonstrated to be effective for the empirical treatment of febrile neutropenic.

Therapy continued until one of the following occurred:

- (a) The patient recovered from neutropenia ($ANC \geq 500/mm^3$; patient could have continued therapy for up to 3 days after recovery)
- (b) The maximum duration of therapy (42 days) was reached
- (c) The patient developed unacceptable toxicity
- (d) The patient required an alternative systemic antifungal agent due to clinical or mycological evidence of worsening fungal infection
- (e) The Investigator decided it was in the patient's best interest to discontinue therapy
- (f) The patient refused further therapy
- (g) The patient died

Premedications or concomitant medications such as hydrocortisone, meperidine, acetaminophen, or diphenhydramine for prevention of possible infusion-related reactions were not administered prior to the first dose of study drug. However, if infusion-related reactions were observed during the first dose, symptomatic treatment could have been

initiated. Premedications could have been administered on subsequent infusions, if clinically indicated.

Conventional amphotericin B, other liposomal amphotericin B products, systemic antifungal agents other than study drug (e.g., systemic azole and triazole antifungal agents), or newer investigational antifungal drugs were prohibited during the study. Topical or non-absorbable antifungal agents (clotrimazole, nystatin) were permitted during the study.

Procedures

Blood samples were collected from a subset of patients for the determination of amphotericin B concentrations as follows:

- On Day 3, prior to the Day 3 infusion (i.e., 24 hours after the Day 2 dose of study drug) and 15 minutes after the end of the Day 3 study drug infusion
- On Day 4, prior to the Day 4 infusion (i.e., 24 hours after the Day 3 dose of study drug).

Amphotericin B serum concentrations were determined at a central laboratory using a

The schedule of procedures is shown in Table 1.

Vital signs (body temperature recorded as oral equivalent temperature, blood pressure, and pulse rate) were recorded at baseline and prior to, and 60 and 120 minutes after, the start of each study drug infusion for the first 5 days of therapy. Throughout the period of study drug therapy and up to 24 hours after discontinuing study drug, temperature was determined every 4 - 6 hours while the patient was awake. Daily minimum and maximum (excluding those within 1 hour of study drug infusion or blood product transfusions) temperatures were recorded. Adverse events were recorded during the study through the 7-day posttreatment follow-up visit. Clinical laboratory profile was determined at baseline and as clinically appropriate through the 7-day posttreatment follow-up visit; however, serum creatinine was to have been measured at least three times per week during study drug administration and ANC was to have been documented daily during neutropenia. Fungal infection status was assessed weekly through the 7-day posttreatment follow-up visit.

**APPEARS THIS WAY
ON ORIGINAL**

Table 1 Schedule of Procedures

Procedure	Baseline	Day 1	Treatment Period	Post-Treatment (7 days)
Informed Consent	X			
Demographics/Medical history	X			
Body Weight/Height	X			
Vital signs	X	X	X	X
Hematology/Serum Chemistry	X		X	X
Pregnancy Test	X			
Physical exam	X		X ^a	
Chest X-Ray	X		X ^a	
Other*	X		X ^a	X ^a
Test Dose		X		
Blood Samples for Ampho B			X	
Fungal Infection Status	X		X ^b	X
Treatment Evaluation				X
Concomitant Medications	X	X	X	X
Adverse Events		X	X	X

e.g. radiological procedures, culture, biopsy;

^a as needed;

^b weekly

Reviewer's comments: *The prohibition of premedication prior to the first dose was appropriate given that it would mask infusion-related reactions. So was the prohibition of systemic antifungals. Monitoring of patients was performed frequently enough to ensure their safety and the detection of adverse events. The timing of the posttreatment follow-up was adequate to detect a subacute adverse event that would have started on the last day of therapy.*

3.2 Endpoints

As defined in Amendment #2 to the protocol, the primary endpoint in this safety study was the incidence of infusion-related chills/rigors on Day 1 and the secondary endpoint was the incidence of nephrotoxicity. Other safety assessments included the incidence of adverse events (including infusion-related reactions), laboratory profile and drug tolerance. In addition, the efficacy of each treatment regimen was evaluated.

Efficacy

Efficacy endpoints included:

- overall success rate based on the physician's evaluation at the 7-day posttreatment follow-up visit,

and the incidence of each component of success –

- absence of a treatment-emergent probable or proven fungal infection
- fever resolution (patient remains afebrile, $\leq 38^{\circ}\text{C}$ or $\leq 100.4^{\circ}\text{F}$, for 24 hours) during the neutropenic period [absolute neutrophil count $<500/\text{mm}^3$]
- improvement/cure for patients with a proven baseline fungal infection
- absence of mortality from fungal infections (as a primary or contributing factor) on study or within 7 days of last dose of study drug

- no discontinuation of study drug due to toxicity
- no treatment with an alternative systemic antifungal agent for a probable or proven fungal infection

Safety

Primary endpoint: incidence of chills/rigors on day 1

The incidence of infusion-related chills/rigors (occurring during infusion or for up to 1 hour postinfusion) on Day 1 was the primary endpoint in this safety study. Patients were not administered premedication to prevent infusion-related chills/rigors prior to the first administration of study drug (Day 1).

Secondary endpoint: incidence of nephrotoxicity

The incidence of nephrotoxicity (from Day 1 through the 7-day follow-up evaluation) was the secondary endpoint in this safety study and was defined as follows:

For pediatric patients (< 16 years of age), nephrotoxicity was defined as an increase in serum creatinine >100% above baseline value (>2X the baseline value). In addition, increases in serum creatinine >50% above baseline value (>1.5X the baseline value) were evaluated.

For adult patients (≥16 years of age) nephrotoxicity was defined as an increase in serum creatinine >100% above baseline value (>2X the baseline value) provided the postbaseline peak serum creatinine value was above 1.2 mg/dl. Increases in serum creatinine >50% above baseline value (>1.5X the baseline value), provided the postbaseline peak serum creatinine value was above 1.2 mg/dl, were also evaluated.

Adverse Events

An adverse event was defined as any reaction, side effect, or other untoward event, regardless of relationship to the study drug, that occurred during the conduct of the clinical trial, (i.e., from the start of therapy through the 7-day follow-up period after discontinuation of study drug). A serious adverse event was defined as any experience that resulted in death, was life-threatening, required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability/incapacity or congenital anomaly/birth defect, or was considered an important medical event.

Infusion-related adverse events, defined as adverse events occurring during infusion or for up to 1 hour postinfusion, included:

- chills/rigors (primary safety endpoint)
- fever (increase in oral equivalent body temperature of $\geq 0.3^{\circ}\text{C}$ above preinfusion temperature; increases of $\geq 0.6^{\circ}\text{C}$ and $\geq 1.0^{\circ}\text{C}$ were also evaluated)
- nausea
- vomiting
- dyspnea
- other significant reactions (e.g., cardiovascular events).

In order to assess the incidence of infusion-related reactions more accurately, patients were not administered premedication to prevent infusion-related reactions prior to the first administration of study drug (Day 1).

Reviewer's comments: Nephrotoxicity, adverse events and infusion-related adverse events were reasonably defined.

Laboratory Evaluations

Clinical laboratory profiles were determined at the investigative centers and included the following parameters:

Hematology: hematocrit, hemoglobin, red blood cells (RBC), white blood cells (WBC) with differential and ANC, platelet count.

Serum Chemistry: creatinine, blood urea nitrogen (BUN), transaminases (AST/SGOT, ALT/SGPT), alkaline phosphatase, total bilirubin, sodium, potassium, magnesium.

Hepatotoxicity was defined as changes from baseline in serum concentrations of AST (SGOT) or ALT (SGPT) as follows:

- an increase to a value $>5X$ baseline in cases where baseline is $<2X$ ULN
- an increase to a value $>3X$ baseline in cases where baseline is $2-5X$ ULN
- an increase to a value $>2X$ baseline in cases where baseline is $>5X$ ULN

Hypokalemia was defined based on serum potassium level; two levels (<3 mEq/L and ≤ 2.5 mEq/L) were evaluated in this study. Anemia was defined as hemoglobin ≤ 8 g/dl.

Drug tolerance was defined as the incidence of:

- study drug discontinuations due to adverse events or infusion-related reactions
- dose reductions (including interruptions) due to adverse events or infusion-related reactions

Reviewer's comments: Laboratory parameters that were monitored were appropriately tailored to the spectrum of adverse effects known to be caused by amphotericin B preparations.

3.3 Statistical Methods

A sample size of 240 patients (80 per treatment group) was based on an estimated 50% incidence of chills/rigors on Day 1 in the Abelcet group and the ability to detect a treatment difference of 25% in the incidence of Day 1 chills/rigors with 80% power at $\alpha = 0.05$. As stated in Amendment #2 (dated April 6, 1998), this sample size was anticipated to also allow the detection of a difference of 20% in the incidence of Day 1 chills/rigors in the combined AmBisome groups versus the Abelcet group.

Populations for Analysis

All randomized patients who received at least one dose of study drug were included in the safety and efficacy analyses. In addition, a per protocol patient population was defined as patients who completed the study without a major protocol deviation

determined during a blinded patient classification review. A per protocol population analysis was performed for the primary endpoint.

Reviewer's comments: The primary dataset is a modified intent-to-treat population and consists of all patients who received at least one dose of study drug.

Statistical Methodology

All analyses were designed before the blind was broken. Unless otherwise specified, all comparisons between and among the treatment groups and all statistical tests were two-tailed with a significance level of 0.05.

