CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: 050740

Trade Name: AMBISOME LIPOSOME FOR INJECTION

Generic Name: AMPHOTERICIN B

Sponsor: FUJISAWA, USA

Approval Date: 8/17/97

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APPLICATION: 050740

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Final Printed Labeling		X		
Medical Review(s)	X			
Chemistry Review(s)	X			
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Pharmacology Review(s)	X			
Statistical Review(s)	X			
Microbiology Review(s)	X			
Clinical Pharmacology Biopharmaceutics Review(s)	X			
Bioequivalence Review(s)				X
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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: 050740

APPROVAL LETTER

Rec'd 8/15/97

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

NDA 50-740

Food and Drug Administration
Rockville MD 20857

Fujisawa, USA
Attention: Laurence R. Meyerson, Ph.D.
3 Parkway North, 3rd Floor
Deerfield, IL 60015-2548

AUG 11 1997

Dear Dr. Meyerson:

Please refer to your new drug application dated November 8, 1996, received November 12, 1996, submitted under section 507 of the Federal Food, Drug, and Cosmetic Act for AmBisome® (amphotericin B) liposome for injection.

We acknowledge receipt of your submissions dated as follows.

January 7, 1997
January 21, 1997
January 27, 1997
February 12, 1997
February 18, 1997
February 19, 1997
February 28, 1997
March 7, 1997
March 10, 1997
March 12, 1997
March 19, 1997
March 24, 1997
March 28, 1997
March 31, 1997
April 4, 1997
April 8, 1997
April 17, 1997
April 25, 1997
April 30, 1997
May 8, 1997
May 23, 1997
May 28, 1997
June 2, 1997
June 13, 1997
August 5, 1997
August 6, 1997
August 7, 1997
August 8, 1997

The original User Fee goal date for this application was May 11, 1997. Your submission of March 28, 1997 extended the User Fee goal date to August 11, 1997.

This new drug application provides for:

1. empirical therapy for presumed fungal infection in febrile, neutropenic patients;

2.

3.

4.

5. 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; and

6. treatment of visceral leishmaniasis.

We have completed the review of this application, including the submitted draft labeling, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the draft labeling in the submission dated August 8, 1997. Accordingly, the application is approved for indications 1, 5 and 6 listed above effective on the date of this letter.

You should note that the Center for Drug Evaluation and Research in conjunction with the Office of Orphan Products Development has determined, according to criteria set forth under the Orphan Drug Act, that AmBisome® (amphotericin B) liposome for injection is a different drug than Abelcet® (amphotericin B lipid complex injection), an approved drug with orphan drug marketing exclusivity for the treatment of invasive fungal infections in patients refractory to or intolerant of conventional amphotericin B therapy. Hence, the approval of AmBisome® for a similar indication is not precluded by the marketing exclusivity obtained by the sponsor of Abelcet®.

We also concluded

Should you pursue these indications in the future, please submit each as a supplement to NDA 50-740 (e.g. S-001). In accordance with the policy described in 21 CFR 314.102 (d) of the new drug regulations, you may request an informal conference with members of the Division of Special Pathogen and Immunologic Drug Products to discuss what further steps you need to take to secure approval for these indications.

The final printed labeling (FPL) must be identical to the draft labeling submitted on August 8, 1997. Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FINAL PRINTED LABELING" for approved NDA 50-740. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

We remind you of your Phase 4 commitments
These commitments, along with any completion dates agreed upon, are listed below.

Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. Should an IND not be required to meet your Phase 4 commitments, please submit protocol, data, and final reports to this NDA as correspondences. In addition, we request under 21 CFR 314.81(b)(2)(vii) that you include in your annual report to this application, a status summary of each commitment. The status summary should include the number of patients entered in each study, expected completion and submission dates, and any changes in plans since the last annual report. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments must be clearly designated "Phase 4 Commitments."

Please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications, HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Please submit one market package of the drug product when it is available.

Should a letter communicating important information about these drug products (i.e., a "Dear Doctor" letter) be issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to these NDAs and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20852-9787

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact Ellen C. Frank, R.Ph., Regulatory Management Officer, at (301) 827-2335.

Sincerely yours.

/S/

Mark J. Goldberger, M.D., M.P.H.
Director
Division of Special Pathogen and Immunologic Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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FINAL PRINTED LABELING HAS NOT BEEN SUBMITTED TO THE FDA.

DRAFT LABELING IS NO LONGER BEING SUPPLIED SO AS TO ENSURE ONLY CORRECT AND CURRENT INFORMATION IS DISSEMINATED TO THE PUBLIC.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 050740

MEDICAL REVIEW(S)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 050740

MEDICAL REVIEW(S)

Date submitted:	11/08/96
Date received:	11/12/96
Advisory Committee:	7/16/97
Regulatory Action:	8/11/97
Review (final) completed:	10/31/97
Reviewers:	Jeffrey S. Murray, M.D. Joyce Korvick, M.D.
Drug name:	AmBisome, Liposomal Amphotericin B
Sponsor:	Fujisawa USA, Inc. 3 Parkway North, 3rd Floor Deerfield, IL 60015-2548
Dosage Form/ Route of Administration:	For intravenous injection. Each vial of drug product contains 50 mg of sterile, lyophilized amphotericin B intercalated into a liposome.
Drug Classification:	Antifungal, liposomal formulation
Proposed Indications:	1) Empirical therapy for presumed fungal infection in febrile, neutropenic patients. 2) Treatment of systemic and/or deep mycoses including *Aspergillus* species and *Candida* species 3) Treatment of disseminated cryptococcosis including meningitis 4) Prophylaxis against systemic fungal infections following chemotherapy, including patients receiving bone marrow transplant 5) Prophylaxis against systemic fungal infections in the immediate postoperative period in patients receiving liver transplant 6) Treatment of patients with fungal infections refractory to traditional amphotericin B, or of patients intolerant to the use of traditional amphotericin B or of patients with renal insufficiency 7) Treatment of visceral leishmaniasis

2 Table of Contents

3 Materials Reviewed

FUSA submitted preclinical reports to NDA #50-740 beginning May 17, 1996. Individual clinical study reports followed. The official NDA, including integrated summary of safety and efficacy reports, was submitted in volumes 15.1-7 on Nov. 8, 1996. Subsequent to the filing date FUSA submitted several additional study reports. Final study reports were submitted to update a manuscript and interim report on studies 104-09 and 104-05, respectively. In addition, FUSA submitted a study report on FUSA U.S. study, 94-0-002, which compared AmBisome vs. amphotericin B for the empirical treatment of fungal infections in febrile neutropenic patients. Since this report was submitted as a major amendment to the NDA package, in the last 3 months of the 6 month regulatory clock, the review was extended by an additional 3 months as permitted by PDUFA regulations.

Table 3.1 lists the titles of the clinical study reports and their respective volume numbers and submission dates.

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Table 3.1. Materials Submitted

Controlled Studies			
Protocol No.	**Protocol Title**	**Date submitted**	**Vol. No.**
104-14	AmBisome (2 dose levels) vs. amphotericin B as empiric antifungal therapy in neutropenic pediatric patients	07/26/92 2/28/97 3/12/97 3/19/97	6.1-6.4 23.1-23.3 26.4-26.5 28.1-28.2
104-13	AmBisome vs. placebo for the prophylaxis of fungal infections	08/01/96	7.1-7.5
104-10	AmBisome vs. amphotericin B in patients with pyrexia unresponsive to antibiotic therapy for 96 hours or with confirmed fungal infection	09/04/96	8.1-8.8
104-08	AmBisome vs. placebo for the prophylaxis fungal infection in liver transplant patients	07/09/96	4.1
104-05	AmBisome vs conventional amphotericin B for confirmed deep fungal infections in patients with neutropenia	10/22/96 (interim) 3/28/97 (final)	12.1 30.1-16
104-09	AmBisome vs amphotericin B in HIV infected patients with Cryptococcal meningitis (manuscript)	09/27/96	10.5
104-19 EORTC protocol 19923	Randomized multicenter trial of 1 mg/kg vs. 4 mg/kg of AmBisome in the treatment of Aspergillosis (summary of available information)	10/23/96	13.1
94-0-002	Randomized, double-blind, multicenter trial of AmBisome 3 mg/kg vs amphotericin B 0.6 mg/kg for empirical treatment of fungal infections in the febrile neutropenic host	4/25/1997	36.2-36.50
Uncontrolled Studies			
Protocol No.	**Protocol Title**	**Date submitted**	**Vol. No.**
104-00	Compassionate use	10/23/96	14.1
104-03	AmBisome for primary therapy of disseminated cryptococcosis in patients with HIV infection	09/27/96	10.1-10.3
104-12	AmBisome in the treatment of visceral leishmaniasis in non-immunocompromised patients and immunocompromised patients	06/24/96	3.1

4 Chemistry/Manufacturing Controls

AmBisome for injection is a sterile lyophilized product for intravenous infusion. Each

vial contains 50 mg of amphotericin B, intercalated consisting of approximately 213 mg hydrogenated soy phosphatidyl choline, 52 mg cholesterol, 84 mg distearoylphophatidylglycerol, 0.64 mg alpha tocopherol, together with 900 mg sucrose, and 27 mg disodium succinate hexahydrate as buffer.

AmBisome is manufactured by NeXstar Pharmaceuticals, Inc. in San Dimas California.

Please refer to Dr. Norman Schmuff's review for comments regarding the chemistry and manufacturing of AmBisome.

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5 Animal Pharmacology/Toxicology

Please refer to Dr. Owen McMasters review of the animal pharmacology and toxicology data. During an AmBisome global assessment meeting, Dr. McMaster commented on the occurrence of liver toxicity among rats receiving the highest dose of AmBisome.

6 Clinical Background

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6.1 Foreign experience

AmBisome is presently marketed in 22 foreign countries and approved, but not yet marketed in two countries. Approvals are pending in 12 other countries. Registration has been granted by every foreign health regulatory agency for which a submission was made except for France. The French Ministry of Health concluded that the application was deficient.

Nearly 1 million vials of AmBisome have been sold; the sponsor estimates that 27,000 patients have been treated with AmBisome worldwide.

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6.2 Human Pharmacology, Pharmacokinetics

Please refer to Dr. Kofi Kumi's review for comments regarding the pharmacokinetics of amphotericin B when administered as AmBisome.

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6.3 Other relevant background information

In the NDA, FUSA cites guidelines for the development of liposomal antifungal products. These "guidelines" were generated in the context of discussions at a DAVDP workshop on April 20, 1994 and an Antiviral Drug Products Advisory Committee meeting conducted on April 3, 1995.

7 Description of Clinical Data Sources

7.1 Clinical Studies

FUSA has proposed seven indications, six of these are for the prophylaxis or treatment of fungal infections and one is for the treatment of visceral leishmaniasis. The visceral leishmaniasis indication was reviewed by Dr. Andrea Meyerhoff in the Division of Infectives (HFD-520). Please see Dr. Meyerhoff's review for a summary of the clinical data submitted to support this indication.

For the purpose of this review, the six antifungal indications proposed by the applicant have been modified to four indication categories. Studies submitted to support antifungal indications are listed under each respective indication. The type of study design, controlled vs. uncontrolled, and the number of patients studied are summarized.

7.1.1 Studies Supporting Indication #1: Empirical Antifungal Treatment of Febrile Neutropenic Patients.

The following studies support this indication. A description of their respective study designs are listed in Table 7.1.

Protocol 94-0-002: A randomized double-blind comparative trial of AmBisome versus amphotericin B in the empiric treatment of the febrile neutropenic patient.

Protocol 104-14: AmBisome (2 dose levels) vs. amphotericin B as empiric antifungal therapy in neutropenic pediatric patients

Protocol 104-10: AmBisome vs. amphotericin B in patients with pyrexia unresponsive to antibiotic therapy for 96 hours or with confirmed fungal infection (Empiric [FUO] Stratum)

Protocols 104-10 and 104-14 were conducted by NexStar in Europe. It should be noted that study 104-10 compared AmBisome with amphotericin B in febrile neutropenic patients (empirical therapy stratum) and in patients with confirmed mycoses (confirmed mycoses stratum). The applicant analyzed these strata separately since the protocol endpoints were different. The confirmed mycoses stratum will be addressed separately under indication #3.

Table 7.1. Empiric Therapy Protocols: Indication # 1

Protocol	Design	Patient Population	Treatment Arms (N)	Treatment Duration (mean days)
92-0-002	Controlled Randomized Double-blind	Adults and children age 2-80	AmBisome 3 mg/kg (343) Amph B 0.6 mg/kg (344)	10.8 days 10.3 days
104-14	Controlled Randomized Open-label	Children Neutropenic	AmBisome 1 mg/kg (70) AmBisome 3 mg/kg (71) Amph B 1 mg/kg (64)	9 days 10.5 days 7.6 days
104-10	Controlled Randomized Open-label	Presumed (FUO) and proven mycoses	AmBisome 1 mg/kg (47) AmBisome 3 mg/kg (46) Amph B 1 mg/kg (40)	13.3 days 15.3 days 10 days

7.1.2 Studies Supporting Indication #2: Prophylaxis of Fungal Infections

The applicant has proposed two prophylaxis indications, one in patients receiving chemotherapy for bone marrow transplant and the second for the immediate post-operative period for liver transplantation. The study designs are compared in Table 7.2.

Protocol 104-13: AmBisome vs. placebo for the prophylaxis of fungal infections

Protocol 104-08: AmBisome vs. placebo for the prophylaxis fungal infection in liver transplant patients

Table 7.2. Prophylaxis protocols

Protocol	Design	Patient Population	Treatment Arms (N)	Treatment Duration
104-13	Placebo-controlled, randomized, double-blind	Chemotherapy for AML or ALL, and bone marrow transplant recipients	AmBisome 2 mg/kg 3X week (75) Placebo 3X week (88)	1-9 doses
104-08	Placebo-controlled randomized double-blind	Orthotopic Liver transplant recipients	AmBisome 1 mg/kg/day X 5 days (40) Placebo X 5 days (37)	5 days

7.1.3 Studies Supporting Indication #3: Treatment of systemic and/or deep mycoses including *Aspergillus* species and *Candida* species

The applicant proposed both "first-line" and "second-line" indications for the treatment of

systemic and deep mycoses. The "second-line" indications are for patients who have failed amphotericin B, are intolerant to amphotericin B or who are unable to take amphotericin B due to renal insufficiency. Both indications may be supported by the same studies. The type of indication granted will depend on the strength of the data from the uncontrolled and controlled studies. Studies that have investigated the treatment of fungal infections (mostly infections with Candida and Aspergillus species) are listed below. Their study designs are compared in Table 7.3. Treatment of Cryptoccal infections is addressed under Indication # 4.

Protocol 104-00 An open-label, uncontrolled compassionate use trial of AmBisome

Protocol 104-05: AmBisome vs conventional amphotericin B for confirmed deep fungal infections in patients with neutropenia.

Protocol 104-10: AmBisome vs. amphotericin B in patients with pyrexia unresponsive to antibiotic therapy for 96 hours or with confirmed fungal infection. (Confirmed mycosis stratum only)

Protocol 104-19: (EORTC-19923) Randomized multicenter trial of 1 mg/kg vs. 4 mg/kg of AmBisome in the treatment of Aspergillosis (summary of available information, full report unavailable)

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Table 7.3. Treatment Protocols: Indication # 3

Protocol	Design	Patient Population	Treatment Arms (N)	Treatment Duration (mean days)
104-05	Controlled Randomized Open-label	Age > 16		14 days 13 days
104-00	Uncontrolled, compassionate use			25 days
104-10	Controlled Randomized Open-label	Presumed (FUO) and proven mycoses	AmBisome 1 mg/kg (21) AmBisome 3 mg/kg (21) Amph B 1 mg/kg (18)	16 days 11 days 15 days
104-19	Randomized dose-ranging open-label	Invasive Aspergillus in patients with malignancies	AmBisome 1 mg/kg (42) AmBisome 4 mg/kg (47)	19 days 24 days

7.1.4 Studies Supporting Indication #4: Treatment of disseminated cryptococcosis including meningitis

The following studies evaluated AmBisome for the treatment of cryptococcosis, primarily cryptococcal meningitis in HIV-infected patients. Study designs are compared in Table 7.4.