Descriptive statistics were performed for demographic and other baseline characteristics to assess comparability of the treatment groups. Prior and concomitant medications were tabulated.

Efficacy

Efficacy endpoints were tabulated by treatment groups and summarized using descriptive statistics. Fisher's exact test was used for the comparison of treatment groups.

Safety

Adverse events were coded using a modified COSTART dictionary. Summary tables are presented by body system and preferred term and treatment group for adverse events experienced during the study period. Changes from baseline in selected laboratory parameters were tabulated and descriptive statistics presented for each treatment group. The primary safety endpoint of chills/rigors on Day 1 was analyzed using Fisher's exact test on the combined AmBisome groups ["BOTH"] versus Abelcet. Since a significant treatment difference was obtained with this comparison, the Fisher's exact test was used to compare each AmBisome arm to the Abelcet arm at an $\alpha = 0.05$.

Chi-squared test was used for the secondary endpoint of nephrotoxicity. Fisher's exact test, chi-squared test, or analysis of variance (ANOVA; GLM) was used for other safety endpoints of interest in the comparison of treatment groups.

Changes from Planned Analysis

There were two minor additions to the planned analysis as set forth in the protocol, the amendments to the protocol, and the statistical analysis plan: two-sided 95% confidence intervals for the difference in overall success rates and 95% confidence intervals for odd ratios for adverse events that showed a difference at the 0.05 level were included.

4. Results

4.1 Patient Disposition

A total of 342 patients underwent screening evaluation; of these, 250 patients were enrolled in the study. Reasons for screening failure included lack of fever (no fever or temperature below that defined in the protocol as fever); positive fungal culture, transplant delay, lack of neutropenia, bacteremia, less than 72 hours of antibacterial therapy, more than two doses of amphotericin B within the last 10 days, and patient

refusal to participate. Six (2 in each arm) of the 250 enrolled patients were randomized but did not receive study drug as follows:

One patient entered an open-label trial instead, staff error delayed dosing after randomization for one patient and his neutrophil count recovered in interim, one patient had a positive *Pneumocystis carinii* culture on the day of randomization, 2 patients withdrew consent and one did not give it. Two patients were inadvertently randomized to the same patient number before re-assigning the second patient a new number. One patient was re-enrolled and discontinued after the error was discovered. Patient populations in this study are summarized in Table 2.

Table 2: Patient Population

	AmBisome			Abelcet 5 mg/kg/d
	3 mg/kg/d	5 mg/kg/d	BOTH	
Randomized	87	83	170	80
MITT	85	81	166	78
Per protocol population	76	70	146	69
Pharmacokinetics subset	26	24	50	18

MITT: modified intent-to-treat; all randomized patients who received at least one dose of study drug.

Per protocol patient population: all randomized patients who received at least one dose of study drug and who completed the study without a major protocol deviation determined during a blinded patient classification review.

Pharmacokinetics subset: randomized patients at seven selected centers who received at least one dose of study drug and for whom amphotericin B concentrations were determined.

Reviewer's comments: Although more patients were randomized in the AmBisome arms, patients in the randomized, MITT and per protocol populations were well balanced among the 3 arms.

The disposition of the modified intent-to-treat population is presented in Table 3.

Table 3: Patient Disposition

	AmBisome			Abelcet 5 mg/kg/d
	3 mg/kg/d	5 mg/kg/d	BOTH	
Randomized and received at least one dose of study drug (MITT)	85	81	166	78
Completed treatment	61 (71.8%)	59 (72.8%)	120 (72.3%)	41 (52.6%)
Discontinued	24 (28.2%)	22 (27.2%)	46 (27.7%)	37 (47.4%)
Adverse event	11 (12.9%)	10 (12.3%)	21 (12.7%)	25 (32.1%)
Lack of efficacy	3 (3.5%)	5 (6.2%)	8 (4.8%)	2 (2.6%)
Administrative reason [†]	10 (11.8%)	7 (8.6%)	17 (10.2%)	6 (7.7%)
Death while on study drug [‡]	0	0	0	4 (5.1%)

[†] Administrative reasons included physician decision, transfer or discharge from hospital, and noncompliance

[‡] A total of 18 patients (7 AmBisome treated and 11 Abelcet treated) died during the entire study period.

A lower percentage of patients in the Abelcet group compared with the AmBisome groups completed their empiric regimen, primarily due to premature discontinuation as a result of an adverse event.

Reviewer's comments: There was a significant difference in discontinuation rates from all causes between AmBisome and Abelcet with p=0.015 (3 mg/kg/d), p=0.009 (5 mg/kg/d) and p= 0.003 (BOTH).

Protocol Deviations

Approximately half of the patients in each treated group had at least one protocol deviation. Most deviations were minor and included missed test dose, inclusion/exclusion criteria exceptions, the use of prohibited concomitant medication or administration of premedication on Day 1, and missed or mistimed vital sign or final evaluations. None of the patients were excluded from the analyses due to a protocol deviation. A total of 215 (88.1%) patients, 146 (88.0%) AmBisome-treated patients (76 in low dose group, 70 in high dose group) and 69 (88.5%) Abelcet-treated patients, completed the study without a major protocol deviation as determined during a blinded patient classification review.

Reviewer's comments: There were more protocol deviations in the low dose AmBisome (59%) and Abelcet (58%) arms than in the high dose AmBisome arm (49%). Patients were excluded from the per protocol analysis if they had a major protocol violation, i.e. did not meet the inclusion/exclusion criteria, were enrolled or randomized twice, received premedication on day 1 or had a positive CSF cryptococcal antigen at baseline and had a culture result at day 14 +/- 1 day. There were 9, 11 and 9 patients with a major protocol violation in the low dose AmBisome, high dose AmBisome and Abelcet arms respectively, and they were thus well balanced. Patients who received premedication prior to the first dose of study drug were also well balanced among the study groups. These were 2 patients in the low dose AmBisome group, 3 in the high dose group and 4 in the Abelcet group.

Demographics and Other Baseline Characteristics

Demographics and other baseline characteristics are summarized in Tables 4 and 5. There were no statistically significant differences between AmBisome and Abelcet treatment groups with respect to demographic and other baseline characteristics, such as transplant and tumor history or baseline laboratory abnormalities. Fifty-three percent of patients were male, 87% were white, and 49% had a bone marrow transplant. Fourteen percent of patients were considered high risk. Mean age was 42 years.

All MITT patients were neutropenic. The majority of patients presented with nonhematologic laboratory parameters of clinical interest in this population within normal limits. At baseline, approximately one-fifth of the patients had a value for hemoglobin of 8.0 g/dl or less. Less than one-tenth of the patients had a baseline serum creatinine value above the upper limit of normal (>1.2 mg/dl). Approximately one-quarter or less of the patients had values above the normal range for parameters indicative of hepatic function.

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Table 4: Demographics and Other Baseline Characteristics

		AmBisome			Abelcet	Total
		3 mg/kg/day	5 mg/kg/day	BOTH	5 mg/kg/day	
Total number of patients		85	81	166	78	244
Sex	Female	34 (40.0%)	43 (53.1%)	77 (46.4%)	37 (47.4%)	114 (46.7%)
	Male	51 (60.0%)	38 (46.9%)	89 (53.6%)	41 (52.6%)	130 (53.3%)
Race	White	71 (83.5%)	71 (87.7%)	142 (85.5%)	70 (89.7%)	212 (86.9%)
	Black	6 (7.1%)	7 (8.6%)	13 (7.9%)	6 (7.7%)	19 (7.8%)
	Other	8 (9.4%)	3 (3.7%)	11 (6.6%)	2 (2.6%)	13 (5.3%)
Age (years)	Mean	41.4	42.0	41.7	42.8	42.0
	SD	20.8	21.2	20.9	19.4	20.4
	Median	45.0	44.0	44.5	47.0	45.0
	Range	3-74	2-84	2-84	2-76	2-84
	<16 years	15 (17.6%)	14 (17.3%)	29 (17.5%)	13 (16.7%)	42 (17.2%)
	≥16 years	70 (82.4%)	67 (82.7%)	137 (82.5%)	65 (83.3%)	202 (82.8%)
Patients with BMT		39 (45.9%)	40 (49.4%)	79 (47.6%)	40 (51.3%)	119 (48.8%)
	Autologous	25 (29.4%)	26 (32.1%)	51 (30.7%)	28 (35.9%)	79 (32.4%)
	Allogeneic	13 (15.3%)	13 (16.0%)	26 (15.7%)	12 (15.4%)	38 (15.6%)
	Syngeneic	1 (1.2%)	1 (1.2%)	2 (1.2%)	0	2 (0.8%)
Risk [†]	High risk	13 (15.3%)	11 (13.6%)	24 (14.5%)	11 (14.1%)	35 (14.3%)
	Low risk	72 (84.7%)	70 (86.4%)	142 (85.5%)	67 (85.9%)	209 (85.7%)

Patient population: all randomized patients who received at least one dose of study drug.

†High risk: use of the immunosuppressants tacrolimus or cyclosporine; Low risk: nonuse of tacrolimus or cyclosporine.

SD: standard deviation; BMT: bone marrow transplant.

Table 5: Baseline Clinical Laboratory Profile

		AmBisome			Abelcet	Total
		3 mg/kg/day	5 mg/kg/day	BOTH	5 mg/kg/day	
Total number of patients		85	81	166	78	244
Total number (%) with						
Low hemoglobin		20 (23.5%)	13 (16.0%)	33 (19.9%)	17 (21.8%)	50 (20.5%)
Elevated serum creatinine		8 (9.4%)	7 (8.6%)	15 (9.0%)	7 (9.0%)	22 (9.0%)
Elevated AST/SGOT		12 (14.1%)	16 (19.8%)	28 (16.9%)	9 (11.5%)	37 (15.2%)
Elevated ALT/SGPT		22 (25.9%)	18 (22.2%)	40 (24.1%)	21 (26.9%)	61 (25.0%)
Elevated total bilirubin		22 (25.9%)	23 (28.4%)	45 (27.1%)	21 (26.9%)	66 (27.0%)
Elevated alkaline phosphatase		19 (22.4%)	16 (19.8%)	35 (21.1%)	18 (23.1%)	53 (21.7%)

Patient population: all randomized patients who received at least one dose of study drug.

Low hemoglobin: ≤ 8 g/dl; elevated serum creatinine: >1.2 mg/dl; elevated AST/SGOT: aspartate transaminase/serum glutamic oxaloacetic transaminase >35 U/L; elevated ALT/SGPT: alanine transaminase/serum glutamic pyruvic transaminase >35 U/L; elevated total bilirubin: >1.2 mg/dl; elevated alkaline phosphatase: >120 U/L.

Reviewer's comments: Reviewer agrees that there was no statistically significant difference between the AmBisome arms and the Abelcet arm in terms of gender, race, age, history of BMT, BMT type, neoplastic disease type, and baseline laboratory abnormalities (creatinine, ALT, AST, bilirubin, alkaline phosphatase, and hemoglobin). Respectively for the low dose AmBisome, high dose AmBisome and Abelcet arms, the mean ANC was 126, 109 and 126 and the mean creatinine value was 0.8 mg/dl for each of the 3 arms.

Prior and Concomitant Therapies

The majority of patients administered AmBisome [70/85 (82.4%) for the low dose AmBisome, 65/81 (80.2%) for the high dose AmBisome, 135/166 (81.3%) for both groups combined] or Abelcet (69/78, 88.5%) received prior antifungal therapy, predominantly fluconazole. As presented in Table 6, a numerically higher percentage of patients administered Abelcet received one potentially nephrotoxic agent during treatment compared with that for either of the AmBisome groups. However, the opposite is noted for those patients receiving three or more potentially nephrotoxic agents with nearly 25% of patients in the AmBisome group falling into this category versus 15% of patients in the Abelcet group.

Table 6: Summary of Potentially Nephrotoxic Agents Administered During Treatment

	AmBisome			Abelcet 5 mg/kg/d
	3 mg/kg/d	5 mg/kg/d	BOTH	
Total number of patients	85	81	166	78
Number who received				
No nephrotoxic agent	12 (14.1%)	7 (8.6%)	19 (11.4%)	6 (7.7%)
1 nephrotoxic agent	23 (27.1%)	20 (24.7%)	43 (25.9%)	30 (38.5%)
2 nephrotoxic agents	31 (36.5%)	32 (39.5%)	63 (38.0%)	30 (38.5%)
≥3 nephrotoxic agents	19 (22.4%)	22 (27.2%)	41 (24.7%)	12 (15.4%)
3 nephrotoxic agents	13 (15.3%)	17 (21.0%)	30 (18.1%)	10 (12.8%)
4 nephrotoxic agents	5 (5.9%)	5 (6.2%)	10 (6.0%)	2 (2.6%)
5 nephrotoxic agents	1 (1.2%)	0	1(0.6%)	0

Patient population: all randomized patients who received at least one dose of study drug.

Potentially nephrotoxic agents: [redacted] cisplatin, cyclosporine A, furosemide, gentamicin, pentamidine, tacrolimus, tobramycin, vancomycin, foscarnet sodium.

A significantly ($p < 0.001$) lower percentage of patients administered AmBisome received medication to treat reactions on Day 1 (43.5%, 37% and 73.1% for the low and high dose AmBisome and Abelcet arms, respectively); or premedication to prevent, or medication to treat infusion-related reactions during the entire study (Tables 7 and 8) compared with those in the Abelcet group.

Meperidine was administered for the prophylaxis of infusion-related reactions to 33% of those in the Abelcet group versus 9% of those in the AmBisome groups. Meperidine as treatment for infusion-related reactions was administered to 71% of patients in the Abelcet group and 25% of patients in the AmBisome groups.

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Table 7: Common Premedications for the Prophylaxis of Infusion-related Reactions

	AmBisome			Abelcet 5 mg/kg/d
	3 mg/kg/d	5 mg/kg/d	BOTH	
Total number of patients	85	81	166	78
Number (%) of patients administered premedication	33 (38.8%)	36 (44.4%)	69 (41.6%)	57 (73.1%)
Drug by WHO name				
Diphenhydramine	25 (29.4%)	29 (35.8%)	54 (32.5%)	52 (66.7%)
Acetaminophen	27 (31.8%)	29 (35.8%)	56 (33.7%)	44 (56.4%)
Hydrocortisone	7 (8.2%)	12 (14.8%)	19 (11.4%)	28 (35.9%)
Pethidine (meperidine)	8 (9.4%)	7 (8.6%)	15 (9.0%)	26 (33.3%)
p-Value (Fisher's Exact Test)				
	<i>AmBisome 3 mg/kg/d vs. Abelcet</i>		<i>AmBisome 5 mg/kg/d vs. Abelcet</i>	
Any premedication	<i>P<0.001</i>		<i>P<0.001</i>	
Diphenhydramine	<i>P<0.001</i>		<i>P<0.001</i>	
Acetaminophen	<i>P=0.002</i>		<i>P=0.011</i>	
Hydrocortisone	<i>P<0.001</i>		<i>P=0.003</i>	
Pethidine (meperidine)	<i>P<0.001</i>		<i>P<0.001</i>	

Patient population: all randomized patients who received at least one dose of study drug.

Common: administered to at least 10% of patients in any treatment group. A patient may have been administered more than one premedication.

A statistically significant treatment difference was not observed for less frequently used premedications.

Table 8: Common Medications for the Treatment of Infusion-related Reactions

	AmBisome			Abelcet 5 mg/kg/d
	3 mg/kg/d	5 mg/kg/d	BOTH	
Total number of patients	85	81	166	78
Number (%) of patients administered medication	52 (61.2%)	52 (64.2%)	104 (62.7%)	70 (89.7%)
Drug by WHO name				
Acetaminophen	37 (43.5%)	38 (46.9%)	75 (45.2%)	51 (65.4%)
Pethidine (meperidine)	18 (21.2%)	24 (29.6%)	42 (25.3%)	55 (70.5%)
Diphenhydramine	13 (15.3%)	14 (17.3%)	27 (16.3%)	23 (29.5%)
Lorazepam	6 (7.1%)	10 (12.3%)	16 (9.6%)	5 (6.4%)
Hydrocortisone	3 (3.5%)	7 (8.6%)	10 (6.0%)	15 (19.2%)
p-Value (Fisher's Exact Test)				
	<i>AmBisome 3 mg/kg/d vs. Abelcet</i>		<i>AmBisome 5 mg/kg/d vs. Abelcet</i>	
Any medication	<i>P<0.001</i>		<i>P<0.001</i>	
Acetaminophen	<i>P=0.007</i>		<i>P=0.025</i>	
Pethidine (meperidine)	<i>P<0.001</i>		<i>P<0.001</i>	
Diphenhydramine	<i>P=0.037</i>		<i>P=0.091</i>	
Lorazepam	<i>P>0.999</i>		<i>P=0.279</i>	
Hydrocortisone	<i>P=0.002</i>		<i>P=0.067</i>	

Patient population: all randomized patients who received at least one dose of study drug.

Common: administered to at least 10% of patients in any treatment group. A patient may have been administered more than one medication.

A statistically significant treatment difference was not observed for less frequently used medications.

Reviewer's comments: *There was a significant difference between AmBisome and Abelcet in terms of medication usage to prevent or treat infusion-related reactions on day 1 and on subsequent days. The 4 most frequently used drugs in this study are the ones most widely used in clinical practice (acetaminophen, meperidine, diphenhydramine, and hydrocortisone), which gives the data more strength in terms of*

applicability. In particular, meperidine, an opiate and usually a drug of last resort, was used significantly less in the AmBisome arms than in the Abelcet arm.

Treatment Compliance and Study Drug Exposure

Study drug administration is summarized in Tables 9 and 10. As shown in Table 9, study drug administration was generally comparable among treatment groups.

Table 9: Study Drug Administration

	AmBisome		Abelcet 5 mg/kg/day
	3 mg/kg/d	5 mg/kg/d	
Total number of patients	85	81	78
Mean ± SD number of days on study drug	8.6±5.5	8.3±7.4	7.5±6.6
Maximum infusion duration during Days 1-5			
≤ 2 hours	9 (10.6%)	11 (13.6%)	10 (12.8%)
>2 - ≤ 3 hours	68 (80.0%)	69 (85.2%)	64 (82.1%)
>3 - ≤ 4 hours	5 (5.9%)	1 (1.2%)	4 (5.1%)
>4 hours	3 (3.5%)	0	0
Number of infusions per patient			
Mean ± SD	8.5±5.4	8.2±7.2	7.2±6.4
Median (range)	[REDACTED]		
Cumulative dose (mg/kg)			
Mean ± SD	25±15.9	40.6±36.7	35.3±31.9
Median (range)	[REDACTED]		

Patient population: all randomized patients who received at least one dose of study drug.
SD: standard deviation

Reviewer's comments: Patients who received study drug in ≤ 2 hours (and thus are more predisposed to infusion-related reactions) were well balanced among the 3 arms.