Protocol 104-03: AmBisome for primary therapy of disseminated cryptococcosis in patients with HIV infection.

Protocol 104-09: AmBisome vs amphotericin B in HIV infected patients with Cryptococcal meningitis (manuscript, submitted with NDA filing, full report submitted with safety update.)

Table 7.4. Cryptococcal protocols

Protocol	Design	Patient Population	Treatment Arms (N)	Treatment Duration
104-03	uncontrolled, open-label	HIV infected adults with cryptococcosis	AmBisome 3 mg/kg (24)	27 days
104-09	controlled randomized open-label	HIV infected adults with cryptococcal meningitis	AmBisome 4 mg/kg/day (16) amph B 1 mg/kg/day	21 days 20 days

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8 Clinical Studies

8.1 Indication # 1: Empirical Antifungal Treatment of Febrile Neutropenic Patients.

For this indication the applicant submitted data from 2 open-label, controlled studies performed in Europe, and one large, double-blind, randomized controlled study performed in the USA. The large study was submitted as a supplement to this NDA.

8.1.1: Trial # 94-0-002: A randomized, double-blind comparative trial of AmBisome versus amphotericin B in the empirical treatment of the febrile neutropenic patient.

8.1.1.1 Protocol

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8.1.1.1.1 Objectives

To evaluate the safety, tolerability and efficacy of AmBisome compared to amphotericin B for the empiric treatment of possible fungal infections in the persistently febrile neutropenic patient unresponsive to broad spectrum antibacterial therapy.

8.1.1.2 Study Design

The study was a randomized, parallel group, double blind, multicenter study comparing amphotericin B and AmBisome in approximately 660 patients with febrile neutropenia. The starting dose was 0.6 mg/kg day for amphotericin B and 3 mg/kg/day for AmBisome. Dose adjustments were permitted. Those experiencing toxicity could receive reduced dose of study drug. After enrollment if evidence of a fungal infection was found, such as a positive blood culture or a pulmonary infiltrate suggestive of aspergillosis, the investigator had the option of increasing the study drug dosage. Doses for study drugs are listed below in Table 8.1.1.

Table 8.1.1. Study dosing schedule

	Standard (Starting) Dose	Reduced Dose	Intermediate Dose	High Dose
AmBisome	3 mg/kg	1.5 mg/kg	4.5 mg/kg	6 mg/kg
Amphotericin B	0.6 mg/kg	0.3 mg/kg	0.9 mg/kg	1.2 mg/kg

Administration of study drug was to continue for the duration of neutropenia (> 250). Investigators were allowed to continue drug for 3 days beyond recovery. The maximum duration of therapy was 42 days unless a positive fungal culture was identified necessitating prolonged treatment.

Comment:
Since empirical antifungal treatment of the febrile neutropenic patient will mean, in some cases, the treatment of early or subclinical infections with Aspergillus species, we suggested (at the end-of phase 2 meeting) that FUSA allow for some flexibility in the dosing of study drug to allow for the use of higher doses for patients infected with more virulent pathogens.

Blinding and Stratification

The sponsor, investigators, patients and nursing staff were blind to the treatment assignment. The pharmacists preparing the solutions were not blinded. This was necessary for preparation of solution and dose adjustments. According tho the original protocol each patient would receive two infusions. A patient randomized to AmBisome received AmBisome in bag A and amphotericin B placebo in bag B. A patient randomized to amphotericin B received AmBisome placebo in bag A and amphotericin B in Bag B. Placebo solutions matched the appearance and color of the active solutions. This was later changed in a protocol amendment such that each patient received only one infusion of either AmBisome or amphotericin B. The infusion bags were covered by an opaque bag and the infusion lines consisted of translucent lines that did not permit the distinction between study drugs. Both study drugs were infused

Patients were stratified by risk factors prior to randomization. The high risk group included patients receiving amphotericin B for an episode of febrile neutropenia within the past 3 months, patients who have received allogeneic bone marrow transplantation or patients receiving chemotherapy for a relapse of acute non-lymphocytic leukemia.

Comment:
Although it is difficult to blind intravenous study medications, the study procedures give us reasonable assurance that this study was truly blinded.

The factors indicating high risk appear to be reasonable choices for defining patients who may be at particularly high risk of developing an infection with fungi, especially Aspergillus species. However, the literature also indicates other potential prognostic variables. For instance in the EORTC trial the difference in response between amphotericin B and placebo was greater in adults (age >15), in those with profound neutropenia (PMN < 100), and in those who had no previous antifungal prophylaxis.

8.1.1.1.3 Study Population

Patients age undergoing chemotherapy, bone marrow transplant, or peripheral blood stem cell transfusion for hematologic or solid tumors were eligible to enroll if they fulfilled the following criteria: had received at least 96 hours of

antibacterial therapy; neutropenia (<500 cells/mm^3); fever (> 38°C) for the last 48 hours or had a recurrence of fever (2 measurements 3 hours apart) after an initial resolution of fever on antibacterial therapy; presence of a central catheter for drug administration.

The following were the protocol exclusion criteria:

Known uncontrolled bacteremia;
Documented systemic fungal infection at randomization;
Received systemic amphotericin B within two days of enrollment;
Patients unlikely to survive more than 2 weeks;
In addition patients were excluded for certain lab abnormalities at baseline including a serum creatinine greater than 2 times the upper limit of normal.

8.1.1.1.4 Study Procedures

Study drugs were infused

Concomitant Therapy

Premedication for infusion reactions were not to be used for the first infusion. No systemic antifungal therapy other than the study drug was permitted. Lipid hyperalimentation was to be interrupted during study drug infusion.

Treatment Assessments

Temperature measurements were to be measured a minimum of every 4 hours while awake. Daily minimum and maximum temperatures separated by at least one hour from study drug infusions and blood product transfusions were to be recorded.

Fungal blood cultures were to be obtained every other day while the patient had fever. Laboratory tests (hematology and serum chemistry) were to be performed 3 times a week during study drug administration, on the last day of treatment and on the 7 day follow-up visit. Absolute neutrophil counts were to be performed daily to document the duration of neutropenia, until the neutrophil count exceeded 500 cells/mm^3 at which time measurements were to be done 3 times a week.

8.1.1.1.5 Endpoints

Efficacy

Because the treatment period was expected to vary for each patient, the day of efficacy evaluation occurred at different times for individual patients.

For the primary efficacy endpoint success was defined as:

a) survival through 7 days after the last day of study drug
b) resolution of fever during the neutropenic period
c) no emergent fungal infections on study drug therapy or within 7 days of the last day of dosing
d) cure of any microbiologically documented study-entry fungal infection
e) study drug is not prematurely discontinued for toxicity or lack of efficacy

Comment:
Since documented fungal infections are relatively infrequent in the empirical treatment setting, the combination success endpoint is driven primarily by the resolution of fever component. Resolution of fever is a surrogate endpoint for resolution of a possible or subclinical fungal infection. Emergence of fungal infections is a clinical endpoint of relevance.

For the most part, diagnosis of specific fungal infections followed the MSG (Mycosis Study Group) criteria. Diagnostic criteria for UTI do not appear to be satisfactory in that a positive culture for fungus from a clean catch urine or a catheterized specimen was all that was necessary. This may not represent fungal infection, but rather colonization of a patient with an indwelling catheter. Superficial as well as systemic infections are included. Definitively diagnosed fungal skin infections, thrush, and vaginitis would be counted as emergent fungal infections.

Secondary Endpoints

time to resolution of fever
total duration of fever while neutropenic
relative duration of fever (days with fever/days neutropenic)
incidence of emergent fungal infection

Safety

Patients were to be specifically evaluated for nephrotoxicity, hepatotoxicity, and infusion associated reactions. Percent incidence in these categories was to be compared.

Nephrotoxicity was defined as a post-baseline peak value of serum creatinine above normal and increased > 50% above the baseline value.

Hepatotoxicity was defined according to baseline concentrations of transaminases. For patients with a baseline less than 2 X ULN, an increase > 5 X baseline was considered hepatotoxicity. For patients with a baseline of , an increase of 3X or 2X baseline, respectively was considered to demonstrate hepatotoxicity.

Infusion reactions were specifically recorded as described below.

The following adverse events were to be recorded during infusion and for one

hour after completion of the study drug infusion:

1. fever (body temperature increase ≥ 0.3°C above pre infusion)
2. chills/rigors
3. nausea
4. vomiting
5. other significant reactions

Comment: *Fever was very carefully defined in this study. Temperatures measured during the infusion period and for 1 hour after were considered study drug related and not a sign of failure of the therapies.*

8.1.1.1.6 Statistical Considerations

The protocol stated that the primary analysis would be based on the intent-to-treat population which would consist of "all patients who were randomized and received at least one dose of drug." The primary statistical analysis will be based on a logistic regression model with effects due to treatments, centers and baseline stratified risk factors.

A number of analyses, in addition to those specified in the protocol, were performed including analyses of fever based on increases of 0.6° and 1°C; evaluation of nephrotoxicity based on ≥ 2X baseline value for serum creatinine (standard definition in other AmBisome studies); evaluation of hypokalemia based on serum potassium ≤ 2.5 mmol/L (standard definition in other AmBisome studies); and variable and subset analyses requested by FDA. In addition, the applicant reviewed the case report forms of all patients identified by the investigators as having baseline and treatment emergent fungal infections using the protocol definition for proven invasive fungal infection. A comparison was made between AmBisome and amphotericin B with respect to the percent confirmed fungal infections that were eradicated by treatment. A blinded, independent review was also performed by an expert in the field.

Comment: *The primary endpoint for the study was constructed as a combination endpoint. While the most desired endpoint would be the prevention of systemic fungal infections, it was not clear that a good estimate of sample size could be made for that endpoint and that the study might be prohibitively large. The additional analysis for fungal infections is appropriate, however, adjustments for multiple comparisons should be considered. This endpoint will be further discussed in the results section.*

Sample size

Although the primary clinical outcome of success is a composite outcome, the rate of defervescence was felt to be the primary factor for sample size calculation. The estimated 70% response rate is based on data from the EORTC trial, in which 69% of

febrile neutropenic (PMNs < 500) individuals defervesced after 5 days compared to 53% on the placebo arm. Given there was only a 16% difference in febrile outcome between placebo and amphotericin B, a delta of 15% would not be sufficiently stringent. This protocol uses a delta of 10%. A sample size of 330 patients per treatment group was planned based on the following:

amphotericin B defervescence rate of 70%
10% difference in defervescence rate
alpha = 0.05
Power =80%

Protocol Amendments

#1 The most significant protocol changes included in this amendment was a change in the method of treatment blinding from a two infusion double-dummy method to a one infusion method with covered bags and translucent lines.

Comment: *This amended method is preferable because with two infusions it would be possible to predict what a patient was receiving by knowing which bag was associated more often with infusion reactions.*

#2 The purpose of this amendment was to modify the inclusion criteria for fever. Patients were required to have a temperature greater than 38C on two occasions in the last 48 hours (instead of once).

Test doses of amphotericin B were also allowed. This could be accomplished by infusing 1 mg of amphotericin B or 5 mL of the study drug.

8.1.1.2 Results

8.1.1.2.1 Patient Disposition and comparability

Patients were enrolled at 32 investigative sites in the USA from January 29, 1995 to July 10, 1996. This study was performed under a US IND. A total of 347 patients were enrolled into the AmBisome arm and 355 into the amphotericin arm. Four patients in the AmBisome arm never received study drug compared to 11 in the amphotericin B arm. Equal numbers of patients were enrolled into the high and low risk stratification groups across treatment arms.

Table 8.1.2. Patient Disposition

	AmBisome	Amphotericin B
Enrolled	**347**	**355**
Randomized and received at least one dose of study drug	**343**	**344**
Risk Stratification High Risk Low Risk	**117 226**	**119 225**
Completed Treatment	**255**	**243**
Discontinued	**88**	**101**
Adverse Event	**25 (7.3%)**	**25 (7.3%)**
Infusion Related Reaction	**8 (2.3%)**	**22 (6.4%)**
Lack of Efficacy	**13 (3.8%)**	**14 (4.1%)**
Death	**10 (2.9%)**	**12 (3.5%)**
Administrative Reason		
Withdrawal	**7 (2.0%)**	**5 (1.5%)**
Physician Decision	**13 (3.8%)**	**12 (3.5%)**
Other	**12 (3.5)**	**11 (3.2%)**

Comment: *Lack of efficacy was determined by the investigator and would be based upon conditions such as: progressive pulmonary infiltrates suspected to be invasive fungal infection, persistent fungemia, progressive sinus infiltrates, organ toxicity or intractable infusion-related toxicity. In several of these cases the fungal infection was suspected but no confirmatory cultures were obtained. Discontinuation due to either the lack of efficacy category or physician decision category were similar. Infusion related reactions will be discussed in the safety section.*

When a fungal infection was diagnosed, the protocol allowed for the patient to continue on the study drug, but at an increased dose. Therefore, the number of discontinuations due to diagnosed fungal infection does not match the overall number of fungal endpoints.

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8.1.1.2.2. Efficacy and Patient Outcomes

8.1.1.2.2.1 Protocol Deviations

For purposes of this study the applicant defined major and minor protocol deviations as follows:

MAJOR: Baseline fungal blood cultures were not obtained; baseline fungal blood cultures were obtained more than 48 hours prior to administration of study drug; broken blind; patient did not receive chemotherapy or bone marrow transplant; patient received the wrong study drug; fluconazole was administered during the majority of the study drug administration period; and any protocol deviation which resulted in the patient not receiving study drug.

MINOR: Administration of lipid preparations during study drug administration; randomization to the wrong risk group; study drug not discontinued despite increased values for live function tests; lack of baseline chest x-ray or baseline chest x-ray obtained more than 48 hours prior to administration of study drug; follow-up examination and/or laboratory tests performed outside of a 5-10 day window; fluconazole administration for less than 50% of the time on study drug; pregnancy test not performed or performed after start of study drug or more than 14 days prior to start of study drug; premedication for prevention of IRR given prior to first dose of study drug; selected inclusion/exclusion criteria not met; study drug dosing and/or duration of administration not per protocol; missing culture, differential count or vital sign and absence of a central catheter.

Table 8.1.3: Protocol Deviations

	AmBisome		Amphotericin B	
	No. Deviations	No. Patients	No. Deviations	No. Patients
Major Protocol Deviations	17	16	18	16
Major Protocol Deviations	290	190	268	183

Comment: *While the number of protocol deviations appear to be similar between both treatment groups, further assessment could not be made because not all of the component characteristics were provided in line listings by the applicant. No information is provided regarding the number of times the blind may have been broken among these cases.*

8.1.1.2.2.2 Patient Characteristics

Patient demographics and baseline vital signs were comparable between treatment groups in both patient populations. Overall, the majority of patients who received at least one dose of study drug were male (54% in the AmBisome group, 55% in the amphotericin B group) and white (88% in the AmBisome group, 85% in the amphotericin B group), with ages ranging from 2 years to 80 years. Mean temperature on study entry was 38.6C in the AmBisome group and 38.5C in the amphotericin B group.