In the pharmacokinetic subset of patients, higher mean trough and maximum serum concentrations of amphotericin B were achieved with AmBisome compared with Abelcet (Table 10).

Table 10: Amphotericin B Concentration

	AmBisome		Abelcet 5 mg/kg/day
	3 mg/kg/d	5 mg/kg/d	
Total number of patients	26	24	18
Mean ± SD Concentration (mcg/ml)	8.6±5.5	8.3±7.4	7.5±6.6
Trough Day 3	1.6±0.9	4.1±3.9	0.9±0.4
Maximum Day 3 (15 min postinfusion)	16.5±9.0	32.1±21.4	2.1±0.7
Trough Day 4	2.3±2.5	3.2±1.9	0.9±0.4

Patient population: all randomized patients who received at least one dose of study drug and were included in the pharmacokinetic subset of patients
[REDACTED]

Reviewer's comments: Higher serum concentrations of Amphotericin B achieved with AmBisome may possibly be due to a faster tissue penetration of Abelcet.

and do not necessarily mean that AmBisome has a more favorable pharmacokinetic profile.

4.2 Efficacy

Efficacy Endpoints

Success rates, as well as treatment difference (AmBisome minus Abelcet) and 95% confidence intervals around the difference in success rates, are summarized in Table 11. There was no statistically significant difference between AmBisome and Abelcet treatment groups with respect to the composite success rate. No statistically significant differences between AmBisome and Abelcet treatment groups were observed with respect to five of the six components of failure (incidence of fever after resolution of neutropenia, nonresponse of baseline fungal infections, emergent fungal infection, requirement for other systemic antifungal agents or death related to fungal infection). However, significantly fewer patients administered AmBisome prematurely discontinued drug therapy due to toxicity compared with those in the Abelcet group (Table 11).

Table 11: Success Rate

	AmBisome			Abelcet 5 mg/kg/d
	3 mg/kg/d	5 mg/kg/d	BOTH	
Total number of patients	85	81	166	78
Success	34 (40.0%)	34 (42.0%)	68 (41.0%)	26 (33.3%)
Failure [†]	51 (60.0%)	47 (58.0%)	98 (59.0%)	52 (66.7%)
Fever after resolution of neutropenia	34 (40.0%)	24 (29.6%)	58 (34.9%)	21 (26.9%)
Persistent or progressive proven baseline fungal infection	1 (1.2%)	0	1 (0.6%)	0
Emergent fungal infection	2 (2.4%)	2 (2.5%)	4 (2.4%)	3 (3.8%)
Required other systemic antifungal agents	5 (5.9%)	4 (4.9%)	9 (5.4%)	4 (5.1%)
Drug discontinued due to toxicity	11 (12.9%)	10 (12.3%)	21 (12.7%)	25 (32.1%)
Death related to fungal infection	1 (1.2%)	0	1 (0.6%)	3 (3.8%)
	<i>AmBisome BOTH vs. Abelcet</i>	<i>AmBisome 3 mg/kg vs. Abelcet</i>	<i>AmBisome 5 mg/kg vs. Abelcet</i>	
<i>Difference in success rates (AmBisome-Abelcet) and 95% Confidence Intervals</i>	7.6% (-5.2%, +20.5%)	6.7% (-8.1%, +21.4%)	8.6% (-6.4%, +23.6%)	
	<i>p-Value (Fisher's Exact Test)</i>			
	<i>AmBisome BOTH vs. Abelcet</i>	<i>AmBisome 3 mg/kg vs. Abelcet</i>	<i>AmBisome 5 mg/kg vs. Abelcet</i>	
<i>Drug discontinued due to toxicity[†]</i>	<i>p=0.001</i>	<i>p=0.004</i>	<i>p=0.004</i>	

Patient population: all randomized patients who received at least one dose of study drug.

Note: some patients may qualify under more than one component of failure.

[†] A statistically significant treatment difference at the 0.05 level was observed only for the failure component "drug discontinued due to toxicity" (discontinuation due to an adverse event or infusion-related reaction).

Six infections were identified at baseline in five patients; three proven infections (one in the AmBisome 3 mg/kg/d group and 2 in the Abelcet group) and 3 probable infections (one in the AmBisome 3 mg/kg per day group and 2 in the AmBisome 5 mg/kg/d group). Of these six infections, one proven infection and one probable infection progressed

throughout the treatment period (both in the AmBisome 3 mg/kg per day group). A total of seven patients had an emergent fungal infection, four administered AmBisome and three administered Abelcet. There were nine emergent fungal infections identified in these seven patients as follows: AmBisome 3 mg/kg/d group: 2 patients; 2 proven infections; AmBisome 5 mg/kg/d group: 2 patients; 1 proven and 2 probable infections; Abelcet 5 mg/kg/d group: 3 patients; 2 proven and 2 probable infections. Infection pathogens included *Acremonium*, *Aspergillus* species, *Aspergillus fumigatus*, and *Candida albicans*. In addition, one patient (AmBisome 3 mg/kg per day group) developed a probable fungal infection (unknown pathogen); however, the investigator did not record the presence of a treatment-emergent fungal infection on the failure criteria sheet of the case report form.

Seven (4.2%) patients administered AmBisome and 11 (14.1%) patients administered Abelcet died while on study. Of these 18 deaths, 0/7 in the AmBisome group and 4/11 in the Abelcet group occurred during the treatment period. Fungal infection was a primary or contributing cause of death for four of these 18 patients, one in the 3 mg/kg per day AmBisome group and three in the Abelcet group.

Efficacy Conclusions

No statistically significant treatment differences were observed with respect to success or five of the six components of failure. Significantly ($p \leq 0.004$) fewer patients administered AmBisome were treatment failures due to toxicity related discontinuation of therapy compared with those in the Abelcet group.

Reviewer's comments: Since this study was not powered to detect a treatment difference between the 2 drugs, no firm conclusions can be drawn from these efficacy data. However, the difference in the rates of drug discontinuation due to toxicity does suggest a better tolerability profile for AmBisome and possibly a higher efficacy rate.

4.3 Safety

Primary Endpoint: Chills/Rigors on Day 1

The primary endpoint was the incidence of infusion-related chills/rigors on Day 1. As presented in Table 12, there was a significantly ($p < 0.001$, applicant's analysis) lower incidence of chills/rigors on Day 1 for patients administered AmBisome (individual dose groups and combined) compared with those administered Abelcet. A similar result was observed in the per protocol population analysis. In addition, a lower incidence of chills/rigors on Day 1 was evident regardless of age, sex, receipt of bone marrow transplant or transplant type, or the use of immunosuppressants.

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Table 12: Infusion-related Chills/Rigors on Day 1

	AmBisome			Abelcet 5 mg/kg/d
	3 mg/kg/d	5 mg/kg/d	BOTH	
Total number of patients	85	81	166	78
Patients with Chills/Rigors (Day 1)	16 (18.8%)	19 (23.5%)	35 (21.1%)	62 (79.5%)
Chills/Rigors by age				
<16 years	4/15 (26.7%)	3/14 (21.4%)	7/29 (24.1%)	8/13 (61.5%)
≥16 years	12/70 (17.1%)	16/67 (23.9%)	28/137 (20.4%)	54/65 (83.1%)
Chills/Rigors by sex				
Male	9/51 (17.6%)	11/38 (28.9%)	20/89 (22.5%)	29/41 (70.7%)
Female	7/34 (20.6%)	8/43 (18.6%)	15/77 (19.5%)	33/37 (89.2%)
Chills/Rigors by BMT				
Without BMT	10/46 (21.7%)	8/41 (19.5%)	18/87 (20.7%)	30/38 (78.9%)
With BMT	6/39 (15.4%)	11/40 (27.5%)	17/79 (21.5%)	32/40 (80.0%)
Autologous	2/25 (8.0%)	8/26 (30.8%)	10/51 (19.6%)	22/28 (78.6%)
Allogeneic	3/13 (23.1%)	3/13 (23.1%)	6/26 (23.1%)	10/12 (83.3%)
Syngeneic	1/1 (100%)	0/1	1/2 (50.0%)	0/0
Chills/Rigors by risk [†]				
High risk	3/13 (23.1%)	3/11 (27.3%)	6/24 (25.0%)	9/11 (81.8%)
Low risk	13/72 (18.1%)	16/70 (22.9%)	29/142 (20.4%)	53/67 (79.1%)
	<i>p-Value (Fisher's Exact Test)</i>			
	<i>AmBisome BOTH vs. Abelcet</i>	<i>AmBisome 3 mg/kg vs. Abelcet</i>	<i>AmBisome 5 mg/kg vs. Abelcet</i>	
<i>Chills/Rigors (Day 1)</i>	<i>p<0.001</i>	<i>p<0.001</i>	<i>p<0.001</i>	

Patient population: all randomized patients who received at least one dose of study drug.

Patients were not administered premedications to prevent infusion-related reactions prior to the Day 1 study drug infusion.

[†] High risk: use of the immunosuppressant tacrolimus or cyclosporine; Low risk: nonuse of tacrolimus or cyclosporine.

BMT: bone marrow transplant

Reviewer's comments: Reviewer agrees with the data presented in this table per the datasets. The incidence of chills/rigors in the per protocol population was 17% (13/76), 26% (18/70) and 80% (55/69) in the low dose AmBisome, high dose AmBisome and Abelcet groups respectively, with $p<0.001$ (FDA's analysis) for either AmBisome group and the combined group when compared with Abelcet.

Secondary Endpoint: Nephrotoxicity

The secondary endpoint in this safety study was the incidence of nephrotoxicity. As presented in Table 13, the incidence of nephrotoxicity by all measures was significantly ($p<0.001$, applicant's analysis) lower for patients administered AmBisome (individual dose groups and combined) compared with Abelcet. Lower nephrotoxicity was evident regardless of age, sex, receipt of bone marrow transplant, transplant type, or use of immunosuppressants.

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Table 13: Nephrotoxicity

	AmBisome			Abelcet 5 mg/kg/d
	3 mg/kg/d	5 mg/kg/d	BOTH	
Total number of patients	85	81	166	78
Number with nephrotoxicity				
1.5X	25 (29.4%)	21 (25.9%)	46 (27.7%)	49 (62.8%)
2X	12 (14.1%)	12 (14.8%)	24 (14.5%)	33 (42.3%)
Peak Creatinine (mg/dl)				
Mean ± SD	1.3 ± 1.0	1.2 ± 0.6	1.2 ± 0.8	1.8 ± 1.2
Median (range)				
Change from baseline to peak serum creatinine value (mg/dl)				
Mean ± SD	0.5 ± 0.8	0.4 ± 0.4	0.5 ± 0.7	1.0 ± 1.0
Median (range)				
	<i>p-Value (Chi-squared Test, Analysis of Variance)</i>			
	<i>AmBisome BOTH vs. Abelcet</i>	<i>AmBisome 3 mg/kg vs. Abelcet</i>	<i>AmBisome 5 mg/kg vs. Abelcet</i>	
1.5X	<i>p<0.001</i>	<i>p<0.001</i>	<i>p<0.001</i>	
2X	<i>p<0.001</i>	<i>p<0.001</i>	<i>p<0.001</i>	
Peak Creatinine	<i>p<0.001</i>	<i>P=0.001</i>	<i>p<0.001</i>	
Change from baseline to peak serum creatinine	<i>p<0.001</i>	<i>p<0.001</i>	<i>p<0.001</i>	

Patient population: all randomized patients who received at least one dose of study drug.

Nephrotoxicity: adults (≥16 years of age), serum creatinine > 1.2 mg/dl and either > 1.5 times or >2 times baseline value (1.5X or 2X); pediatric patients (<16 years of age), serum creatinine > 1.5 times or >2 times baseline value (1.5X or 2X).

SD: standard deviation.

A higher percentage of patients in the Abelcet group had peak creatinine greater than 2.5 mg/dl (17.9%), or greater than 3 mg/dl (12.8%), than that in the combined AmBisome group (5.4%, 4.2%, respectively) or in either the 3 mg/kg per day (7.1%, 7.1%, respectively) or 5 mg/kg per day (3.7%, 1.2%, respectively) AmBisome group.

Reviewer's comments: Reviewer agrees with the data presented in this table per the datasets. All p values were verified by the FDA statistical reviewer.

Other Safety Variables: Adverse Events

Nearly all patients experienced at least one adverse event during the study period. There were no statistically significant differences in the overall incidence of adverse events between AmBisome and Abelcet treatment groups. However, statistically significant differences between AmBisome and Abelcet treatment groups were observed for some individual events as summarized in Table 14.

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Table 14: Adverse Events: Test for Significance

		Incidence and p-Value (Fisher's Exact Test)	
		AmBisome 3 mg/kg vs. Abelcet	AmBisome 5 mg/kg vs. Abelcet
Body As A Whole	Chills [chills/rigors]	40.0% vs. 89.7% p<0.001	48.1% vs. 89.7% p<0.001
Cardiovascular System	Hypertension	10.6% vs. 23.1% p=0.037	19.8% vs. 23.1% p=0.700
	Hypotension	10.6% vs. 19.2% p=0.129	7.4% vs. 19.2% p=0.035
	Tachycardia	9.4% vs. 23.1% p=0.020	18.5% vs. 23.1% p=0.559
Metabolic & Nutritional	Creatinine Increased	20.0% vs. 48.7% p<0.001	18.5% vs. 48.7% p<0.001
Nervous System	Confusion	12.9% vs. 3.8% p=0.050	8.6% vs. 3.8% p=0.329
Respiratory System	Hypoxia	7.1% vs. 20.5% p=0.020	6.2% vs. 20.5% p=0.009
	Hyperventilation	3.5% vs. 9.0% p=0.197	1.2% vs. 9.0% p=0.032
	Asthma	0 vs. 5.1% p=0.050	1.2% vs. 5.1% p=0.204

Patient population: all randomized patients who received at least one dose of study drug.

Adverse events are those reported anytime during the entire study period. There were no statistically significant treatment differences for adverse events not represented in the table.

Patients administered AmBisome (3 mg/kg per day and/or 5 mg/kg per day) had a statistically lower incidence of chills, hypertension, hypotension, tachycardia, increased creatinine, hypoxia, hyperventilation and asthma than those administered Abelcet. These adverse events were 2.5 to 13 times more frequent for patients in the Abelcet group compared with those administered AmBisome. Confusion was more common (nearly 4 times more frequent) with 3 mg/kg per day AmBisome than with Abelcet.

Reviewer's comments: Patients administered AmBisome 3 mg/kg per day had a statistically significant lower incidence of chills, hypertension, tachycardia, increased creatinine, hypoxia, and asthma than those administered Abelcet. Patients administered AmBisome 5 mg/kg per day had a statistically significant lower incidence of chills, hypotension, increased creatinine, hypoxia and hyperventilation. The only events that occurred at a statistically significant lower incidence in both AmBisome groups were chills, increased creatinine and hypoxia. The difference in the incidence of confusion was not statistically significant. All p values were verified by the FDA statistical reviewer.

Infusion-related Reactions

The overall incidence of infusion-related events on Day 1, as well as for individual infusion-related events other than chills/rigors, was significantly lower for patients administered AmBisome compared with Abelcet (Tables 15 and 16). Fever, chills/rigors

and hypoxia were significantly lower for each AmBisome group compared with the Abelcet group. The infusion-related event hypoxia was reported for 11.5% of Abelcet-treated patients compared with 0% of patients administered 3 mg/kg per day AmBisome and 1.2% of patients treated with 5 mg/kg per day AmBisome (Table 16). After Day 1, when premedication to prevent infusion-related reactions was permitted, the overall incidence of infusion-related reactions was still statistically different between AmBisome and Abelcet treatment groups (Table 17) ($p=0.043$, applicant's analysis). The incidence of chills (3 mg/kg and 5 mg/kg groups) remained significantly lower for patients administered AmBisome ($p=0.001$ for each of the AmBisome groups, applicant's analysis) compared with those administered Abelcet. Tachycardia also occurred at a statistically significant lower incidence in the 3mg/kg/d AmBisome group.

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Table 15: Infusion-related Reactions on Day 1

	AmBisome			Abelcet
	3 mg/kg/day	5 mg/kg/day	BOTH	5 mg/kg/day
Total number of patients	85	81	166	78
Total number with IRR ¹	44 (51.8%)	39 (48.1%)	83 (50.0%)	69 (88.5%)
Patients with fever				
≥0.3°C increase in temperature	47 (55.3%)	43 (53.1%)	90 (54.2%)	64 (82.1%)
≥0.6°C increase in temperature	37 (43.5%)	29 (35.8%)	66 (39.8%)	58 (74.4%)
≥1.0°C increase in temperature	20 (23.5%)	16 (19.8%)	36 (21.7%)	45 (57.7%)
Patients with nausea	9 (10.6%)	7 (8.6%)	16 (9.6%)	9 (11.5%)
Patients with vomiting	5 (5.9%)	5 (6.2%)	10 (6.0%)	11 (14.1%)
Patients with other significant reactions ²	16 (18.8%)	21 (25.9%)	37 (22.3%)	32 (41.0%)
	<i>p-Value (Chi-squared Test)</i>			
	<i>AmBisome BOTH vs. Abelcet</i>	<i>AmBisome 3 mg/kg vs. Abelcet</i>	<i>AmBisome 5 mg/kg vs. Abelcet</i>	
Total number with IRR ¹	<i>p<0.001</i>	<i>p<0.001</i>	<i>p<0.001</i>	
Patients with fever				
≥0.3°C increase in temperature	<i>p<0.001</i>	<i>p<0.001</i>	<i>p<0.001</i>	
≥0.6°C increase in temperature	<i>p<0.001</i>	<i>p<0.001</i>	<i>p<0.001</i>	
≥1.0°C increase in temperature	<i>p<0.001</i>	<i>p<0.001</i>	<i>p<0.001</i>	
Patients with nausea	<i>p=0.648</i>	<i>p=0.847</i>	<i>p=0.544</i>	
Patients with vomiting	<i>p=0.036</i>	<i>p=0.078</i>	<i>p=0.097</i>	
Patients with other significant reactions ²	<i>p=0.002</i>	<i>p=0.002</i>	<i>p=0.043</i>	

Patient population: all randomized patients who received at least one dose of study drug. Patients were not administered premedications to prevent infusion related reactions prior to the Day 1 study drug infusion. IRR: infusion related reaction. Patients could be included in more than one category. Fever temperature categories are not mutually exclusive.

¹The most conservative definition of fever was used for reporting the total number of IRRs (i.e., a ≥1.0°C increase in temperature).

²Other reactions included pain, hypertension, tachycardia, chest pain, vasodilatation, hypotension, etc.