Underlying disease
Acute leukemia was the primary disease diagnosis for 168 of 343 patients (49.0%) in the AmBisome group and 165 of 344 patients (48.0%) in the amphotericin B group. Chronic leukemia was the primary disease diagnosis for 23 of 343 patients (6.7%) in the AmBisome group and 15 of 344 patients (4.4%) in the amphotericin B group. All but six patients, 1 of 343 (0.3%) in the AmBisome group and 5 of 344 (1.4%) in the amphotericin B group, received chemotherapy. There was a substantial number of patients who received bone marrow transplantation: 154/343 (44.9%) patients on AmBisome; 161/344 (46.8%) in the amphotericin B group.

A total of 157/343 (45.8%) in the AmBisome group and 161/344 (46.8%) in the amphotericin B group were receiving systemic antifungal prophylaxis at baseline. In each treatment group approximately 15% of patients were anemic at baseline. Elevated serum creatinine at base line was seen in 5.5% of the AmBisome group and 4.9% of the amphotericin B group.

Regarding baseline ANC, 33 patients who received at least one dose of study drug (14 AmBisome group, 19 amphotericin B group) had a baseline absolute neutrophil count (ANC) > 250/mm^3 and ≤ 500/mm^3. For 21 of these patients (10 AmBisome, 11 amphotericin B group), the ANC fell below 250/mm^3 during the study. One patient administered amphotericin had no additional ANC recorded. Six patients received study drug despite baseline ANC above 500/mm3 (4 AmBisome group, 2 amphotericin B group). All 39 of these patients were included in the study analyses.

Comment: *In general baseline characteristics for the two treatment groups were comparable. In addition, the investigators were able to enroll a substantial proportion of patients at high risk for developing fungal infections which enabled the applicant to attain a substantial number of fungal endpoints for efficacy evaluation.*

8.1.1.2.3 Efficacy Evaluation

PRIMARY STUDY ENDPOINT: Success was defined as resolution of fever during neutropenia, survival, lack of emergent fungal infection, completion of study drug therapy (did not withdraw prematurely). The following is a table of these events, each subject could have one or more of these events during the study.

TABLE 8.1.4 OVERALL SUCCESS RATE

	AmBisome	Amphotericin B
Number of Patients	343	344
Overall Success	171 (49.9%)	169 (49.1%)
Conditions for Success:		
Survived through 7 days post study drug	318 (92.7)	308 (89.5%)
Fever resolved during neutropenic period	199 (58.0%)	200 (58.1%)
Baseline fungal infection cured	9 (2.6%)	8 (2.3%)
No emergent fungal infection **	294 (85.7%)	297 (86.3%)
Study drug not prematurely discontinued	294 (85.7%)	280 (81.4%)

Table 4.1, vol 36.2

The success rates for AmBisome and the conventional formulation of amphotericin B were equivalent (p=0.94, CMH; 95% CI for the difference in success: -6.8%, +8.2%; confidence interval weighted by investigator: -6.4%, 7.8%).

Comment: *The FDA review of the primary endpoint is in agreement with the applicant's analysis. This endpoint supports the claim that AmBisome is at least as effective as amphotericin B in preventing the combined endpoint in the febrile neutropenic. Further analysis of the underlying components especially emergent fungal infections and withdrawal due to AE are reviewed below. These analysis will address concerns from the previous advisory committee regarding specific endpoint characteristics.*

FDA investigation of the overall success rate was performed using a hierarchy of events. Only one event was counted for each individual. The rank order was as follows: death, continued fever, emergent fungal infection, premature withdrawals. The results of this analysis are listed in the table below.

TABLE 8.1.5: Overall Success by Primary Hierarchal Endpoint

	AMBISOME (patients)		AMPHOTERICIN B (patients)	
Patients Enrolled	**343**		**344**	
		-25		-36
Survived through day 7 post study drug	**318**		**308**	
		-125		-116
Fever resolved during neutropenic period	**193**		**192**	
		-14		-13
No emergent fungal infections	**179**		**179**	
		-8		-10
COMPLETED THERAPY SUCCESSFULLY	**171**		**169**	

Comment: *Overall there are not any differences in the outcomes between the two study groups, however, one should note that the fungal endpoint is overshadowed by the deaths and fevers which were evenly distributed between treatment arms. Note that discontinuations of study medication(10 vs 8) were of low frequency when component events of fever, death, resolution of neutropenia were considered. It is important in the evaluation of a component endpoint for efficacy to ensure that the underlying failures due to a disease process are not overwhelmed by a toxicity event. This was not the case here.*

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FUNGAL ENDPOINTS

The previous advisory committee commented on the study design of an empirical fungal study. They suggested that the endpoint of interest in such trials would be clearly documented fungal infections. However, they realized the difficulty of powering a study for this endpoint given the large sample size it would require. Additional exploration of the fungal endpoint was undertaken by the sponsor and reviewed by the FDA.

Baseline fungal infections: The protocol specified that patients with documented fungal infections would be enrolled and treated. As part of the component endpoint,

baseline fungal infections were evaluated. There were 11 in the AmBisome group and 10 in the amphotericin group, according to the investigators. These infections and the outcomes of therapy are listed below.

Table 8.1.5: Baseline Fungal Infection Outcomes

AmBisome				Amphotericin B			
Pt. ID	Infection	Investigator evaluation of response	Applicant evaluation of response	Pt. ID	Infection	Investigator evaluation of response	Applicant evaluation of response
002006	Candida-urine	-----	cure	004053	Candida-unspecified	not assessed	Not cure
012017	torulopsis-blood	micro cure	cure	012018	Candida-urine	----	Not cure
012054	parasilopsis-stool	----	cure	057018	Aspergillus skin	clinical cure	Cure
035064	C. Krusei-blood	micro cure	cure	062017	lusitaniae-blood	micro cure	cure
052005	skin-Candida	clinical improve	NO cure	062063	Rhizopus-skin	improved	Not cure
059060	C. tropicalis-blood	persisted	NO cure	067026	glabrata-blood	micro cure	Cure
062072	C. Krusei-blood	clinical cure	cure	069006	skin-unspecified	not assessed	Cure
064010	Candida-blood	micro cure	cure	070017	C. glabrata-blood	micro cure	Cure
065056	C. tropicalis-blood	micro cure	cure	071060	Candida-urine	micro cure	Cure
066005	Candida-blood	micro cure	cure	074001	Candida-urine	----	Cure
080056	parasilopsis-blood	clinical cure	cure				

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Comment: *Closer review reveals, that for all of the serious systemic infections (not within the shaded boxes) there were 1-2 failures in each group. This evaluation differs somewhat according to the investigator and applicant. In the table: Overall Success*

Rate, the applicant includes all of the infections in the outcome response. This does not change the overall cure rate, which is similar between the two treatment groups.

Emergent fungal infections

The protocol defines fungal endpoints as either PROVEN or PRESUMED. In general the protocol sets out conditions for each of these categories which parallels the Mycosis Study Group (MSG) criteria for diagnosis fungal infections. The MSG categories are definite, probable, possible, based upon certain characteristics of each infection. A positive BAL culture for Aspergillus species would be a proven infection in this study (probable by MSG criteria), while a positive BAL for Candida sp. would be considered a presumed fungal infection (not even possible by MSG criteria).

TABLE 8.1.6. Emergent Fungal Infection Reclassification

	AMBISOME		AMPHOTERICIN B		Comparison of proven EFI**
	PROVEN	PRESUMED	PROVEN	PRESUMED	PROVEN
INVESTIGATORS	16 (4.7%)	29 (28)*	32 (9.3%)	15 (11)*	0.017
SPONSOR	11 (3.2%)	33	27 (7.8%)	14	0.009
INDEPENDENT REVIEWER	10 (2.9%)	34	26 (7.6%)	15	0.007

*NOTE: FDA evaluation counting duel cases as proven only. In the presumed category 4/15 and 1/29 had a proven emergent fungal infection and were also counted in the proven column.

** CMH p-value

Comment: *During the planning stages of this study, the emergence fungal infections was recognized as an important endpoint, however, because of the uncertainty of predicting the actual number of fungal infections, the study was powered based upon the compound endpoint which included resolution of fever. Overall there was no difference in emergent fungal infections (proven or presumed): 45 proven or presumed fungal infections for the AmBisome group; 47 for the Amphotericin B group.*

Further review of the fungal infections was performed in a blinded manner by the sponsor and an expert. Based upon protocol definitions, infections were classified as proven or presumed. Based upon strict criteria for proven emergent fungal infection, there was a better outcome for AmBisome compared to Amphotericin B; however, the opposite was true for presumed infections.

Investigator Proven Emergent Fungal Infection:
Of the 16 infections (AmBisome group) classified as proven by the invesitgators, ten were considered proven by the sponsor and by an independent reviewer based on protocol-specific criteria. Of the six reclassified as presumed, one patient (#062071) had a pneumonic process with bronchoscopy cultures positive for Candida species. Three patients (# 032014, 070005, 070020) were women with urine cultures positive for Candida species. One patient (#059008) had a stool culture positive for Candida species and one patient (#067059) had a pneumonic process with a nasal, but not bronchoscopic, culture for Aspergillus fumigatus.

Within the amphotericin B group, 26 of 32 investigator-designated proven emergent fungal infections were classified as proven by the independent reviewer. The remaining six were designated as presumed (not meeting protocol-specified criteria for proven). Patient # 002023, with sinusitis, had a culture of A. nidulans from the left turbinate, but not biopsy-proven involvement. Patient 050055 had a pneumonic process with Saccharomyces cerevisiae grown from sputum. Two patients (#042012, 07014) had positive Candida cultures from BAL fluid. One Patient (#070059) with esophagitis had budding yeast detected in a brushing specimen smear and one patient (#052001) had a positive stool culture for C. glabrata.

The applicant also considered the same 26 of the 32 patients identified by the investigators as proven emergent fungal infections, but differed from the independent reviewer on one patient. Patient #002023, mentioned above, was considered by the applicant to have a proven infection because of a progressive pulmonary process while on study drug and disseminated aspergillosis at death. Patient # 073007, with a case of candidemia, was reclassified by the applicant as a baseline infection.

Comment: *Based upon blinded review by the FDA medical officer of the cases listed above, the medical reviewer agrees with the applicant's reclassification of the proven emergent fungal infections. Additional review of the patients who were reclassified did not demonstrate an increase in deaths among those patients which may indicate severity. One of the six AmBisome presumed reclassifications died (#067059: possible paranasal/paraorbital cellulitis?). Two of the six reclassified in the amphotericin B group died (# 050055 possible Aspergillus species pneumonia by CT: #07014 died of a sepsis like syndrome positive culture for Candida on the BAL).*

Given these data, there appears to be a difference in proven emergent fungal infections between the two groups, favoring AmBisome. Prevention of these serious infections is clinically important, as will be discussed after review of presumed infections below.

Investigator-designated Presumed Emergent Fungal Infections:
The independent reviewer did not reclassify any of the presumed emergent fungal infections as proven infections. In contrast, the applicant reclassified one patient in

each group as having proven aspergillosis. One AmBisome-treated patient (# 076005) had autopsy-proven Aspergillus species pneumonia and one amphotericin B-treated patient (#012019) had a biopsy diagnosis of simusitis with Aspergillus species made on Day 9 post-study drug.

In addition, one patient with proven C. parapsilosis fungemia (#002001) also had an investigator-designated presumed Candida endophthalmitis which the applicant already had classified as proven.

Comment: *In general the medical officer reviewing this study agrees with the applicant's reclassification of the presumed infections. Few patients were reclassified into the presumed category. All reclassifications were made before the blind was broken and by two separate reviewers. The FDA medical reviewer also assessed these cases (CRFs and line listings reviewed) in a masked fashion and was in agreement with the applicant.*

Since there were about twice as many presumed infections in the AmBisome group, it is important to explore two questions.. What kinds of cases are represented by the presumed category? What is the significance of infections designated as presumed?

TABLE 8.1.7. Types of Presumed Emergent Fungal Infections According to Applicant's Classification (Number of Patients)

	AmBisome	Amphotericin B
Pneumonia	22	10
Abnormal Liver Scans	3	1
Urine cultures +	3	0
Stool Culture +	1	2
Persistent Fever	1	0
Renal Infarcts	1	0
Nasal Culture +	0	0
Sinusitis	1	0
Esophageal brushing culture	0	1
Unknown	1	0
TOTAL Patients with Presumed Emergent Fungal Infection	33	14

Of the patients with a presumed pulmonary process in the AmBisome group, 2 patients

had BAL positive for Candida sp. (#06271, 064016), one had a positive stool for C.krusei (#067011), and one had a positive nasal culture for A. fumigates (067059). None of these patients had definitive cultures to document fungal pneumonic process. One patient had a positive halo sign on CT scan but not culture evidence. Urine cultures by themselves are not indicative of systemic infection, nor are stool cultures.

Of the patients with presumed pulmonary process in the amphotericin B group, one patient had Candida on a BAL (#074014) and one had a CT scan with a positive halo sign (#012022). None of these patients had definitive cultures to document fungal pneumonic process. CT of the liver revealed suspicious lesions. Stool cultures for yeast are not indicative of systemic infections. The liver lesion was documented by CT.

Comment: *Many of the presumed emergent fungal infections were possible pneumonias. Without cultures (except for those noted above) the investigators were attributing the process to either Candida or Aspergillus species, based on appearance of CXR. Given the underlying disease state of these patients (cancer) without documented fungal culture, it would be difficult to prove the causative agent let alone distinguish between cancer and infection or another process.*

What is the clinical significance of these infections? The severity of these infections might be judged by the number of deaths within each group. Proven emergent fungal infections, which are assumed to be systemic in nature, should be more serious and hence have a higher mortality rate than presumed infections. The mortality rates for proven and presumed emergent fungal infections are listed below by treatment arm.

TABLE 8.1.8. Mortality Rates for Applicant Classification of Proven and Presumed Emergent Fungal Infection.

	AmBisome	Amphotericin B
Deaths in Presumed EFI	4/33 (12%)	3/14 (21%)
Deaths in Proven EFI	5/11 (46%)	13/27 (48%)
Death Without EFI	16/229 (5.4%)	20/303 (6.7%)

As demonstrated above, fewer deaths occurred in the Presumed group compared to the Proven group. While the numbers are small, this supports the hypothesis that the presumed category did not have a worse outcome than the proven category, in fact for both groups, with presumed infection and treatment with an antifungal, mortality rates were low. There is not a no-treatment arm with which to compare the above rate.

Seven day follow up is all that is available for these patients, so the potential "late" morbidity may not be recognized. However, these types of patients undergo multiple induction chemotherapy courses within 14 days of recovery of neutropenia, making the

interpretation of additional follow up difficult.

Analysis of Success by Subgroups:
The applicant performed several subgroup analyses on the overall success rates according to baseline systemic antifungal prophylaxis, risk factor, age, concomitant administration of CSF, and antibiotic modification during the study.

TABLE 8.1.9 Tests for Interaction Among Selected Variables

Characteristic	Presence of Characteristic		Absence of Characteristic	
	AmBisome	***Amphotericin B***	***AmBisome***	***Amphotericin B***
Baseline Systemic Antifungal Prophylaxis	75/157 (47.8%)	76/161 (47.2%)	96/186 (51.6%)	93/183 (50.8%)
High Risk	53/117 (45.3%)	58/199 (48.7%)	118/226 (52.2%)	111/225 (49.3%)
Adult (≥ 13 yo)	150/305 (49.2%)	147/307 (47.9%)	21/38 (55.3%)	22/37 (59.5%)
G-CSF/GM-CSF	104/213 (48.8%)	106/213 (49.8%)	67/130 (51.5%)	63/131 (48.1%)
Antibiotic Modification*	58/71 (82%)	34/46 (74%)	113/128 (88%)	135/154 (88%)

* only 399 total patients were included in the evaluation for this criteria based upon whether they had fever resolution during neutropenia.