Table 16: Other Common Infusion-related Reactions (Day 1)

		Incidence and p-Value (Fisher's Exact Test)	
		AmBisome 3 mg/kg vs. Abelcet	AmBisome 5 mg/kg vs. Abelcet
Cardiovascular	Hypertension	4.7% vs. 15.4% <i>p=0.033</i>	8.6% vs. 15.4% <i>p=0.226</i>
	Tachycardia	2.4% vs. 17.9% <i>p=0.001</i>	9.9% vs. 17.9% <i>p=0.171</i>
Respiratory	Dyspnea	4.7% vs. 10.3% <i>p=0.233</i>	9.9% vs. 10.3% <i>>0.999</i>
	Hypoxia	0 vs. 11.5% <i>p=0.001</i>	1.2% vs. 11.5% <i>p=0.008</i>

Patient population: all randomized patients who received at least one dose of study drug.

Other: other than chills/rigors, fever, nausea, vomiting.

Common: experienced by at least 10% of patients in any treatment group

Table 17: Infusion-related Reactions on >Day 1

	AmBisome			Abelcet 5 mg/kg/day
	3 mg/kg/day	5 mg/kg/day	BOTH	
Total number of patients	85	81	166	78
Patients with infusion related reactions ¹	47 (55.3%)	39 (48.1%)	86 (51.8%)	51 (65.4%)
Patients with chills/rigors	21 (24.7%)	21 (25.9%)	42 (25.3%)	40 (51.3%)
Patients with fever				
≥0.3°C increase in temperature	59 (69.4%)	58 (71.6%)	117 (70.5%)	57 (73.1%)
≥0.6°C increase in temperature	45 (52.9%)	44 (54.3%)	89 (53.6%)	46 (59.0%)
≥1.0°C increase in temperature	19 (22.4%)	28 (34.6%)	47 (28.3%)	34 (43.6%)
Patients with nausea	9 (10.6%)	14 (17.3%)	23 (13.9%)	10 (12.8%)
Patients with vomiting	7 (8.2%)	8 (9.9%)	15 (9.0%)	8 (10.3%)
Patients with other significant reactions ²	25 (29.4%)	16 (19.8%)	41 (24.7%)	26 (33.3%)

1 Patient population: all randomized patients who received at least one dose of study drug.

2 Patients were permitted premedication to prevent infusion related reactions after the Day 1 study drug infusion.

3 Patients could be included in more than one category. Fever temperature categories are not mutually exclusive.

4 Overall incidence of infusion related reactions was determined using the most conservative definition of fever (i.e., a ≥1.0°C increase in temperature).

5 Other reactions included asthenia, back pain, hypertension, hypotension, tachycardia, etc.

Reviewer's comments: For day 1, fever and hypoxia were the only individual reactions that occurred at a statistically significant lower rate in either AmBisome arm than with Abelcet. The difference in the incidence of tachycardia and hypertension was statistically significant between the low dose AmBisome and Abelcet arms. All p values were verified by the FDA statistical reviewer.

Other Adverse Events

Common non-infusion-related adverse events are summarized in Table 18. The renal event "creatinine increased" was significantly (p<0.001, applicant's analysis) lower in each of the AmBisome groups (20.0%, 18.5%) compared with Abelcet (48.7%). Of the remaining non-infusion-related events, rash was numerically less frequent in Abelcet-treated patients (11.5%) compared with those treated with either AmBisome 3 mg/kg per day (23.5%) or AmBisome 5 mg/kg per day (22.2%).

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Table 18: Common Non-Infusion Related Adverse Events

	AmBisome			Abelcet
	3 mg/kg/day	5 mg/kg/day	BOTH	5 mg/kg/day
Total number of patients	85	81	166	78
Number of patients with a non-infusion related adverse event	82 (96.5%)	77 (95.1%)	159 (95.8%)	78 (100.0%)
Body As A Whole				
Abdominal Pain	11 (12.9%)	8 (9.9%)	19 (11.4%)	9 (11.5%)
Sepsis	11 (12.9%)	6 (7.4%)	17 (10.2%)	9 (11.5%)
Chills [chills/rigors]	9 (10.6%)	16 (19.8%)	25 (15.1%)	8 (10.3%)
Transfusion Reaction	9 (10.6%)	7 (8.6%)	16 (9.6%)	4 (5.1%)
Asthenia	6 (7.1%)	5 (6.2%)	11 (6.6%)	9 (11.5%)
Cardiovascular				
Hypotension	8 (9.4%)	4 (4.9%)	12 (7.2%)	12 (15.4%)
Digestive				
Diarrhea	12 (14.1%)	14 (17.3%)	26 (15.7%)	11 (14.1%)
Nausea	11 (12.9%)	7 (8.6%)	18 (10.8%)	14 (17.9%)
Vomiting	11 (12.9%)	11 (13.6%)	22 (13.3%)	10 (12.8%)
Liver Function Test Abnormal	9 (10.6%)	6 (7.4%)	15 (9.0%)	9 (11.5%)
Metabolic/Nutritional				
Hypokalemia	32 (37.6%)	35 (43.2%)	67 (40.4%)	31 (39.7%)
Creatinine Increased	17 (20.0%)	15 (18.5%)	32 (19.3%)	38 (48.7%)
BUN Increased	17 (20.0%)	15 (18.5%)	32 (19.3%)	22 (28.2%)
Bilirubinemia	14 (16.5%)	9 (11.1%)	23 (13.9%)	9 (11.5%)
Hypomagnesemia	13 (15.3%)	21 (25.9%)	34 (20.5%)	12 (15.4%)
Edema	11 (12.9%)	10 (12.3%)	21 (12.7%)	10 (12.8%)
Hypocalcemia	9 (10.6%)	4 (4.9%)	13 (7.8%)	4 (5.1%)
Hypervolemia	7 (8.2%)	9 (11.1%)	16 (9.6%)	11 (14.1%)
Hyperglycemia	7 (8.2%)	7 (8.6%)	14 (8.4%)	11 (14.1%)
Alkaline Phosphatase Increased	6 (7.1%)	7 (8.6%)	13 (7.8%)	10 (12.8%)
Nervous				
Confusion	9 (10.6%)	7 (8.6%)	16 (9.6%)	2 (2.6%)
Anxiety	9 (10.6%)	5 (6.2%)	14 (8.4%)	7 (9.0%)
Headache	4 (4.7%)	10 (12.3%)	14 (8.4%)	5 (6.4%)
Respiratory				
Lung Disorder	12 (14.1%)	10 (12.3%)	22 (13.3%)	10 (12.8%)
Dyspnea	12 (14.1%)	10 (12.3%)	22 (13.3%)	9 (11.5%)
Epistaxis	8 (9.4%)	7 (8.6%)	15 (9.0%)	11 (14.1%)
Skin/Appendages				
Rash	20 (23.5%)	18 (22.2%)	38 (22.9%)	9 (11.5%)
	<i>p-Value (Fisher's Exact Test)</i>			
	<i>AmBisome 3 mg/kg vs. Abelcet</i>		<i>AmBisome 5 mg/kg vs. Abelcet</i>	
<i>Creatinine Increased</i>	<i>p<0.001</i>		<i>p<0.001</i>	
<i>Hypotension</i>	<i>p=0.340</i>		<i>p=0.035</i>	

Patient population: all randomized patients who received at least one dose of study drug. Common: experienced by at least 10% of patients in any treatment group. Adverse events are those reported anytime during the entire study period. BUN: Blood urea nitrogen. There were no statistically significant treatment differences for less common non-infusion related events.

Deaths, Other Serious Adverse Events, and Adverse Events Resulting in Discontinuation

A total of 18 patients died during the course of the study; causes of death for these patients are listed in Table 19. The causes of death are consistent with the underlying diseases of the patient population under study. In 14 of the 18 cases, death occurred during the 1-week follow-up period (within 1 week after discontinuation of study drug). There was significantly ($p=0.009$, applicant's analysis, Fisher's exact test) less mortality associated with AmBisome (combined and 5 mg/kg per day group) compared with Abelcet.

Table 19: Causes of Death

AmBisome 3 mg/kg Group	
Number of Deaths/Total Patients	5/85 (5.9%)
Number of Patients	Cause of Death
1	<i>Candida krusei</i> sepsis/fungemia [†]
1	Veno-occlusive disease
1	Retroperitoneal hemorrhage
1	Adult respiratory distress syndrome
1	Refractory acute myelogenous leukemia
AmBisome 5 mg/kg Group	
Number of Deaths/Total Patients	2/81 (2.5%)
Number of Patients	Cause of Death
1	Sepsis with bacteremia
1	Relapse of acute myelogenous leukemia
Abelcet 5 mg/kg Group	
Number of Deaths/Total Patients	11/78 (14.1%)
Number of Patients	Cause of Death
1	Disseminated candidiasis [†]
1	Cardiopulmonary arrest [†]
1	Respiratory failure [†]
1	Viral pneumonia
1	Septicemia
1	Cardiopulmonary arrest
1	Cyclophosphamide-induced myocarditis
1	Sepsis
1	Refractory acute lymphoblastic leukemia
1	Respiratory failure
1	Small cell lymphocytic lymphoma

Patient population: all randomized patients who received at least one dose of study drug.

Deaths are those that occurred during the study period. One patient in the AmBisome 3 mg/kg group died due to acute lymphoblastic leukemia 11 days after receiving the last dose of study drug and is not included in this table.