Comment: *All of the above comparisons were tested by the CMH, and Chi-square; Breslow-Day test and no significant interactions were seen. There were slightly more patients in the AmBisome group that had antibiotic modification, but the differences in success were not statistically different.*

The applicant also reviewed the fever endpoint, as per protocol. The results are presented below.

Table 8.1.10: Evaluation of Fever Endpoints

	AmBisome	Amphotericin B
Resolution of fever during the neutropenic period	58%	58%
Time to resolution of fever while neutropenic	4.09 days	3.39 days
Relative duration of fever (time to/duration of neutropenia)	0.40	0.37
Overall time to resolution of fever	4.34 days	3.45 days

Comment: *Resolution of fever in the AmBisome group was slightly longer than in the amphotericin group; however, both responses were clinically similar.*

8.1.1.3 Safety Comparisons

8.1.1.3.1 Extent of Exposure

Both study groups received a similar number of days of study drug therapy; however, the AmBisome group received approximately 5 times as much amphotericin.

TABLE 8.1.11: Extent of Exposure to Study Drug

	AmBisome	Amphotericin B
Total Number of patients	343	344
Mean ± SD Number of days on study drug	10.8 ± 8.9	10.3 ± 8.9
Mean ± SD cumulative dose (mg/kg)	33.4 ± 30.8	6.1 ± 7.0
Dose reduced due to toxicity	36 (10.5%)	101 (29.4%)
Dose Reduced due to AE	32 (9.3%)	83 (24.1%)
Dose reduced due to IRR	5 (1.5%)	21 (6.1%)
Dose discontinued due to AE	25 (7.3%)	25 (7.3%)
Dose discontinued due to IRR	8 (2.3%)	22 (6.4%)

Nearly three times as many patients administered conventional amphotericin b required a reduction in dose due to toxicity or discontinuation of study drug due to an infusion related reaction compared with those administered AmBisome.

Of the total doses infused, 3506 (97%) of the AmBisome administrations delivered a standard or higher dose compared with 3065 (90%) of the amphotericin B infusions.

8.1.1.3.2 Adverse Events Overall

Adverse events are summarized in Table 8.1.12; included are all cause.

TABLE 8.1.12. All Cause Adverse Events

	AmBisome N=343	**Amphotericin B N=344**

Events Occurring with ≥ 20% Frequency		
Fever	307 (89.5%)	313 (91.0%)
Chills	163 (47.5%)	261 (75.9%)
Hypokalemia	147 (42.9%)	174 (50.6%)
Nausea	136 (39.7%)	133 (38.7%)
vomiting	109 (31.8%)	151 (43.9%)
Diarrhea	104 (30.3%)	94 (27.3%)
Rash	85 (24.8%)	84 (24.4%)
Dyspnea	79 (23.0%)	100 (29.1%)
Hyperglycemia	79 (23.0%)	96 (27.9%)
Increased Creatinine	77 (22.4%)	145 (42.2%)
Increased alkaline phosphatase	76 (22.2%)	66 (19.2%)
Increased BUN	72 (21.0%)	107 (31.1%)
Hypomagnesemia	70 (20.4%)	88 (25.6%)
Abdominal pain	68 (19.8%)	75 (21.8%)
Headache	68 (19.8%)	72 (20.9%)
Hypocalcemia	63 (18.4%)	72 (20.9%)
Increased cough	61 (17.8%)	75 (21.8%)
Epistaxis	51 (14.9%)	69 (20.1%)
Hypotension	49 (14.3%)	74 (21.5%)
Tachycardia	46 (13.4%)	72 (20.9%)
Events Occurring 10-20% Frequency		
Asthenia	45 (13.1%)	37 (10.8%)
Back Pain	41 (12.0%)	25 (7.3%)
Pain	48 (14.0%)	44 (12.8%)
Transfusion Reaction	63 (18.4%)	64 (18.6%)
Chest Pain	41 (12.0%)	40 (11.6%)
Hypertension	27 (7.9%)	56 (16.3%)
Gastrointestinal Hemorrhage	34 (9.9%)	39 (11.3%)

Bilirubinemia	62 (18.1%)	66 (19.2%)
Edema	49 (14.3%)	51 (14.8%)
Hypernatremia	14 (4.1%)	38 (11.0%)
Hypervolemia	42 (12.2%)	53 (15.4%)
Peripheral edema	50 (14.6%)	59 (17.2%)
SGOT Increased	44 (12.8%)	44 (12.8%)
SGPT Increased	50 (14.6%)	48 (14.0%)
Anxiety	47 (13.7%)	38 (11.0%)
Confusion	39 (11.4%)	46 (13.4%)
Insomnia	59 (17.2%)	49 (14.2%)
Hypoxia	26 (7.6%)	51 (14.8%)
Lung Disorder	61 (17.8%)	60 (17.4%)
Pleural Effusion	43 (12.5%)	33 (9.6%)
Rhinitis	38 (11.1%)	38 (11.0%)
Pruritus	37 (10.8%)	3 (10.2%)
Hematuria	48 (14.0%)	48 (14.0%)

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The applicant applied statistical testing to a selected number of adverse events: fever, chills, increased creatinine, increased BUN, anemia and hypokalemia. Patients in the AmBisome group experienced a significantly lower incidence of chills and increased creatinine compared with patients in the amphotericin B group, as well as a significantly lower incidence of hypokalemia.

Patients in the AmBisome group experienced a numerically lower incidence of vomiting, hypotension, tachycardia, hypernatremia, dyspnea, epistaxis and hypomagnesemia compared to those in the amphotericin B group.

Of interest in the events occurring with a frequency of between 10 and 20% was the similarity between liver function abnormalities reported between both groups.

Comment: *It appears that, overall, AmBisome is better tolerated than amphotericin B.*

8.1.1.3.3 Withdrawals due to Adverse Events
Withdrawals from study medication occurred in 40 patients in the AmBisome group and

58 in the amphotericin B group. Adverse events were listed as death in 13 patients on the AmBisome group and 23 patients in the amphqtericin B group.

Adverse events were reviewed in the CRFs supplied by the applicant. Types of adverse events of interest include infusion related reactions, increases in creatinine/renal failure, and increases in liver function tests.

Infusion-related reactions causing permanent discontinuation of medication occurred in 8 of the AmBisome patients and 18 of the amphotericin B patients. Three of the events in the AmBisome group were rash, 2 were shortness of breath, and one each of chest pain, back pain or tachycardia. Of the patients in the amphotericin B group 9 patients had fever/chills/rigors, 5 had shortness of breath, 1 had hypotension, 2 had tachycardia, and one was unknown upon CRF review.

Increased creatinine caused permanent discontinuation of medication in 5 of the AmBisome and 15 of the amphotericin B patients.

Increased liver functions causing permanent discontinuation of medication occurred in a small number of patients: 6 in the AmBisome group and 2 in the amphotericin B group. Several of these were isolated elevations in bilirubin. After discontinuation of study drug these laboratory abnormalities improved.

Comment: *Overall, there were more patients in the amphotericin B group who discontinued study medication especially for adverse events related to increases in creatinine and infusion related reactions. More patients in the amphotericin B group had to discontinue due to respiratory problems. Liver test abnormalities were few in number, occurring more frequently in the AmBisome group; resolving when the drugs were stopped.*

8.1.1.3.4 Serious Adverse Events

Serious adverse event incidence is presented in Table 8.1.13. There was no difference between the treatment groups with respect to overall incidence of serious adverse events. Numerically, dyspnea, respiratory distress, kidney failure and shock were experienced by more patients treated with amphotericin B, while the event coded as "abnormal liver function test" was experienced by more patients administered AmBisome.

Comment: *Liver function tests will be reviewed further in the laboratory section.*

Table 8.1.13. Serious Adverse Events

	AmBisome N= 434	Amphotericin B N = 344
Total number of patients with serious AE	62 (18.1%)	77 (22.4%)
Respiratory Failure	15 (4.4%)	13 (3.8%)
Sepsis	8 (2.3%)	9 (2.6%)
Dyspnea	6 (1.7%)	15 (4.4%)
Hypotension	6 (1.7%)	8 (2.3%)
Bilirubinemia	6 (1.7%)	4 (1.2%)
Heart arrest	5 (1.5%)	3 (0.9%)
Abnormal liver function test	5 (1.5%)	0 (0%)
Increased creatinine	4 (1.2%)	4 (1.2%)
Kidney failure	3 (0.9%)	7 (2.0%)
Lung edema	3 (0.9%)	5 (1.5%)
Venocclusive liver disease	3 (0.9%)	4 (1.2%)
Respiratory distress syndrome	2 (0.6%)	6 (1.7%)
Shock	2 (0.6%)	7 (2.0%)

8.1.1.3.5 Deaths

A total of 25 patients administered AmBisome and 36 patients administered conventional amphotericin B died either during the study or within the follow-up period. In addition, one patient who was randomized to amphotericin B never received study drug, dying the day before scheduled administration as a result of a fungal infection. Of those who died 10 and 12 patients died during the study period in the AmBisome and amphotericin B groups respectively. The primary cause of death is listed in table 8.1.14 below.

TABLE 8.1.14 Primary Cause of Death

	AmBisome	Amphotericin B
Total Number of Patients	343	344
Total number of patients who died	25	36
Primary Cause of Death		
Fungal infections	1	2
Sepsis/other infection	3	4
Underlying disease	4	6
Multi-organ failure-infection	0	5
Multi-organ failure-VOD/other	2	0
Cardiorespiratory arrest	6	7
Respiratory failure	6	11
Shock/hemorrhage	2	1
Hypercalcemia	1	0

Vol 36.2, Table 6.5

Fungal infection was a primary or contributing cause of death for 4 patients in the AmBisome group compared with 11 patients in the amphotericin B group.

Comment: *FDA review of the applicant's narratives of death is in agreement with the investigator's evaluation, none of the deaths were attributable to study drug.*

8.1.1.3.6 Infusion Related Reactions

Prior to the Day 1 study drug infusion, patients were not administered premedications to prevent infusion related reactions. Table 8.1.15 lists the incidence of infusion related reactions on Day 1.

TABLE 8.1.15. Infusion Related Reactions Day 1

	AmBisome	Amphotericin B
Total number of patients	343	344
Patients with fever Increase in temperature of ≥ 0.3C Increase in temperature of ≥ 0.6C Increase in temperature of ≥ 1.0C	 181 (52.8%) 127 (37.0%) 58 (16.9%)	 224 (65.1%) 196 (57.0%) 150 (43.6%)
Patients with chills/rigors	63 (18.4%)	187 (54.4%)
Patients with nausea	42 (12.2%)	35 (10.2%)
Patients with vomiting	21 (6.1%)	28 (8.1%)
Patients with other significant reactions	57 (16.6%)	82 (23.8%)

Vol 36.2, table 6.7

The percentages of patients experiencing fever and chills/rigor on Day 1 was lower in the AmBisome group compared to the amphotericin B group.

Despite the use of premedication for the remainder of the study, there were still more frequent infusion related events in the amphotericin B group, with the exception of vasodilatation (5.2% in the AmBisome group vs 0.6% in the amphotericin B group). Patients in the AmBisome group experienced a numerically lower incidence of chills, hypotension, tachycardia, hypertension, vomiting and hypoxia compared with patients in the amphotericin B group. The cardiovascular adverse events hypotension, tachycardia, and hypertension had a higher (≥ 2X) incidence in the amphotericin B group compared with the AmBisome group as did dyspnea and hypoxia. (Dyspnea 16 vs 25 patients for AmBisome vs amphotericin B, respectively).

Comment: *One of the infusion reactions of interest was dyspnea or hypoxemia, which appeared to occur more frequently in the amphotericin B group in this study.*

8.1.1.3.7 Abnormalities in Laboratory Tests
The incidence of nephrotoxicity is listed below. In general, the AmBisome arm had less nephrotoxicity than the amphotericin B arm.

TABLE 8.1.16 Nephrotoxicity in Study 94-0-00

	AmBisome	Amphotericin B	p-value
Total number of patients receiving at least one dose of study drug	343	344	----
Nephrotoxicity (> 1.5 X Baseline)	101 (29.4%)	170 (49.4%)	<0.001
Nephrotoxicity (> 2.0X Baseline)	64 (18.7%)	116 (33.7%)	<0.001
Mean peak creatinine (mg/dL)	1.24	1.52	<0.001
Mean change from baseline in creatinine (mg/dL)	0.48	0.77	<0.001
Hypokalemia (≤ 2.5 mmol/L)	23 (6.7%)	40 (11.6%)	<0.025

FUSA Background package, Table 6.9.

Comment: *In addition, FDA performed analysis of mean changes in creatinine from baseline over time. FDA plots showed that there were lower levels of creatinine increases in the AmBisome arms (graphic presentations can be viewed in the statistical review portion of the review).*

Anemia (hemoglobin ≤ 8 g/dl) was seen in a comparable percentage of patients in the AmBisome group (125/343, 36.4%) and in the amphotericin B group (134/344, 39.5%).

In order to explore the potential hepatotoxicity of these compounds the applicant presented the information displayed in table 8.1.17 below. The parameters used were prespecified in the study protocol.

TABLE 8.1.17. Hepatotoxicity

	AmBisome	Amphotericin B
Experience hepatotoxicity	61 (17.8%)	70 (20.3%)
Duration of Hepatotoxicity	11.5 days	11.8 days
Change in AST from BL to peak*	48.4	58.9
Change in ALT from BL to peak*	52.7	47.8
Change in Tbili from BL to peak*	1.6	1.8
Change in ALKP from Bl to peak*	115.4	117.6

*Mean change

Comment: *In general the amount and degree of hepatotoxicity appears to be similar*

between both groups.

8.1.1.4 Reviewers Comments/Conclusions of Study 94-0-002 Results

8.1.1.4.1 Efficacy Summary

AmBisome is a liposomal preparation of amphotericin B. Amphotericin B is the clinical standard for empirical therapy of the febrile neutropenic patient after several days of empirical antibiotic therapy. Concerns regarding the potential differences in distribution between the liposomal preparation and amphotericin B resulted in a requirement for a well designed clinical trial for this indication along with data supporting the clinical efficacy of AmBisome for the treatment of serious fungal infections.

This was a well designed, randomized, double-blind clinical trial. It was designed utilizing response of fever as well as several component features of clinical response to assess the outcome of each therapy. The design also attempted to enroll those at high risk for fungal infection, thus enriching the study population to ensure the potential to review a substantial number of fungal failures on each arm. The protocol attempted to define microbiologically proven fungal infections as well. The protocol generally followed the MSG criteria. There is some discussion as to how clearly this was defined as a secondary endpoint compared to the overall definition which included proven and presumed. The FDA was willing to investigate this endpoint in an exploratory manner to determine if an antifungal effect of AmBisome could be detected directly. One important consideration from a statistical point of view was the multiple comparison problem (see statistical review).

Overall, for the composite endpoint there was equivalence between AmBisome and amphotericin B within relatively narrow confidence intervals (Success: AmBisome 171/343 [49.9%]; amphotericin B 169/244 [49.1%]: -6.8%, 8.2%). If one hypothesized that the population at risk, those with subclinical infections, comprised 30% of the patients enrolled, the confidence intervals would widen, but remain at or near the $\pm$20% difference. Thus, this data is robust for the overall composite endpoint.

Exploratory analysis of the fungal endpoint is a difficult matter to dissect. The clinicians were able to designate a patient as having an emergent fungal infection and were directed to check a box on the case report form for proven or presumed infection. While the difference in proven infections favored the AmBisome group, the difference in presumed infections favored the amphotericin B group to a similar degree. Exact statistical analysis is difficult to apply here for reasons of multiple comparisons. However, if the presumed difference occurred by chance then what is the likelihood that the proven occurred by chance? It was the impression of the Advisory Committee that the problem was in the definition of presumed which was not well thought out. In the

end, there may be a numerical advantage for the proven fungal events for AmBisome. An additional study may clarify these findings. However, the overall number of emergent fungal infections (proven plus presumed) were similar between groups with a relatively narrow confidence interval (45 for AmBisome and 47 for amphotericin B). In addition, both groups had similar rates of success in treating baseline infections. This evidence supports the equivalence claim.

Safety was seen to be generally improved in the AmBisome group compared to the amphotericin B group. Infusion related reactions were seen with less frequency in the AmBisome group. In addition, nephrotoxicity appeared to be lower in the AmBisome group compared to the amphotericin B group.

Overall, AmBisome appears to be equivalent to amphotericin B for the treatment of the febrile neutropenic patient and may have a somewhat better safety profile.

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8.1.2 Trial # 104-14: AmBisome (Two Dose Levels) vs. Amphotericin B as Empiric Antifungal Therapy in Neutropenic Pediatric Patients.

8.1.2.1 Protocol

8.1.2.1.1 Objective/Rationale

To evaluate the safety and efficacy of two dose levels of AmBisome with that of amphotericin B in the empiric therapy of fungal infections in neutropenic children.

8.1.2.1.2 Design

The study design was multicenter, open-label and controlled. It was conducted in England and Scotland between August 1992 thru February 1994, and was not performed under a US IND.

8.1.2.1.3 Population

Pediatric patients with chemotherapy-induced neutropenia (neutrophils < 0.5 x 10^9/L) and fever > 38.0 C who had not responded to 96 hours of broad spectrum antibacterial therapy were eligible for the study.

Patients were excluded if they had evidence of either a deep or disseminated fungal infection, or had received antifungal therapy within the last 28 days (other than antifungal agents administered for prophylaxis which were not systemically absorbed). Also, if serum creatinine was > two times the upper limit of normal.

Comment: *The data forms only captured the fever entry criteria as a dichotomous variable (yes/no), and therefore the type of fever curves upon which the patients were judged eligible were not available for review.*

8.1.2.1.4 Procedures

Patients were randomized to receive either amphotericin B (0.3 mg/kg day 1, 0.6 mg/kg day 2, and 1.0 mg/kg daily thereafter), or AmBisome 1 mg/kg daily, or AmBisome 3 mg/kg daily. Randomization schedules were held in sealed envelopes, which were to be opened sequentially as each patient was enrolled into the protocol.

Comment: *One investigator at site 07 deviated from this procedure. The last three patients at this site were administered AmBisome 3 mg/kg, contrary to the randomization assignment. Participation of this site in the study was terminated at that time. Those three patients were excluded from the analysis.*

All patients were to undergo the following pre-study evaluations: History and physical examination, cultures, hematology, BUN, chemistry, chest X-ray, and documentation of previous / concomitant medication. During the study treatment period the patients were

to have BUN/creatinine drawn at least 3 times weekly. Repeat fungal cultures were to be obtained weekly during therapy.

Comment: *Standard surveillance cultures were not specifically outlined in the study schedule, other than "follow-up" cultures. The culture sites chosen by the investigator were left to "local practice". This omission may lead to a sampling error regarding the fungal endpoint. Serologic testing for fungi was also permitted even though simultaneous, confirmatory blood cultures were not required. Fungemia was based on positive blood cultures.*

All patients were to continue on study drug until any one of three endpoints were reached: 1.) Resolution of fever, in conjunction with a return of the neutrophil count to greater than 0.5 x 10^9/L, for at least three consecutive days; 2.) A serious, non-resolving adverse event; 3.) The patient or investigator decides that withdrawal is in the best interest of the patient.

Comment: *There were no provisions for study drug cross-over in this study, however, it did occur during the study. There were 7 amphotericin B patients who switched to AmBisome (3 to the 1 mg/kg and 3 to the 3 mg/kg/day doses [information is missing for one patient]). The cumulative dose of amphotericin B before the switch ranged from 12 to 176 mg. The potential for bias and a trend toward equivalence of therapies may be introduced by this procedure.*

8.1.2.1.5 Endpoints

The efficacy was to be determined by the investigator's assessment of the resolution of the clinical signs and symptoms in addition to resolution of fever and neutropenia. Patients were to be afebrile for 3 consecutive days to be considered a success.

Comment: *As outlined above endpoints were reported on the data form as dichotomous variables (Yes/No) based on the evaluation of the clinical investigator. The applicant's presentation of the results includes a re-classification, according to documented data collected throughout the study. For further discussion of this change on the efficacy analysis see "results" section.*

For safety endpoints, only nephrotoxicity was defined in the original protocol, for the purposes of adverse event management: "if serum creatinine increases to more than 100% of the base line value and cannot be explained by other drugs...."

Comment: *Additional definitions were applied to the analysis post-hoc.*

8.1.2.1.6 Statistical considerations

According to the protocol, the sample size was calculated based on an hypothesized

15% reduction in "serious" toxicity comparing amphotericin B with AmBisome, from an incidence of 20% to 5%. The applicant proposed to analyze the total duration of antifungal therapy, duration of hospitalization and overall survival, in order to compare the relative efficacy of the three regimens for empirical treatment of fungal infections.

Comment: *The statistical section of the protocol is limited to the above. It is assumed that the efficacy comparisons were to be performed using an equivalence test; however, confidence intervals for such a test were not pre-specified. In addition, the analysis of safety is vague, not specifying which parameters will be evaluated and how much of a change within a parameter would be significant. The calculations presented above appear to be based on dichotomous variables (serious toxicity; yes/no).*

8.1.2.2 Results

To assess the efficacy of AmBisome, the sponsor retrospectively classified patient outcomes as success or failure as follows:

Successful response: a minimum of three consecutive days without fever (<38°C) until the end of treatment with the originally randomized antifungal drug.

Failure to respond included any of the following: 1) failure of resolution of fever during neutropenia; 2.) development of an emergent fungal infection on study drug, 3.) addition of another systemically active fungal agent (eg. fluconazole).

Retrospectively the applicant defined the development of an emergent fungal infection as "being based on a culture from the blood, other normally sterile sites, or in a sample collected during bronchoscopy. Confirmed fungal infections in samples collected from the pharynx, stool, rectum, oral swabs or wounds, in the absence of confirmed blood or bronchial fungal infection, were not considered treatment failures.

Comment: *The protocol did not specify what constituted a definitive fungal diagnosis. There is also difficulty relying exclusively on the fungal culture data, for example, a positive fungal culture from blood without clinical symptoms may be a contaminant.*

8.1.2.2.1 Patient Disposition, comparability

Two-hundred and fourteen patients were randomized into the study. Four patients were excluded from all analyses since no case report forms were filled out at the sites. Three patients treated with AmBisome 3 mg/kg were excluded from all analyses because the site investigator violated the randomization scheme. One patient never received study drug. One patient received amphotericin B, but no study data were recorded. Thus the efficacy and safety population data bases both include 205 patients (vol 6.2; section 16.2.3 of submission). (Patients excluded: 07035, 07037, 07039, 01034, 06010, 06016, 06026, 07007).

Comment: *The "randomization violation" site enrolled a total of 27 patients prior to the violations. The violations were reported to be the last three patients enrolled at that site. Because of this, stratification by site for the efficacy analysis will be important to perform. Regarding the safety analysis any patient who received the study drug should be included, the three "violation" patients would fit this category.*

8.1.2.2.2 Efficacy endpoint outcomes

8.1.2.2.2.1 Protocol Deviations:

Ten patients did not meet the strict criteria of body temperature $\geq$ 38°C and neutrophil count $\leq$ 500 cells/m^3. These patients were included in the analysis. Eight had temperatures between recorded on the pre-treatment record. One patient (06026) was listed as not neutropenic on the entry form. An additional patient had a pre-treatment neutrophil count of 600 cells/m^3.

Comment: *There were 2 patients on the amphotericin B group who were afebrile at the pre-treatment visit, 4 on AmBisome 1 mg/kg and 3 on the AmBisome 3 mg/kg group. Only one patient on the AmBisome 1 mg/kg group never had a documented episode of fever at any time on study therapy. Several of these patients were failures according to the criteria. It appears that bias was not introduced by this inclusion.*

One patient who was randomized had a positive fungal culture at baseline and was excluded from all analysis.

Patients receiving concomitant systemic antifungal medication were to be excluded according to the protocol; however, thirty-four deviated from this criterion and were included in the analysis. The distribution is shown in the following table (8.1.18).

TABLE 8.1.18: Use of Systemic Antifungal Therapy: Protocol Violations

Use of Systemic Antifungal	Amphotericin B N=64	AmBisome 1 mg/kg N=70	AmBisome 3 mg/kg N-71	Total N=205
Within 28 days prior to starting study medication:	12 (18.8%)	11 (15.7%)	10 (14.1%)	33 (16.1%)
* Stopped prior to starting study med	6	7	7	20
* Stopped after a few days of starting study med	3	3	1	7
* Continued throughout period of study drug	3	1	2	6
Initiated during study medication use	1	0	0	1
TOTAL	13 (20.3%)	11 (15.7%)	10 (14.1%)	34 (16.6%)

(table 14.1.7. Vol 6.1)

Comment: *According to the sponsor only one patient initiated systemic antifungal therapy after entering into the study (amphotericin B group), and only 6 (2.9%) patients continued antifungal therapy throughout the study period. Most of the therapies were oral fluconazole, only three were intravenous agents. Taken in sum, there was a substantial number of protocol violations (17% of patients) involving the use of concomitant systemic antifungal therapy; the use of concomitant antifungals was somewhat higher in the amphotericin B group compared to the AmBisome 3 mg/kg group. This may serve to make the groups more alike in efficacy by decreasing the overall risk of infection with Candida species, thus masking the true difference in efficacy of the agents.*

8.1.2.2.2.2 Reasons for treatment discontinuation according to the investigators are listed in Table 8.1.19.

TABLE 8.1.19: Treatment Discontinuation Reasons

INVESTIGATOR'S REASON	Ampho B N=64	AmBisome 1 mg/kg N=70	AmBisome 3 mg/kg N=71
Afebrile	31 (48%)	42 (60%)	47 (66%)
Severe Adverse Event or Death	6 (9%)	1 (1%)	3 (4%)
Investigator Decision/Patient Request/Other:	27 (43%)	27 (39%)	21 (30%)
Afebrile with recovering neutrophils	13	12	12
Afebrile with persistent neutropenia	3	5	3
Treatment failure	3	7	1
Toxicity	6	0	0
Miscellaneous:	2	3	5
No neutropenic at entry	1	1	0
Afebrile with increasing WBC	1	0	0
Bacteremic	0	0	2
Intercurrent illness	0	1	2
Terminal care requested	0	1	1

(Table 14.1.1 vol 6.1)

Comment: *These results were verified via a review of line listings. Overall, withdrawals due to severe adverse events/deaths/toxicities were greater for the amphotericin B group (12 [19%]), compared to either AmBisome 1 mg/kg (1 [1%]) or AmBisome 3 mg/kg (3 [4%]). Included are the specific etiologies under "miscellaneous" reasons for discontinuation. There were more of these in the AmBisome 3 mg/kg group.*

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8.1.2.2.2.3 Patient Characteristics

A majority of patients had acute lymphoblastic leukemia, and the general distribution across arms was comparable. See Table (8.1.20).

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TABLE 8.1.20 Underlying Diseases

	Amphotericin B N=64	AmBisome 1 mg/kg N=70	AmBisome 3 mg/kg N=71	Total N=205
Acute Lymphoblastic Leukemia	36 (56.3%)	33 (47.1%)	31 (43.7%)	100 (48.8%)
Acute Myeloid Leukemia	14 (21.9)	13 (18.6)	10 (14.1)	37 (18.1)
Non-Hodgkin's Lymphoma	3 (4.7)	6 (8.6)	7 (9.9)	16 (7.9)
Blastoma	1 (1.6)	2 (2.9)	7 (9.7)	10 (4.9)
Other	10 (15.6)	16 (22.9)	16 (22.5)	42 (20.5)

(Table 14.1.3 vol 6.1)

Comment: *Given the advances in therapies for neutropenia, potential length of a neutropenic episode may be reduced by the use of GMCSF or GCSF. However, the opposite may be true in that the oncologist may utilize more intensive chemotherapy than prior to the availability of such therapies. Overall, GMCSF (GCSF) was administered in 20% of patients, with similar use among the three treatment arms: 13 (20%), 12 (17%), 16 (23%), for amphotericin B and AmBisome 1 and 3 mg/kg, respectively. While there was no disproportionate use of colony stimulating factors among treatment arms, the risk of fungal infection may have been been decreased, subsequently providing fewer fungal endpoints. In addition, there were 13 (6.3%) bone marrow transplantations equally distributed among the groups. This would comprise a group at high risk for fungal infection, but represents only a small subpopulation in the study.*

Demographics: The three treatment groups were well balanced for demographic characteristics. The median age of these children was 6 years with a range from 0 to 16. The majority of the subjects were Caucasian (approximately 80%). The majority of patients were male (58.5%).

8.1.2.2.3 Efficacy Evaluation: The results of the applicant's and FDA's evaluation of success is presented in TABLE 8.1.21. The applicant's calculated Chi-square value is associated with a p-value of 0.35 for the comparison across study groups.

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Table 8.1.21: Number of Patients with Successful Outcome

	Amphotericin B N=64	AmBisome 1 mg/kg N=70	AmBisome 3 mg/kg N=71
Success	34 (53%)	45 (64%)	45 (63%)
Failure	30 (47%)	25 (36%)	26 (37%)
Febrile	29	23	25
Systemic Infection	0	2	1
Systemic Antifungal	1	0	0
FDA EVALUATION:	N=63	N=70	N=71
Success	32* (51%)	44 (63%)	45 (63%)
Failure	31 (49%)	26 (37%)	26 (37%)
Systemic Infection	1	3**	2**
Systemic Antifungal	4	3	1
Febrile	26	20	23

* one patient excluded because they were never febrile thus unevaluable.
** based on line listings generated from data disks

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Comment: *In table 8.1.21 the applicant's estimation of efficacy was based data presented in table 4.2.1 vol 6.1 of the NDA. The applicant submitted revised efficacy evaluation via SAS diskettes . FDA's assessment is based on data provided in these diskettes. Review of line-listings agreed with the applicant's outcome assessment. The reason for the difference between the applicant's reporting in TABLE 8.1.21 and the FDA analysis is based on the use, by the FDA, of a mutually exclusive hierarchy which recognized systemic infection first, use of systemic antifungals second, and continued fever last. CRFs were reviewed for these endpoints. Both positive Aspergillus species cultures were documented to have occurred post therapy. However, one patient in the AmBisome 1 mg/kg group was a failure because of continued presence of fever, and the other was coded by the applicant as a systemic fungal infection.*

There is no significant difference in the outcome results (See Table 4.2 A in statistical review). Generally, for the applicant's results, the confidence intervals were narrow enough to be consistent with clinical equivalence up to ± 20%

8.1.2.2.3.1 Systemic Fungal Infections: There were 6 systemic documented fungal infections described by the applicant: one in the amphotericin B group (07012); three in the AmBisome 1 mg/kg group (01030, 05011, 05047); two in the AmBisome 3 mg/kg group. One patient in each AmBisome group had a positive culture for Aspergillus

species, the remainder were blood-stream infections with Candida species.