[†] Fungal infection was listed as the primary or contributing cause of death

Reviewer's comments: Death narratives were reviewed. Study drugs did not seem to be the cause of death in any of the cases. Death rates were 5.5%, 2.5% and 14.1% in the low and high AmBisome and Abelcet groups respectively. Among patients who died, there were 8 patients with acute leukemia in the Abelcet arm, compared with 2 in the low dose and one in the high dose AmBisome arms. Although there were proportionately more patients with bone marrow transplant or lymphoma enrolled in the Abelcet arm, these differences did not explain the higher mortality in the Abelcet arm.

A significantly ($p < 0.001$, applicant's analysis) greater percentage of patients in the Abelcet group experienced a severe/life-threatening event during the course of the study compared with the AmBisome groups (Table 20). The incidence of severe/life-threatening fever, and chills was significantly ($p \leq 0.002$, applicant's analysis) higher in the Abelcet group than in either the AmBisome 5 mg/kg per day group or the AmBisome 3 mg/kg per day group. Serious adverse events are shown in Table 21. A significantly higher ($p \leq 0.027$, applicant's analysis) percentage of patients in the Abelcet group experienced a serious adverse event during the study compared with each AmBisome group. The incidence of serious hypoxia and acute kidney failure was significantly higher ($p = 0.027$, applicant's analysis) in the Abelcet group than the AmBisome 5 mg/kg

per day group. There were no significant differences in the incidence of any individual serious adverse event in the Abelcet group compared with the AmBisome 3 mg/kg per day group.

Table 20: Incidence of Common Severe/Life-threatening Adverse Events

	AmBisome			Abelcet
	3 mg/kg/day	5 mg/kg/day	BOTH	5 mg/kg/day
Total number of patients	85	81	166	78
Number with adverse event	42 (49.4%)	32 (39.5%)	74 (44.6%)	61 (78.2%)
Body as a whole				
Fever	10 (11.8%)	6 (7.4%)	16 (9.6%)	29 (37.2%)
Chills	6 (7.1%)	9 (11.1%)	15 (9.0%)	25 (32.1%)
Sepsis	2 (2.4%)	3 (3.7%)	5 (3.0%)	5 (6.4%)
Cardiovascular				
Hypotension	2 (2.4%)	1 (1.2%)	3 (1.8%)	6 (7.7%)
Tachycardia	0	2 (2.5%)	2 (1.2%)	3 (3.8%)
Digestive				
Vomiting	1 (1.2%)	3 (3.7%)	4 (2.4%)	3 (3.8%)
Nausea	0	2 (2.5%)	2 (1.2%)	3 (3.8%)
Metabolic/Nutritional				
Bilirubinemia	5 (5.9%)	0	5 (3.0%)	1 (1.3%)
Hypokalemia	3 (3.5%)	2 (2.5%)	5 (3.0%)	8 (10.3%)
BUN increased	3 (3.5%)	0	3 (1.8%)	1 (1.3%)
Creatinine increased	2 (2.4%)	0	2 (1.2%)	4 (5.1%)
Respiratory				
Dyspnea	4 (4.7%)	2 (2.5%)	6 (3.6%)	6 (7.7%)
Respiratory failure	3 (3.5%)	1 (1.2%)	4 (2.4%)	4 (5.1%)
Lung edema	3 (3.5%)	0	3 (1.8%)	1 (1.3%)
Pneumonia	2 (2.4%)	4 (4.9%)	6 (3.6%)	3 (3.8%)
Lung disorder	2 (2.4%)	0	2 (1.2%)	4 (5.1%)
Hypoxia	1 (1.2%)	1 (1.2%)	2 (1.2%)	5 (6.4%)
Apnea	0	0	0	3 (3.8%)
Urogenital				
Acute kidney failure	2 (2.4%)	1 (1.2%)	3 (1.8%)	6 (7.7%)
Kidney failure	2 (2.4%)	1 (1.2%)	3 (1.8%)	3 (3.8%)
	<i>p-Values (Fisher's Exact Test)</i>			
	<i>AmBisome 3 mg/kg vs. Abelcet</i>		<i>AmBisome 5 mg/kg vs. Abelcet</i>	
Number of patients with any event	<i>p<0.001</i>		<i>p<0.001</i>	
Body as a whole	<i>p<0.001</i>		<i>p<0.001</i>	
Fever	<i>p<0.001</i>		<i>p<0.001</i>	
Chills	<i>p<0.001</i>		<i>p=0.002</i>	

Patient population: all randomized patients who received at least one dose of study drug. Adverse events are those reported anytime during the entire study period. Events include infusion-related reactions. Common: experienced by at least 3% of patients in any treatment group. There were no statistically significant treatment differences for less common events.

Table 21: Incidence of Common Serious Adverse Events

	AmBisome			Abelcet
	3 mg/kg/day	5 mg/kg/day	BOTH	5 mg/kg/day
Total number of patients	85	81	166	78
Number with serious adverse event	14 (16.5%)	10 (12.3%)	24 (14.5%)	25 (32.1%)
Body as a Whole				
Sepsis	1 (1.2%)	0	1 (0.6%)	3 (3.8%)
Chills (chills/rigors)	1 (1.2%)	0	1 (0.6%)	2 (2.6%)
Cardiovascular				
Atrial fibrillation	1 (1.2%)	1 (1.2%)	2 (1.2%)	0
Tachycardia	1 (1.2%)	1 (1.2%)	2 (1.2%)	0
Hypotension	0	0	0	3 (3.8%)
Heart arrest	0	0	0	2 (2.6%)
Nervous				
Convulsion	0	0	0	2 (2.6%)
Respiratory				
Dyspnea	3 (3.5%)	1 (1.2%)	4 (2.4%)	4 (5.1%)
Respiratory failure	2 (2.4%)	1 (1.2%)	3 (1.8%)	4 (5.1%)
Pneumonia	2 (2.4%)	1 (1.2%)	3 (1.8%)	2 (2.6%)
Pleural effusion	1 (1.2%)	1 (1.2%)	2 (1.2%)	0
Hypoxia	1 (1.2%)	0	1 (0.6%)	5 (6.4%)
Lung hemorrhage	0	1 (1.2%)	1 (0.6%)	2 (2.6%)
Apnea	0	0	0	3 (3.8%)
Respiratory distress syndrome	0	0	0	2 (2.6%)
Urogenital				
Kidney failure	2 (2.4%)	1 (1.2%)	3 (1.8%)	3 (3.8%)
Acute kidney failure	2 (2.4%)	0	2 (1.2%)	5 (6.4%)
	<i>p-Values (Fisher's Exact Test)</i>			
	<i>AmBisome 3 mg/kg vs. Abelcet</i>		<i>AmBisome 5 mg/kg vs. Abelcet</i>	
Number of patients with any serious adverse event	<i>p=0.027</i>		<i>p=0.004</i>	
Respiratory Hypoxia	<i>p=0.105</i>		<i>p=0.027</i>	
Urogenital Acute kidney failure	<i>p=0.261</i>		<i>p=0.027</i>	

Patient population: all randomized patients who received at least one dose of study drug.

Adverse events are those reported anytime during the entire study period.

Events include infusion related reactions.

Common: experienced by a total of at least two patients in either the combined AmBisome or Abelcet treatment groups. There were no statistically significant treatment differences for less common events.

A significantly higher ($p=0.004$, applicant's analysis) percentage of patients in the Abelcet group discontinued the study drug due to an adverse event than in the AmBisome groups (Table 22). The incidence of discontinuations due to increased creatinine was significantly higher ($p\leq 0.049$, applicant's analysis) in the Abelcet group than in the AmBisome 5 mg/kg per day group or the AmBisome 3 mg/kg per day group. In addition, the incidence of discontinuation was significantly higher in the Abelcet group than in the AmBisome 3 mg/kg per day group due to fever ($p=0.023$, applicant's analysis) and in the AmBisome 5 mg/kg per day group due to hypoxia ($p=0.013$, applicant's analysis).

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Table 22: Common Adverse Events Leading to Discontinuation

	AmBisome			Abelcet
	3 mg/kg/day	5 mg/kg/day	BOTH	5 mg/kg/day
Total Number Of Patients	85	81	166	78
Number Discontinued Due To Adverse Event	11 (12.9%)	10 (12.3%)	21 (12.7%)	25 (32.1%)
Body As A Whole				
Sepsis	2 (2.4%)	0	2 (1.2%)	2 (2.6%)
Chills	1 (1.2%)	1 (1.2%)	2 (1.2%)	5 (6.4%)
Fever	0	1 (1.2%)	1 (0.6%)	5 (6.4%)
Cardiovascular				
Chest Pain	1 (1.2%)	2 (2.5%)	3 (1.8%)	0
Vasodilatation	0	2 (2.5%)	2 (1.2%)	1 (1.3%)
Digestive				
Nausea	0	2 (2.5%)	2 (1.2%)	0
Vomiting	0	2 (2.5%)	2 (1.2%)	0
Metabolic/Nutritional				
Creatinine Increased	2 (2.4%)	1 (1.2%)	3 (1.8%)	8 (10.3%)
Bilirubinemia	2 (2.4%)	0	2 (1.2%)	0
Respiratory				
Dyspnea	1 (1.2%)	3 (3.7%)	4 (2.4%)	4 (5.1%)
Hypoxia	1 (1.2%)	0	1 (0.6%)	6 (7.7%)
Hyperventilation	0	0	0	2 (2.6%)
Urogenital				
Acute Kidney Failure	1 (1.2%)	1 (1.2%)	2 (1.2%)	4 (5.1%)
Kidney Failure	1 (1.2%)	1 (1.2%)	2 (1.2%)	1 (1.3%)
	<i>p-Value (Fisher's Exact Test)</i>			
	<i>AmBisome 3 mg/kg vs. Abelcet</i>		<i>AmBisome 5 mg/kg vs. Abelcet</i>	
Discontinued due to an adverse event	<i>p=0.004</i>		<i>p=0.004</i>	
Fever	<i>p=0.023</i>		<i>p=0.112</i>	
Creatinine Increased	<i>p=0.049</i>		<i>p=0.016</i>	
Hypoxia	<i>p=0.055</i>		<i>p=0.013</i>	

Patient population: all randomized patients who received at least one dose of study drug.