Comment: *Because the criteria for failure were applied post-hoc in this non-blinded study, there is potential for loss of information and bias. In several clinics fungal infection was presumed or suspected as a result of serologic testing for Candida sp. Often a second surveillance blood culture was not done. Thus, information regarding reasons for failure might not be captured when relying solely on positive cultures of sterile body sites. In addition, sampling for fungal infection might have been more or less intense when the investigators knew what drug the patients were assigned.*

8.1.2.3 Safety Comparisons

8.1.2.3.1: Extent of Exposure: The duration of treatment on initial study drug was significantly longer for patients randomized to AmBisome than amphotericin B. In addition, those patients who received amphotericin B received lower average doses than the planned 1 mg/kg/day. The average duration of initial treatment was 6.6 days for the amphotericin B group, 9.0 days for the AmBisome 1 mg/kg group and 10.5 days for the AmBisome 3 mg/kg group. The average total dose of study drug was 794 mg, 972 mg, 2768 mg, respectively, for each of the treatment arms (amphotericin B, AmBisome 1 mg/kg, AmBisome 3 mg/kg). Ten patients in the amphotericin B group had an interruption in their treatment compared to one and four patients in the respective 1 and 3 mg/kg AmBisome study groups.

Comment: *The longer average exposure period and dose received by the AmBisome groups could lead to increased toxicity; however, this was not seen, as the data presented below will demonstrate. The average length of neutropenia was similar for each group (10.9, 11 and 12.9 days respectively for amphotericin B, AmBisome 1 mg/kg, and AmBisome 3 mg/kg); thus, the average time at risk for infection was comparable. The difference in duration of study drug treatment did not appear to be dependant on the duration of neutropenia.*

8.1.2.3.2 Adverse Events Overall: Table 8.1.22 represents the sponsor's presentation of the adverse events reported by body system in the study for events occurring with a greater than 3.1% frequency (1 or 2 events).

TABLE 8.1.22: Overall Adverse Events

Body System	Adverse Event	Amphotericin B N= 64 n %	AmBisome 1 mg/kg N=70 n %	AmBisome 3 mg/kg N=71 n %
BODY AS WHOLE	Abdominal Pain	3 (4.7)	4 (5.7)	3 (4.2)
	Chest Pain	1 (1.6)	3 (4.3)	0 (0)
	Fever	3 (4.7)	3 (4.3)	2 (2.8)
	Infection	1 (1.6)	0 (0)	3 (4.2)
	Injection Site Inflammation	2 (3.1)	4 (5.7)	2 (2.8)
	Mucositis NOS	4 (6.3)	4 (5.7)	3 (4.2)
	Rigors	5 (7.8)	7 (10.0)	2 (2.8)
CARDIOVASCULAR	Hemorrhage NOS	0 (0)	1 (1.4)	3 (4.2)
	Hypotension	0 (0)	3 (4.3)	0 (0)
DIGESTIVE	Diarrhea	2 (3.1)	4 (5.7)	6 (8.5)
	Nausea	1 (1.6)	3 (4.3)	1 (1.4)
	Stomatitis Ulcerative	1 (1.6)	3 (4.3)	0 (0)
	Vomiting	2 (3.1)	4 (5.7)	6 (8.5)
METABOLIC AND NUTRITIONAL	Hypocalcemia	1 (1.6)	1 (1.4)	3 (4.2)
	Hypokalemia	15 (23.4)	1 (1.4)	12 (16.9)
	Hypomagnesemia	3 (4.7)	2 (2.9)	5 (7.0)
	Hypoproteinemia	2 (3.1)	1 (1.4)	4 (5.6)
NEUROLOGIC	Convulsions	2 (3.1)	0 (0)	1 (1.4)
RESPIRATORY	Bronchospasm	2 (3.1)	1 (1.4)	0 (0)
	Coughing	3 (4.7)	2 (2.9)	3 (4.2)
	Dyspnea	0 (0)	0 (0)	2 (2.8)
	Pulmonary Edema	2 (3.1)	0 (0)	0 (0)
SKIN	Rash	8 (12.5)	11 (15.7)	11 (15.5)
UROGENITAL	Toxic Nephropathy	4 (6.3)	0 (0)	0 (0)

Comment: *Fever and rigors occurred slightly more frequently in the amphotericin B group. There was a slight increase in the percentage of patients experiencing diarrhea or vomiting in the AmBisome groups relative to the amphotericin B group. Hypokalemia was the most common metabolic event and was seen more frequently in the amphotericin group followed by the AmBisome 3 mg/kg group. It was striking to note that only 1.4% of patients receiving AmBisome 1 mg/kg were reported to have hypokalemia. Rash was seen relatively frequently in this study ranging from across treatment groups. The sponsor reported that 4 patients had nephrotoxicity in the amphotericin B group compared to none in either AmBisome group.*

8.1.2.3.3: Withdrawals due to adverse events/toxicities, as mentioned above were more frequent in the Amphotericin B group. The events are listed in Table 8.1.23.

TABLE 8.1.23: Withdrawals due to Adverse Events/Toxicities

	Amphotericin B	AmBisome 1 mg/kg	AmBisome 3 mg/kg
Rash	1	0	1
Hyponatremia	4	0	1
Nephrotoxicity	6	0	0

(Review of line listings vol 6.3, table 16.2.7.b)

Comment: *Nephrotoxicity was most frequently noted in the amphotericin B group.*

8.1.2.3.4: Serious Adverse Events: The applicant reported a total of 8 serious events (2, 2, 4 events for amphotericin B, AmBisome 1 mg/kg and AmBisome 3 mg/kg, respectively). Six of these events were either possibly related or related to study drug. The remaining two events were related to the underlying disease according to the investigator. Two amphotericin patients were listed as having serious events related to study drug (renal failure, heart failure), one AmBisome 1 mg/kg patient was listed as having cardiac failure possibly related to study drug, and three AmBisome 3 mg/kg patients, one each, were listed as possibly related (status epilepticus) and probably related (pulmonary hemorrhage), and related (allergic reaction).

Comment: *Most of the serious adverse events are related to progression of the underlying disease. Upon review of the CRFs for these events, perhaps two were directly related to the therapy, they include: Amphotericin B renal toxicity (04003); AmBisome 3 mg/kg allergic reaction (08028). The allergic reaction was described as swollen face, lips, eyes and hands with a marked wheeze and hoarse voice. The patient recovered with treatment and went on to receive AmBisome over a 4 hour infusion for a total of 3 weeks without repeat incident.*

8.1.2.3.5: Deaths: A total of 14 patients died during or after the trial, 4 in the conventional amphotericin B group, 3 in the AmBisome 1 mg/kg and 7 in the AmBisome 3 mg/kg group, respectively. Five deaths (1 on amphotericin B, 1 on AmBisome 1 mg/kg, and 3 on AmBisome 3 mg/kg) occurred either while on study drug or within one week thereafter. Five other deaths occurred within 30 days of study drug discontinuation. The other deaths occured between Twelve of the 14 patients deaths were related to underlying disease or disease-related complications. Only two deaths were considered related to study drug (one in each AmBisome group).

TABLE 8.1.24: Causes of Death

Amphotericin B	AmBisome 1 mg/kg	AmBisome 3 mg/kg
Disease progression = 2	CMV pneumonia = 1	Disease progression = 4
GVHD = 1	Pulmonary hemorrhage due to thrombocytopenia = 1	Progressive Multifocal Leukoencephalopathy = 1
Fungal pneumonia = 1	Aspergillosis = 1*	Fungal infection = 2*

* deaths related to drug therapy according to investigator.

Comment: *All causes of death were verified through CRFs and narratives provided by the applicant. The two deaths designated as related to study drug are described below.*

> ***07028:*** *A 10 month old girl receiving chemotherapy for acute myeloid leukemia, received 1 mg/kg of AmBisome for 5 days. It was then discontinued when the X-ray revealed worsening of pulmonary infiltrate. Amphotericin B was initiated after study discontinuation, but no improvement was noted. AmBisome, at a dose of 3 mg/kg escalated to 5 mg/kg, was reintroduced. She died of pulmonary hemorrhage and disseminated infection 28 days post study treatment. Autopsy confirmed the presence of pulmonary hemorrhage due to a cavitating pulmonary infection with Aspergillus species. The investigator believed death was related to study drug.*
>
> ***07037:*** *A 4 year old boy with acute lymphoblastic leukemia, and perihilar infiltrate was randomized to AmBisome 3 mg/kg/day. Repeated thoracic x-rays showed alveolar opacification. Culture of BAL fluid grew C. albicans; in addition, a skin biopsy was positive for Candida species. He also had pneumocystis pneumonia. Adverse events reported included: a papular rash, pharyngeal bleeding post-intubation, hypotension, hematuria, nose bleeding, pulmonary hemorrhage and respiratory distress. He died after 7 days of AmBisome therapy.*

Note that both cases, which were considered related to therapy appear to be due to overwhelming fungal infections. There appears to be a similar number of deaths due to fungal infection across arms.

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8.1.2.3.6: Special Considerations:

BRI AUDIT: In order to prepare for the NDA, the applicant contracted with BRI International to perform an audit of all CRFs (100% source data verification of the CRFs). The BRI audit of the source document revealed additional clinical events. These additional clinical events were reviewed with each investigator who judged whether the event was disease-related or non-disease-related. The applicant then reviewed all of these additional clinical events. All clinical events meeting the criteria for a serious adverse event and all non-disease-related clinical events were added to the data base as adverse events. Disease-related clinical events were not entered in the data base since the investigator considered them attributable to the patient's underlying disease. Approximately 60% of all other findings from the BRI audit were incorporated into the data base.

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Comment: *Review of the BRI audit sheets provided in the application reveals an appropriate process which followed the above algorithm.*

RESPIRATORY SYMPTOMS: Because of previous observations of pulmonary adverse events with the infusion of lipid compounds, pulmonary adverse events were closely reviewed. There were 5 patients in the Amphotericin B group who reported any symptom related to the lung, 8 in the AmBisome 1 mg/kg group and 5 in the AmBisome 3 mg/kg group (Table 8.1.25).

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TABLE 8.1.25: Pulmonary Adverse Events

	Amphotericin B N= 6 (%)	AmBisome 1 mg/kg N= 8 (%)	AmBisome 3 mg/kg N= 5 (%)
Respiratory insufficiency/failure	1	2	1
Bronchospasm	2	1	1
Chest pain	0	3	0
Pulmonary hemorrhage	0	1	0
Dyspnea	0	0	1
Cough	1	1	2
Allergic reaction	1	0	0
Patient ID	*06024, 08007, 08010, 08018, 08027, 08041*	*05052, 07004, 07024, 08012, 08034, 05032, 08022, 08039*	*07037, 08021, 08033, 07021, 08029*

Of these events, 5 were related to study drug therapy by the investigators (1, 2, 2,

respectively, for amphotericin B, AmBisome 1 mg/kg, AmBisome 3 mg/kg). Summaries of the 5 cases are listed below. Review of line listings and CRFs of the remaining cases reveal the events were most likely related to underlying disease processes. One case was due to therapeutic failure (overwhelming fungal infection).

08007: respiratory failure
07024: respiratory disorder, cardiac failure (no additional details were submitted)
08034: bronchospasm
07037: respiratory insufficiency secondary to fungal/pneumocystis pneumonitis with pulmonary hemorrhage
08033: dyspnea

Comment: *Pulmonary toxicity due to AmBisome was NOT demonstrated in this clinical trial.*

Liver Toxicity: Animal toxicity studies with AmBisome suggested a potential for liver dysfunction. In order to determine whether liver toxicity was occurring in the AmBisome group, CRFs of patients with adverse event listings consistent with symptoms and signs of liver toxicity were reviewed. Only 4 such events were discovered.

08042: Increased ALT: the patient received 8 days of amphotericin B with increasing ALT, which resolved after discontinuing study drug.
08035: Increased ALT: the patient received 5 days of AmBisome 1 mg/kg increase in ALT which resolved after discontinuing study drug.
08028: Hepatosplenomegaly: This occurred after the first infusion with AmBisome 3 mg/kg. In addition, the patient experienced an acute reaction including swelling of the face, hands, lips, marked wheezing and horse voice. The drug was reintroduced but administered over a 4 hour period without further events. Hepatosplenomegaly resolved within 5 days.
08044: Increased ALT: the patient received 3 days of AmBisome 3 mg/kg with increasing ALT, which resolved after discontinuing study drug.

Comment: *Because of the low number of events, no conclusions can be drawn regarding an association of AmBisome and liver toxicity from this study. Review of laboratory values follows.*

8.1.2.3.6 Laboratory Abnormalities: No differences between treatment groups were observed for most of the laboratory parameters except for nephrotoxicity and hypokalemia. Approximately one quarter (23.7%) of the amphotericin B treated patients had nephrotoxicity (increase of serum creatinine greater than 100%) compared

to 9.5% and 13.9% in the AmBisome 1 mg/kg and AmBisome 3 mg/kg patients, respectively (p=0.01, for the overall comparison). Similarly, for hypokalemia (potassium ≤ 2.5 meq/L), one-quarter of the amphotericin B group had hypokalemia compared to 9.2% and 12.1% in AmBisome 1 mg/kg and AmBisome 3 mg/kg, respectively (p=0.04, overall). For liver tests, only 1 patient had an abnormal increase in alkaline phosphatase (≥ 1000 IU/L); 18 patients had abnormal ALTs and 11 patients had abnormal ASTs (≥ 105 IU/L). There was no statistically significant difference between treatment groups for these parameters.

Comment: *Review of the laboratory data provided on SAS diskettes revealed many discrepancies in lab values and units. FDA requested the applicant to verify the data and resubmit the data diskette along with 10% of the CRFs in order for the FDA to verify the data. Rates quoted above are from the original submission. Subsequent analyses of LFTs, creatinine, and potassium revealed similar results to those above. The frequency of liver function abnormalities was low with slighty more events in the AmBisome groups.*

8.1.1.4 Reviewer's Comments/Conclusions of Study Results

8.1.1.4.1 Efficacy Summary: AmBisome is a liposomal preparation of amphotericin B. Amphotericin B is the clinical standard for empirical therapy of the febrile neutropenic patient, although not licensed as such. Concern regarding distribution differences between amphotericin B and the liposomal product has resulted in the requirement for a well designed clinical trial for this indication as well as data supporting the clinical efficacy for treatment of fungal infections.

Empirical therapy includes patients who may not have subclinical fungal infections. There are no reliable estimates of the percentage of febrile neutropenic patients that develop subclinical fungal infections if not treated with amphotericin B. Depending on the underlying disease, it may be of the patients enrolled. This study was powered to detect a difference in clinical toxicity, but not efficacy. Toxicity is clinically important especially for those who are administered this agent and do not have a subclinical fungal infection.

Study 104-14 has several significant problems in design: open label; data quality issues; inadequacy of sample size for efficacy evaluation; number of proven fungal infections too small; many of the endpoints and "success" criteria were applied after the study was over and not specified in the original protocol document; one way cross-overs were permitted to AmBisome only; protocol violations regarding the use of oral fluconazole.

No statistically significant difference in success rates across treatment arms was

demonstrated by this study. In order to judge whether these agents are equivalent requires evaluation of Confidence Intervals. Because of the sample size and the small portion of patients who had a documented breakthrough fungal infection, the confidence intervals around the events of interest (prevention of fungal infections) are wider than those for study 002 (see statistical review). Thus, this study is viewed as supportive of the equivalence claim, but <u>not a pivotal</u> trial demonstrating a claim for equivalence of AmBisome and amphotericin B.

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8.1.3 Trial #104-10: AmBisome (two dose levels) versus Amphotericin B in Patients with Pyrexia Unresponsive to Antibiotic Therapy for 96 hours, or with Confirmed Fungal Infections.

8.1.3.1 Protocol

8.1.3.1.1: Objective/Rationale: To compare the safety and efficacy of two dose levels of AmBisome with that of amphotericin B in the empirical treatment of fungal infections in neutropenic patients.

8.1.3.1.2: Design: This study design was multicenter, open-label and controlled. There were two strata: 1.) empirical therapy (FUO); 2.) treatment of confirmed mycosis. This section will concern itself with the empirical therapy group. For review of the confirmed mycosis treatment stratum refer to Section 8.3.2 of this review. This study was conducted in Europe, and was not performed under a US IND, between May 1992 and January 1994.

8.1.3.1.3: Population: Patients who were older than 15 years of age, with neutropenia (neutrophils < 1.0 x 10^9/L) due either to chemotherapy or underlying hematologic disease and with fever of unknown origin (>38C) which had not responded to broad spectrum antibiotic therapy for 96 hours were eligible.

Patients were excluded if they had evidence of either a deep or disseminated fungal infection, or were not able to discontinue fungal prophylaxis with orally absorbed agents. Patients with serum creatinine levels greater than two times the upper limit of normal patients were excluded.

Comment: *The data forms only captured the fever entry criteria as a dichotomous variable (yes/no), and therefore the type of fever curves upon which the patients were judged eligible were not available for review.*

8.1.3.1.4: Procedures: Patients were to be randomized to receive either amphotericin B 1 mg/kg/day, AmBisome 1 mg/kg/day, or AmBisome 3 mg/kg/day. Randomization schedules were held in sealed envelopes, which were to be opened sequentially as each patient was enrolled into the protocol. Separate randomization schedules were maintained for each stratum.

Patients were to undergo the following pre-study evaluations: History and physical examination, cultures, hematology, BUN, chemistry, chest X-ray, and documentation of previous/concomitant medication. During the study treatment period the patients were to have BUN/creatinine measurements and hematology assessments at least 3 times weekly. The chemistry labs were to be done at least once weekly. Repeat fungal

cultures were to be performed at the discretion of the investigator as a patient's condition warranted.

Comment: *Standard surveillance cultures were not specifically outlined in the study schedule. This omission may lead to a sampling error regarding the fungal endpoints and an underestimation of events, or bias due to the open-label study design.*

All patients were to remain on study drug until an endpoint was reached (see below).

Comment: *There were no provisions for study drug crossovers in the original protocol, however, this did occur during study. Nine (22.5%) patients on the amphotericin B crossed over to AmBisome treatment. None of the AmBisome patients crossed to amphotericin B. Potential bias and trends toward apparent equivalence may be introduced by this procedure in an intent-to-treat analysis.*

8.1.3.1.5: Endpoints: The efficacy was to be determined by the investigators' assessment of the resolution of the clinical signs and symptoms in addition to resolution of fever and neutropenia. 1.) Resolution of symptomatology must occur in conjunction with a return of the neutrophil count to greater than 1.0 x 10^9/L for at least three consecutive days; 2.) A serious, non-resolving adverse event; 3.) The patient or investigator decides that withdrawal is in the best interest of the patient.

Comment: *As outlined above, endpoints were reported on the data form as dichotomous variables (Yes/No) based on the evaluation of the clinical investigator. The applicant's presentation of the results includes a re-classification, according to documented data collected throughout the study. For further discussion of this change for the efficacy analysis see "results" section.*

8.1.3.1.6: Statistical Considerations: The sample size of this study was to be 200 patients. This was based upon an ability to detect a 15% reduction in "serious" toxicity comparing amphotericin B with AmBisome, from an incidence of 20% to 5%. This would provide an alpha level of 0.05 and statistical power of 80% for detecting the hypothesized differences.

Comment: *The statistical section of the protocol is limited to the above. It is assumed that the efficacy comparison will be for equivalence, a delta was not pre-specified. In addition, the analysis of safety is vague, not specifying which specific parameters will be evaluated and how much of a change within a parameter would be significant. The calculations presented above appear to be based on a dichotomous variable (serious toxicity; yes/no).*

8.1.3.2: Results: To assess the efficacy of AmBisome, the sponsor retrospectively

classified patient outcomes as success or failure as follows:

Successful response: a minimum of three consecutive days without fever (≤ 38 C) until study end. This must occur in the absence of failure, as defined below.

Failure to respond: persistence of fever, addition of a systemically active antifungal medication during study of the development of a documented systemic fungal infection while on study.

Comment: *Retrospectively, the applicant defined the development of an emergent fungal infection as "being based on a culture from the blood, other normally sterile sites, or in a sample collected during bronchoscopy". According to the original protocol, efficacy analysis was to compare the "relative efficacies of these three regimens in treating empiric fungal infections". Parameters to be followed and analyzed include total duration of antifungal therapy, duration of hospitalization, and overall survival. Ultimately the applicant redefined the outcome analysis to include treatment failure (continued fever, documented fungal infection, concomitant use of systemic antifungal agent).*

8.1.3.2.1 Patient Disposition, comparability:
One hundred thirty-four patients were randomized; however, one patient assigned to AmBisome 1 mg/kg group was excluded from all safety and efficacy analyses, but included in the demographics. The reason for this is that the investigator failed to fill in CRF's.

8.1.3.2.2 Efficacy endpoint outcomes

8.1.3.2.2.1: Protocol deviations: Four patients had pre-treatment temperature values of less than 38°C (two in each of the AmBisome treatment groups). Three patients were confirmed as having mycosis at pre-treatment and were included in the analysis (all three of these were in the AmBisome 1 mg/kg/day group).

Comment: *Review of the initial data base reveals some confusion as to the assignment between the Confirmed Mycosis and Fever of Unknown Origin Groups. Patients who were randomized within the Confirmed Mycosis Group and subsequently had negative cultures for fungus, were not counted in either group for analysis of efficacy.*

Of the four patients with temperatures recorded as < 38°C on the pre-treatment day, three (1017,12015, 13002) had fevers documented during the study and are evaluable for the fever endpoint . One patient never had a recorded fever during the entire study. This patient is unevaluable for the failure endpoint and should be excluded from the analysis (1006).

Regarding positive blood cultures at baseline, it is possible to judge fungal failures and these patients should be included in the analysis (2036, 7008,7010).

Patients were permitted to have received orally absorbable antifungal prophylaxis prior to study entry; however, they were required to stop these agent prior to initiating therapy. Table 8.1.26 describes these agents according to study group.

TABLE 8.1.26 Use of Systemic Antifungal Therapy Prior to Study Entry

Systemic Antifungal	Amphotericin B N= 40	AmBisome 1 mg/kg N= 47	AmBisome 3 mg/kg N=46	Total N= 133
Amphotericin B IV	1	1	0	2
Fluconazole IV	2	3	3	8
Fluconazole PO	12	12	16	40
Intraconazole	5	7	10	22
TOTALS	20 (50%)	23 (49%)	29 (63%)	72 (54%)

Comment: *On average 54% of patients were receiving systemic prophylaxis prior to study entry, 14% of patients received these agents intravenously. Only 4 patients received systemic antifungal therapy other than assigned drug during study: 1 patient on amphotericin, 3 patients on AmBisome 1 mg/kg, and 0 patients on AmBisome 3 mg/kg.*

8.1.3.2.2.2: Reasons for treatment discontinuation

Reasons for discontinuation of study drug are shown below in Table 8.1.27. Four of the five patients discontinuing due to a severe adverse event had received amphotericin B. Nine patients discontinuing amphotericin B crossed over to AmBisome due to nephrotoxicity (7 patients), allergic reaction (1 patient), and treatment failure (1 patient).

TABLE 8.1.27: Reasons for Treatment Discontinuation

	Amphotericin B *	AmBisome 1 mg/kg	AmBisome 3 mg/kg
Number	40	47	46
Afebrile	7 (17.5)	12 (25.5)	17 (37.0)
Severe Adverse Event	4 (10.0)	1 (2.0)	0 (0)
Death	2 (5.0)	8 (17.0)	5 (10.9)
Crossover Patients	9 (22.5)	NA	NA
Investigator's Decision/Patient Request/ Other	18 (45.0)	26 (55.3)	24 (52.2)
Afebrile recovering neutrophils	3	8	11
Afebrile persistent neutropenia	6	4	3
Treatment Failure	5	8	7
Toxicity	4	4	2
Miscellaneous	0	2	1

(Table 14.1.1 vol 8.1)

Comment: *The above classification of withdrawals was verified by comparing the events to the line listings. Note that these categories were based upon the CRF completed by the physician who determined the reason for discontinuation. Only amphotericin B patients were allowed to crossover to the other study regimens; therefore, a review of the reasons for this change was undertaken. Among the 9 patients switched, 3 were classified as having severe adverse events, one was listed as "afebrile", 4 were listed under the investigator decision category. Further examination of the "other category" revealed an additional 6 patients being switched to AmBisome. Thus, there were a total of 15 crossovers from amphotericin B to AmBisome. Upon review of all of these patients (section 16.2.1 and table 14.2.7), it appears that 13 of the 15 crossovers were due to nephrotoxicity, 2 were due to fever, chills and rash.*

8.1.3.2.2.3 Patient Characteristics

TABLE 8.1.28 Underlying Diseases

	Amphotericin B	AmBisome 1 mg/kg	AmBisome 3 mg/kg	Total
Number	40	48	46	134
Acute Lymphoblastic Leukemia	7 (17.5)	4 (8.3)	4 (8.7)	15 (11.2)
Acute Myeloid Leukemia	21 (52.5)	28 (58.3)	23 (50.0)	72 (53.7)
Non-Hodgkin Lymphoma	6 (15.0)	8 (16.7)	10 (21.7)	24 (17.9)
Other	6 (15.0)	8 (16.7)	9 (19.6)	23 (17.2)

(Table 14.1.5 vol 8.1)

Comment: *The majority of patients (>80%), enrolled in the FUO strata, had a hematologic malignancy as their underlying condition. The distribution across groups was comparable for each of the classifications listed above.*

The use of GCSF (or GMCSF) among treatment groups was 21% on average, 7 patients on amphotericin B, 7 patients on AmBisome 1 mg/kg and 14 patients on AmBisome 3 mg/kg. In addition, there were 21 patients with transplantations, 4 in the amphotericin B group, 12 in the AmBisome 1 mg/kg group and 5 in the AmBisome 3 mg/kg group. On average 25% of the patients had neutrophil counts <250 cells/mm3.

Comment: *These patients would comprise a high risk group for fungal infection, and there were more In the AmBisome 1 mg/kg group, which could have caused a less favorable outcome for the AmBisome 1 mg/kg group.*

Demographics: The three treatment groups were well balanced for demographic characteristics. The median age of these patients was 46 years with a range from 17 to 79 years. The majority of the subjects were Caucasian (approximately 80%).

8.1.3.2.3 Efficacy Evaluation: The results of the applicant's and FDA's evaluation of success is presented in TABLE 8.1.29. For the 3-arm comparison for the efficacy endpoint, "afebrile for last 3 days, no concomitant use of systemic antifungal agent and lack of development of a fungal infection", there were no statistically significant differences (p=0.21).

TABLE 8.1.29: Number of Patients with Successful Outcome FUO Stratum

	Amphotericin B N=40	AmBisome 1 mg/kg N=47	AmBisome 3 mg/kg N=46
Success			
Afebrile for last 3 days, no concomitant use of systemic antifungal agents and the lack of development of a fungal infection	22 (55.0%)	21 (44.7%)	29 (63.0%)
Afebrile for last 3 days	23 (57.5%)	25 (53.2%)	29 (63.0%)
Failures			
Febrile for last 3 days	17 (42.5%)	22 (46.8%)	17 (37.0%)
Concomitant use of antifungal agent	1 (2.5%)	3 (6.4%)	0
Development of fungal infection	1 (2.5%)	3 (6.4%)	1 (2.2%)
FDA's EVALUATION			
Success*			
Afebrile for last 3 days, no concomitant use of systemic antifungal agents and the lack of development of a fungal infection	20/39 (51.3%)**	20/46 (43.5%)	28/45 (62.2%)
Failures	19 (48.7%)	26 (56.5%)	17 (37.8%)
Febrile for last 3 days	16 (41.0%)	20 (43.5%)	16 (35.6%)
Concomitant use of antifungal agent	2 (5.1%)	3 (6.5%)	0 (0%)
Development of fungal infection	1 (2.6%)	3 (6.5%)	1 (2.2%)

* One patient in each group was not evaluable due to lack of culture data (01031, 01006, 01029), they were not included in the analysis.
** One patient received a dose of systemic antifungal and therefore was counted as a failure (12012).

Comment: *In Table 8.1.29 the applicant's evaluation was based upon table 14.2.1 vol. 8.1. The applicant submitted revised efficacy evaluations via SAS diskettes. FDA review is based on these data diskettes. Review of line-listings agreed with the applicant's outcome assessment. The difference between the applicant's reporting in TABLE 8.1.29 and the FDA analysis is based on the use, by the FDA, of a mutually*

exclusive hierarchy which recognized systemic infection first, systemic antifungals second and continued fever last. CRFs were reviewed for these endpoints. Three patients were excluded from the FDA analysis (one in each group) for lack of culture data upon which to evaluate the endpoint. These were not counted as successes as the sponsor had. The applicant states that there is no significant difference in the outcome results. FDA calculation of the Confidence Intervals indicate that the 3 mg/kg AmBisome dose was equivalent to amphotericin B within a 20% range; however, the 1 mg/kg dose was not. Given the uncertainty, as represented by the CI, and the small sample size, these data do not establish the equivalence of AmBisome and amphotericin B but provide supportive evidence.

Fungal Events:

Fungal events based upon criteria for "proven" fungal infections is discussed below.

Table 8.1.30. Failures Due to Development of Fungal Infection

	Amphotericin B	AmBisome 1 mg/kg	AmBisome 3 mg/kg
Applicant results	1/40	3/47	1/46
FDA results	2/40	2/47	0/46

Comment: *An additional case of C. Krusei was found on a CRF. The reason listed for the failure on the line listings was cross-over to AmBisome, and the positive blood culture result was not listed in the fungal culture line listings. Based upon the stricter criteria which do not include C. albicans culture from a bronchoscopy specimen to represent "proven" infection these patients were omitted from the list (# 7008. # 13010).*

Since definitions were not outlined in the protocol, the classification of proven or presumed has not been rigorously applied by the applicant. The applicant looked for cases with culture proven infection indicating systemic infection. The investigators were also using antigenemia to diagnose infection, and other softer criteria, when they decided to make a change in therapy. There was no prospectively defined "presumed" category.

The severity of fungal infections may be assessed by analyzing mortality rates for categories of infection. The applicant presented a table which attributes death to either disease progression, fungal infection or study drug. A review of fungal infection deaths is presented below.

TABLE 8.1.31: Patient's death attributed to fungal infection

Amphotericin B	AmBisome 1 mg/kg	AmBisome 3 mg/kg
12018	2023	07001- Aspergillus species grown from ear swab, CT showed invasive external and middle ear otitis, he received 11 days of therapy. He died of a cerebral hemorrhage
8004- autopsy supported the investigator's diagnosis of generalized fungal infection. Candida species had been isolated on a sputum culture during Rx.	7010	APPEARS THIS WAY ON ORIGINAL
12031- left knee Aspergillus infection as well as recurrent leukemia		

Source: review of Death Narratives vol 8.1, table 14.4
NOTE: shaded boxes represent patients who died but were not listed as having failed due to fungal infections.

From Table 8.1.31 it can be seen that "proven" and life threatening fungal infections were more common in the Amphotericin B group and less so in the AmBisome groups in a dose dependent manner.

The data regarding fungal infections occurs in too low a frequency, and with enough imprecision that a strict statistical analysis is not informative. In general, this study is supportive and indicates that AmBisome is as least as good as Amphotericin B. The number of fungal endpoints were too small to apply statistical testing.

8.1.3.2.3.1 Systemic Fungal Infections: There were five documented, systemic fungal infections: one in the amphotericin B group (12018); three in the AmBisome 1 mg/kg group(2036, 7008, 7010); 1 in the AmBisome 3 mg/kg group (13010).