Discontinuation: discontinuation of study drug. Common: experienced by a total of at least two patients in either the combined AmBisome or Abelcet treatment groups. There were no statistically significant treatment differences for less common events.

Reviewer's comments: The significantly different rates of serious and severe adverse events as well as discontinuations due to serious adverse events provide further reassurance as to a real difference in the safety profile of the 2 drugs.

Other Safety Variables: Clinical Laboratory Evaluation

Hepatotoxicity

There were no statistically significant differences between AmBisome and Abelcet treatment groups with respect to hepatotoxicity (Table 23).

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Table 23: Hepatotoxicity

		AmBisome			Abelcet
		3 mg/kg/day	5 mg/kg/day	BOTH	5 mg/kg/day
Total number of patients		85	81	166	78
Number with hepatotoxicity		11 (12.9%)	9 (11.1%)	20 (12.0%)	8 (10.3%)
Change from baseline to peak:					
AST (U/L)	N	69	68	137	67
	Mean ± SD	25.5±65.1	21.6±35.3	23.5±52.3	45.5±139.5
	Median	14.0	11.5	13.0	8.0
	Range				
ALT (U/L)	N	68	67	135	65
	Mean ± SD	27.3±87.1	26.3±40.2	26.8±67.7	34.2±119.3
	Median	10.5	13.0	12.0	5.0
	Range				
Total Bilirubin (mg/dL)	N	77	73	150	73
	Mean ± SD	1.1±2.9	0.6±1.5	0.9±2.3	0.7±2.1
	Median	0.3	0.2	0.2	0.3
	Range				

Patient population: all randomized patients who received at least one dose of study drug. ULN: upper limit of normal. Hepatotoxicity: an increase in AST (SGOT) or ALT (SGPT) to a value >5X baseline in cases where baseline is <2X ULN; or an increase to a value >3X baseline in cases where baseline is 2-5X ULN; or an increase to a value >2X baseline in cases where baseline is >5X ULN.

Reviewer's comments: Reviewer agrees that there is no statistically significant difference in hepatotoxicity, although mean changes in transaminase levels were higher for Abelcet.

Hypokalemia and Anemia

The incidence of hypokalemia and anemia is presented in Table 24.

Table 24: Hypokalemia and Anemia

	AmBisome			Abelcet
	3 mg/kg/d	5 mg/kg/d	BOTH	5 mg/kg/d
Total number of patients	85	81	166	78
Number with hypokalemia				
≤2.5 mmol/l	4 (4.7%)	6 (7.4%)	10 (6.0%)	9 (11.5%)
<3 mmol/l	19 (22.4%)	23 (28.4%)	42 (25.3%)	29 (37.2%)
Number with anemia†	31 (36.5%)	33 (40.7%)	64 (38.6%)	46 (59.0%)
	<i>p-Value (Chi-squared Test)</i>			
	<i>AmBisome BOTH vs. Abelcet</i>	<i>AmBisome 3 mg/kg vs. Abelcet</i>	<i>AmBisome 5 mg/kg vs. Abelcet</i>	
Number with hypokalemia‡	<i>P=0.070</i>	<i>P=0.041</i>	<i>P=0.310</i>	
Number with anemia‡	<i>P=0.003</i>	<i>P=0.004</i>	<i>P=0.021</i>	

Patient population: all randomized patients who received at least one dose of study drug.

† Anemia: ≤8 g/dL hemoglobin.

‡ Hypokalemia: <3 mmol/L.

A statistically higher incidence of hypokalemia defined as serum potassium less than 3 mmol/L was observed in the Abelcet group compared with the AmBisome 3 mg/kg group. There was no statistically significant difference between the Abelcet group and the AmBisome 5 mg/kg group; or between treatment groups for hypokalemia defined as

serum potassium less than or equal to 2.5 mmol/L. A statistically higher incidence of anemia was observed in the Abelcet group compared with the AmBisome groups.

Reviewer's comments: The higher incidence of hypokalemia raises the question whether a larger study would show a more significant difference. The relation of anemia and hypokalemia to the higher death rate seen with Abelcet cannot be totally excluded.

Dose Adjustments and Interruptions:

Dose Adjustments and Interruptions are summarized in Table 25. There more dose interruptions due to an infusion-related reaction in the Abelcet group than in AmBisome groups (individual dose groups or combined). Dose reductions were frequent. As noted in the efficacy section, study drug discontinuation due to toxicity (non-infusion-related adverse events plus infusion-related reactions) occurred more frequently in the Abelcet-treated patients than in the AmBisome-treated patients.

Table 25: Dose Adjustments and Interruptions

	AmBisome			Abelcet 5 mg/kg/day
	3 mg/kg/day	5 mg/kg/day	BOTH	
Total number of patients	85	81	166	78
Number of dose interruptions				
1	3 (3.5%)	1 (1.2%)	4 (2.4%)	10 (12.8%)
2	0	1 (1.2%)	1 (0.6%)	0
Dose interrupted due to:				
AE	0	1 (1.2%)	1 (0.6%)	0
IRR	3 (3.5%)	2 (2.5%)	5 (3.0%)	10 (12.8%)
Dose reduced due to:				
AE	3 (3.5%)	4 (4.9%)	7 (4.2%)	4 (5.1%)
IRR	3 (3.5%)	0	3 (1.8%)	4 (5.1%)
Dose discontinued due to:				
AE	9 (10.6%)	5 (6.2%)	14 (8.4%)	16 (20.5%)
Drug Related AE	6 (7.1%)	3 (3.7%)	9 (5.4%)	13 (16.7%)
IRR	2 (2.4%)	5 (6.2%)	7 (4.2%)	9 (11.5%)

Patient population: all randomized patients who received at least one dose of study drug.
N/A: not applicable; the event was not observed in either one of the treatment groups being compared.

Reviewer's comments: Because there were more adverse events occurring in the Abelcet arm, it is not surprising that adjustments and interruptions were more common in that arm. Since this is a double-blind study, this represents a meaningful observation.

5. Conclusions

By multiple safety measures in this study, including the primary and secondary study endpoints, patients administered AmBisome for the empirical treatment of febrile neutropenia presented a better safety profile than did those administered Abelcet. Compared with Abelcet, AmBisome was associated with a significantly lower incidence of infusion-related chills and rigors on Day 1, significantly fewer patients with nephrotoxicity, a significantly lower incidence of some infusion-related reactions other

than chills/rigors on Day 1, and a significantly lower incidence of chills/rigors on days when premedication was permitted. Abelcet-treated patients required significantly more medication for the treatment and prevention of infusion-related reactions compared with patients receiving AmBisome. Significantly fewer patients administered AmBisome experienced a severe/life-threatening event during the course of the study or discontinued due to an adverse event than did those in the Abelcet group. There were no apparent trends or safety differences between the AmBisome 3 mg/kg per day and the AmBisome 5 mg/kg per day groups. These safety advantages of AmBisome were observed despite mean serum trough concentrations of amphotericin B that were 1.8 to 4.5 times higher with AmBisome than those attained with Abelcet dosing.

A statistically significant difference between AmBisome and Abelcet treatment groups was not observed with respect to overall success rate. However, the number of patients in this trial is inadequate to draw a conclusion about the efficacy equivalence of AmBisome and Abelcet. A significantly higher incidence of the failure criterion "discontinuation for drug toxicity" was observed for Abelcet compared with AmBisome.

AmBisome at 5 mg/kg per day or 3 mg/kg per day presented a better safety profile than Abelcet 5 mg/kg per day, with significantly less infusion-associated chills/rigors and significantly lower nephrotoxicity.

Reviewer's comments: Data in this trial were well documented on case report forms and presented in electronic databases. Review of a 10% random sample of the case report forms that were submitted to FDA did not reveal major documentation issues. Reviewer agrees that AmBisome was shown in this trial to have a better tolerability profile compared to Abelcet. All p values calculated by the applicant were verified by the statistical reviewer. AmBisome was clearly shown to cause less chills/rigors and less nephrotoxicity in the population studied, and this further confirms that the 2 drugs are not the same. Although Abelcet is not approved for empirical therapy in febrile neutropenic patients and an adequate dose for this patient population has not been established, the potential exists for its "off-label" use in this setting at 5 mg/kg/d. Thus, AmBisome should be deemed safer than Abelcet for the empirical treatment of febrile neutropenic patients when compared at an equal dose. The applicant submitted a request to change the label of AmBisome to reflect these new findings. Comparative claims of safety should be supported by adequate and well-controlled studies. This study was well conducted and adequately controlled and is supported by analyses of comparative safety in animals and clinical studies where the 2 drugs were compared to amphotericin B as described in the memorandum of Jeffrey Murray, M.D., dated August 8, 1997.

APPEARS THIS WAY
ON ORIGINAL

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NDA 50-740 Division File
HFD-590/Dir/Goldberger
HFD-590/MTL/Cavallé-Coll
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