Comment: *While reviewing CRFs for safety data, an additional fungal blood culture was noted which was not included by the sponsor in the line listings or as a cause of failure (2021). This patient was noted to be a failure because of use of systemic antifungal drug and not due to an emergent fungal infection. The investigator notes that the reason for the medication switch is because of C. Krusei in the blood. This finding establishes further evidence that there may be problems with the accuracy of the applicant's data base regarding this study.*

In addition, there was potential for bias in this study because the criteria for failure were applied post-hoc in this open-label study. Sampling for fungal infection might have

been more or less intense when the investigators knew the assignment of treatment regimen.

8.1.2.3 Safety Comparison:

8.1.2.3.1 Extent of Exposure The average overall treatment duration was 10.8 days in the amphotericin B group, 13.3 days in the AmBisome 1 mg/kg group and 15.3 days in the AmBisome 3 mg/kg group. Patients treated with amphotericin B received a substantially lower daily dose than 1 mg/kg/d (ave. = 0.85 mg/kg/day). In the amphotericin B group, 30% of the patients (12/40) had interruptions in their treatment compared to 11% (5/47) and 7% (3/46) in the 1 mg/kg and 3 mg/kg AmBisome groups respectively. The average total dose of study drug was 794.1 mg, 972.0 mg, 2768.5 mg, respectively for amphotericin B, AmBisome 1 mg/kg, and AmBisome 3 mg/kg. Patients receiving amphotericin B were treated for a significantly shorter period of time than AmBisome.

Comment: *The longer average exposure period and dose received by the AmBisome groups could lead to increased toxicity; however, this was not seen, as the data presented below will demonstrate. In addition, the average length of neutropenia was similar for each group (16.6 days, 16 days, 15 days, respectively for* amphotericin B, AmBisome 1 mg/kg, and AmBisome 3 mg/kg*); thus, the average time at risk for fungal infections was comparable. The difference in duration of study drug administration did not appear to be dependant on the neutrophil count.*

8.1.3.3.2 Adverse Events Overall: Table 8.1.32 shows the sponsor's presentation of adverse events, occurring with a greater than 5% frequency (1 or 2 events).

TABLE 8.1.32 Overall Adverse Events (FUO strata)

Body System	Adverse Event	Amphotericin B N=40 n %	AmBisome 1 mg/kg N = 48 n %	AmBisome 3 mg/kg N= 46 n %
BODY AS WHOLE	Abdominal Pain	0 (0)	3 (6.3)	2 (4.3)
	Chest Pain	2 (5.0)	2 (4.2)	2 (4.3)
	Fever	8 (20.0)	4 (8.3)	1 (2.2)
	Headache	0 (0)	2 (4.2)	3 (6.5)
	Infection Fungal	3 (7.5)	4 (8.3)	1 (2.2)

	Mucositis NOS	0 (0)	1 (2.2)	3 (6.5)
	Pain	2 (5.0)	3 (6.3)	3 (6.3)
	Rigors	5 (12.5)	3 (6.3)	3 (6.5)
	Sepsis	0 (0)	1 (2.1)	3 (6.5)
CARDIOVASCULAR	Cardiac arrest	0 (0)	2 (4.2)	0 (0)
	Hypertension	0 (0)	4 (8.3)	1 (2.2)
	Tachycardia	0 (0)	2 (4.2)	0 (0)
DIGESTIVE	Diarrhea	3 (7.5)	8 (16.7)	12 (26.1)
	Hepatic Function Abnormality	2 (5.0)	0 (0)	1 (2.2)
	Hepatocellular damage	1 (2.5)	2 (4.2)	1 (2.2)
	Jaundice	1 (2.5)	1 (2.1)	2 (4.3)
	Nausea	2 (5.0)	5 (10.4)	4 (8.7)
	Vomiting	4 (10.0)	5 (10.4)	6 (13.0)
METABOLIC AND NUTRITIONAL	Alkaline Phos increased	0 (0)	2 (4.2)	1 (2.2)
	Hypokalemia	12 (30.0)	0 (0)	5 (10.9)
	NPN Increased	3 (7.5)	0 (0)	1 (2.2)
NEUROLOGIC	Coma	0 (0)	2 (4.2)	0 (0)
RESPIRATORY	Coughing	0 (0)	1 (2.1)	3 (6.5)
	Dyspnea	2 (5.0)	7 (14.6)	4 (8.7)
	Hemoptysis	0 (0)	2 (4.2)	1 (2.2)
	Pulmonary edema	2 (5.0)	0 (0)	0 (0)
	Respiratory Insufficiency	1 (2.5)	2 (4.2)	0 (0)
SKIN	Rash	4 (10.0)	3 (6.3)	5 (10.9)
	Rash Erythematous	1 (2.5)	2 (4.2)	2 (4.3)
	Rash Maculo-Papular	1 (2.5)	2 (4.2)	1 (2.2)
UROGENITAL	Dysuria	0 (0)	0 (0)	2 (4.3)

	Hematuria	0 (0)	0 (0)	3 (6.5)
	Renal Function abnormal	7 (17.5)	0 (0)	2 (4.3)
	Toxic Nephropathy	5 (12.5)	0 (0)	0 (0)

(Table 14.3.4 vol 8.1)

APPEARS THIS WAY ON ORIGINAL

Comment: *Fever and rigors appear to have occurred more frequently in the amphotericin B group. Diarrhea was as frequent in the AmBisome 1 mg/kg and 3 mg/kg groups. Nausea and vomiting occurred equally across all groups. Hepatocellular damage occurred at a rate of across the study groups. Hypokalemia, BUN increase, creatinine increase, renal function abnormal, toxic nephropathy were present in an increased incidence in the amphotericin B group compared to either experimental group. Dyspnea was more frequent in the AmBisome groups. Pulmonary complaints will be further discussed below in the special considerations section.*

APPEARS THIS WAY ON ORIGINAL

8.1.3.3.3 Withdrawals Due To Adverse Events: as mentioned above they were more frequent in the Amphotericin B group. The events are listed in Table 8.1.32.

APPEARS THIS WAY ON ORIGINAL

TABLE 8.1.33: Withdrawals Due to Adverse Events

	Amphotericin B N=40	AmBisome 1 mg/kg N= 47	AmBisome 3 mg/kg N = 48
Kidney Toxicity	10	0	1
Fever/Chills	5	1	0
Liver Function Abnormalities	2*	2	2
Other	1	2	0
TOTAL	18 (45%)	5 (10%)	3 (6%)

(Table 16.2.1 vol 8.4)

* one patient also had renal toxicity, and one fever in addition to liver toxicity.

APPEARS THIS WAY ON ORIGINAL

Comment: *In contrast to the applicant's table 14.1.1, table 16.2.1 is a more complete listing of discontinuations due to adverse events. A larger portion of patients treated with amphotericin B discontinued study drug due to an adverse event that either AmBisome arm. Of the adverse events leading to discontinuation of study drug, eighteen events in the amphotericin B group (10 with kidney toxicity, 5 with fever, 2 LFT abnormalities, 1 other), 5 in the AmBisome 1 mg/kg group (1 rash, 1 nausea/vomiting, 1 chills, 2 liver function abnormalities), and 3 in the AmBisome 3 mg/kg group (2*

abnormal liver function, 1 kidney toxicity). These were verified by review of line listings and selected CRFs. Hepatotoxicity will be considered in the special considerations section.

8.1.3.3.4 Serious Adverse Events:

Serious adverse events are listed by the sponsor in section 16.2.6.3. They were classified as related, possibly related, probably related and not related by the investigators. The frequencies of any serious adverse event for the three treatments are listed in Table 8.1.34.

Table 8.1.34: Frequency of Serious Adverse Events in the FUO Strata

Amphotericin B N=40	AmBisome 1 mg/kg N=47	AmBisome 3 mg/kg N=48
10 (25%)	11 (23%)	11 (23%)

(Appendix 16.2.6.3 vol 8.8)

Most of the events listed as serious were due to the patient's underlying disease, progression of a fungal infection and/or a concomitant illness such as sepsis. Of those events classified as being related to study drug, 2 were reported in the amphotericin group (1 cardiac arrhythmia and 1 nephrotoxicity), 1 was reported in the AmBisome 1 mg/kg group (one patient reported chest pain, dyspnea and atrial fibrillation which resolved before death from progressive carcinoma), and none in the AmBisome 3 mg/kg group. A brief description of these patients is listed below.

2004: A 48 y.o. male with non-Hodgkin Lymphoma and underling hepatitis B, had icterus at baseline. After 5 days of amphotericin B therapy the patent experienced cardiac arrhythmias and died. The investigator felt that the death was most likely due to progression of underlying disease, but possibly due to study medication.

2021: This 70 y.o. male was treated with amphotericin B, and experienced nephrotoxicity. Drug was discontinued because a positive blood culture returned for C. Krusei.

12011: This 53 y.o. male, treated with AmBisome 1 mg/kg, had T-cell Lymphoma. He experienced chest pain, dyspnea, and atrial fibrillation which resolved before death. Autopsy findings revealed extensive pulmonary infiltrate of T-cells and no evidence of pulmonary fungal infection. This adverse event may have been related to underlying disease and possibly related to study drug.

Comment: *Review of CRFs and line listings presented by the applicant, verified the*

above findings. Additional review of pulmonary related events follows below.

8.1.3.3.5 Deaths: There were thirty-eight deaths in the FUO strata. Table 8.1.35 describes the reasons for these deaths by study group.

TABLE 8.1.35 Overview of Deaths in FUO Strata

	Amphotericin B N=40	AmBisome 1 mg/kg N=47	AmBisome 3 mg/kg N= 48
Complication or Progression of Underlying Disease	8 (20.0%)	10 (21.3%)	10 (20.8%)
Fungal Infection	3 (7.5%)	2 (4.3%)	1 (2.1%)
Other Infection	0 (0%)	2 (4.3%)	2 (4.2%)

(Table 12.4.1 vol 8.1)

The applicant reports that only one death was thought to be due to study drug, This occurred in a patient in the amphotericin B group (pt id # 02004; cardiac arrhythmia).

Comment: *The synopsis and selected CRFs were reviewed and attribution reported by the sponsor was validated.*

8.1.3.3.6 Special Considerations:

BRI AUDIT: In order to prepare the NDA the applicant contracted with BRI International to perform an audit of all CRFs (100% source data verification of the CRFs). The BRI audit of the source documents re-evaluated additional clinical adverse events. These additional events were reviewed with each investigator who judged whether the event was disease-related or non-disease-related. The applicant then reviewed all of these additional clinical events. All clinical events meeting the criteria for a serious adverse event and all non-disease-related clinical events were added to the data base as adverse events. Disease-related clinical events were not entered in the data base. Approximately 60% of all other findings from the BRI audit were incorporated in to the data base.

Comment: *Review of the BRI audit sheets provided in the application reveals an appropriate process which followed the above algorithm.*

Pulmonary Adverse Events: Due to reports of respiratory adverse events associated with the infusion of lipid preparations, pulmonary adverse events were closely reviewed. There were 2 patients with dyspnea in the amphotericin B group (12023, 12018), 7 patients in the AmBisome 1 mg/kg group (12033, 12020, 12019, 12016, 12011, 12004,

2016), and 4 in the AmBisome 3 mg/kg group (13008, 12021, 12015, 1010). All were described by the investigator as not related to study drug except one patient in the AmBisome 1 mg/kg group, patient 12011, who is described above. This reaction may have been related to his underlying disease.

Comment: *Review of cases listed above does not disclose any apparent drug-related pulmonary toxicities across groups, and FDA's review is in agreement with the investigator's evaluation.*

Liver Toxicity: Animal toxicity studies suggest a potential for liver dysfunction. In order to determine whether liver toxicity was occurring in the AmBisome groups, CRF's of patients with adverse event listings consistent with symptoms and signs of liver toxicity were reviewed. Six cases are described below.

1001: A 53 y.o. female with acute myeloid leukemia had an evaluated SGPT. During the second week of therapy with AmBisome 3 mg/kg her SGPT rose to . The investigator noted that her fever resolved during the 4th day of treatment. Drug was discontinued with subsequent improvement of liver functions.

1004: A 26 y.o. female with aplastic anemia was treated with AmBisome 1 mg/kg for 1 month. The patient had viral hepatitis prior to enrollment. The investigator believed the liver enzyme elevations were most likely due to underlying hepatitis. Drug was discontinued.

5006: A 23 y.o. male treated with 1 mg/kg AmBisome for 3 days experienced an elevation in bilirubin. The patient had AML and a bone marrow transplant receiving cyclosporin. Drug was discontinued and bilirubin levels improved.

8003: This 41 y.o. male with T-cell lymphoma was treated with AmBisome 3 mg/kg. At baseline the alkaline phosphatase was . On day 7 of study drug alkaline phosphatase continued to rise. The investigator noted that this was probably due to the underlying disease or conditioning medications when the granulocyte count was

13003: This 38 y.o. female was treated with amphotericin B and was noted to have an abnormal bilirubin at baseline. The patient subsequently developed liver and renal insufficiency. The investigator felt this was due to overwhelming pseudomonas sepsis.

18015: This 73 y.o. male with hairy-cell leukemia was treated with amphotericin B. At baseline the alkaline phosphatase was The patient also suffered a

splenic infarct. After withdrawal of amphotericin B the liver functions became less abnormal.

Comment: *Because of the low number of events, no definite conclusions can be drawn regarding association of AmBisome and liver toxicity from this study; however, there does not appear to be any differences in hepatic toxicity between study groups.*

8.1.3.3.6 Laboratory Abnormalities: No statistically significant differences were observed for any of the laboratory parameters except for nephrotoxicity (doubling of serum creatinine), hypokalemia (potassium < 2.5 meq/L) and anemia (hemoglobin ≤ 8 g/dL). For the two strata (AmBisome 1 mg/kg and AmBisome 3 mg/kg) combined, there was approximately one-third the incidence of nephrotoxicity with either AmBisome treatment group compared with conventional amphotericin B (overall, 13.4% vs 16.1%, vs. 43.1%, p=0.001). A Kaplan-Meier analysis of time until first evidence of nephrotoxicity is presented by the sponsor. The onset of nephrotoxicity is significantly earlier in the conventional amphotericin B group compared to the two AmBisome dose regimens.

Comment: *Review of the laboratory data provided on SAS diskettes revealed many discrepancies in the values and units. FDA requested the applicant to verify the data and resubmit the data diskette along with 10% of the CRFs in order for the FDA to verify the data. Rates quoted above are from the original submission. Analysis of creatinine, potassium and liver functions revealed similar results to those above. The frequency of liver function abnormalities was low with a slight trend toward more events in the AmBisome groups. Anemia was more frequent in the amphotericin B group.*

8.1.3.1.4 Reviewer's Comments/Conclusions of Study Results

8.1.3.1.4.1 Efficacy Summary: Study 104-10 has several significant problems in design: open-label; data quality issues; inadequacy of sample size for efficacy evaluation; many of the endpoints and "success criteria were applied after the study was completed and not specified in the original protocol document; one way cross-overs were permitted to AmBisome only; confirmed mycosis were not included in the efficacy of empirical therapy.

No statistically significant difference in success rates across treatment arms was demonstrated by this study. In order to judge whether these agents are equivalent requires the evaluation of Confidence Intervals associated with the difference in treatment effect. Because of the small sample size and the small proportion of patients who are subclinically infected, the confidence intervals around the endpoints of interest (prevention of fungal infections) become wider than that calculated for study 002

approaching 20% (see statistical review). Thus, this study is viewed as supportive of efficacy, and not a pivotal trial demonstrating a claim for equivalence of AmBisome and amphotericin B.

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