CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-740/SE1-002

MEDICAL REVIEW

A RANDOMIZED, DOUBLE-BLIND, COMPARATIVE TRIAL OF TWO DOSES OF AMBISOME® (LIPOSOMAL AMPHOTERICIN B) VERSUS AMPHOTERICIN B, FOLLOWED BY FLUCONAZOLE IN THE TREATMENT OF ACUTE CRYPTOCOCCAL MENINGITIS IN AIDS PATIENTS

Medical Officer Review

NDA 50-740, SE1-002

DRAFT

Date Submitted: 6 July 1999
Date Received : 7 July 1999
Date Completed: 12 June, 2000

Drug Name:	**AmBisome®**
Generic Name:	**amphotericin B liposome for injection**
Applicant:	**Fujisawa Healthcare, Inc.** **Research and Development** **Three Parkway North** **Deerfield, Illinois 60015**
Indication:	**Acute cryptococcal meningitis in AIDS patients**
Protocol Number:	**94-0-013**
Study Initiation Date:	**29 June 1995**
Study Completion Date:	**22 April 1998**
Study Monitors:	**John Gordon, Ph.D., Clinical Project Manager** **Fujisawa Healthcare, Inc..** **(847) 317-8208** **Donald N. Buell, M.D., Medical Director** **Fujisawa Healthcare, Inc.** **(847) 317-1085**
Reviewer:	**Ziad Akl, M.D.**

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1. Rationale and Objective

Clinical data indicate that AmBisome has a better safety profile than that observed with conventional formulations of amphotericin B. The results of two noncomparative studies indicated that AmBisome may represent a clinically and mycologically superior formulation for the treatment of cryptococcal infection in AIDS patients. The objective of this study was to compare the safety, tolerability, and efficacy of two doses of AmBisome versus amphotericin B, followed by fluconazole, for treatment of acute cryptococcal meningitis in AIDS patients.

Recently, improved antiretroviral and protease inhibitor therapies for HIV-infected patients have resulted in higher T-cell counts and, consequently, a decrease in AIDS-associated conditions, including cryptococcal meningitis. During its first year (i.e., June 1995 - May 1996), this study had an average patient accrual of 11 patients per month. During the next year the average monthly accrual fell to 8 patients. It fell further still during the latter half of 1997 to only 5 patients per month despite a network of approximately 40 centers. Because of this, the trial was terminated prior to reaching 300 evaluable patients as was originally planned.

Reviewer's comments: *Given the increasing resistance of the human immunodeficiency virus to available therapies, a resurgence in the incidence of cryptococcal meningitis in AIDS patients is possible and a safer alternative to conventional amphotericin B may be needed. It is appropriate and desirable to compare the 2 drugs for such an indication. This study was part of phase 4 commitments agreed upon between the sponsor and the FDA and specified in a submission dated August 8, 1997.*

2. Study Design

This was a randomized (1:1:1), three-arm, double-blind, multicenter, parallel-comparative phase 3 trial. AIDS patients with confirmed cryptococcal meningitis received either 3.0 mg/kg or 6.0 mg/kg amphotericin B as AmBisome or amphotericin B deoxycholate (Fungizone®) at 0.7 mg/kg once daily via a 2-4 hour infusion during an 11-21 day induction phase. This was followed by daily consolidation therapy with fluconazole (400 mg, p.o. or i.v.) to complete a total of 10 weeks of therapy. Patients were evaluated at least twice weekly for clinical signs and symptoms and laboratory profile during the induction phase, and weekly or biweekly during the consolidation phase. The primary efficacy endpoint was the rate of culture conversion (cerebrospinal fluid [CSF] culture negative for *C. neoformans*) at week 2 (14±4 days) among the mycologically evaluable population. The secondary efficacy endpoints were:

1) therapeutic success at week 10 among the mycologically evaluable patients who completed study treatment or died during weeks 2-10.
2) survival at week 10 among the intent-to-treat population.

Safety was primarily assessed based on the incidence of infusion-related reactions, drug tolerability, nephrotoxicity, and hepatotoxicity.
Intravenous amphotericin B over a 2-week period followed by oral fluconazole antifungal therapy is currently the standard of care for cryptococcal meningitis in patients with AIDS and thus was compared to two regimens of AmBisome followed by fluconazole. AmBisome at 3 mg/kg per day was reported to be effective in treating cryptococcosis in AIDS patients, some of whom had not responded to amphotericin B. It was hypothesized that 6 mg/kg per day, as has been administered to some neutropenic patients, would result in better responses without compromising safety.

This multicenter study was conducted at 35 study sites. Eight of these centers enrolled more than ten patients. Analyses for determination of clinical laboratory profiles were performed locally. Study drug concentrations and antigen titers were analyzed by a central laboratory. To ensure patient safety, an independent Data Safety Monitoring Board (DSMB) monitored blinded study results and performed one closed-session review of unblinded results.

Reviewer's comments: *Double blinding is the preferred design for a trial comparing the safety and efficacy of 2 drugs. The dose of conventional amphotericin B used is appropriate. Approved doses of AmBisome are between 3 and 5 mg/kg/day. A dose of 6 mg/kg/d is, however, expected to be well tolerated given that the drug has been administered at much higher doses without untoward adverse events. The total duration of therapy is also appropriate. Fluconazole is the drug of choice for maintenance. Primary and secondary endpoints were appropriate and will all be considered in FDA's analyses. The study was strengthened by the inclusion of an independent DSMB to ensure the safety of study subjects.*

3. Protocol

3.1 Population and Procedures

Inclusion Criteria
Patients were eligible for inclusion in the study if they met all of the following criteria:
• A diagnosis of acute cryptococcal meningitis defined as:
(a) Definitive - a positive CSF culture OR
(b) Presumptive - clinical evidence of meningitis plus one of the following:
(1) biopsy compatible with a cryptococcal infection of the central nervous system.
(2)positive culture of *Cryptococcus neoformans* from a non-CSF site
(3)positive cryptococcal antigen test in CSF or in serum
(4)positive India Ink results from CSF
All presumptive diagnoses had to be confirmed with a positive CSF cryptococcal culture. Patients whose baseline culture was negative after 4 weeks of incubation could have remained in the study through 10 weeks. However, a patient may have been withdrawn if it was determined that there was no evidence of cryptococcal disease (e.g., negative antigen titers).

• Prior diagnosis of AIDS or HIV+, as determined by positive HIV-1 antibodies completed by enzyme linked immunosorbent assay (ELISA) with Western Blot, serum p24 antigen or positive HIV culture recovery. Patients with a history of high-risk behavior for HIV infection (bisexual or homosexual men, intravenous drug abusers, recipients of blood or blood products prior to May 1985, or sexual partners of any of the foregoing) may have been enrolled pending receipt of HIV documentation.
• Antifungal treatment for the present episode of meningitis of not more than 2.4 mg/kg (0.8 mg/kg per day over 3 days) amphotericin B, 15 mg/kg (5 mg/kg per day over 3 days) Abelcet, and 1200 mg (400 mg per day over 3 days) fluconazole. Treatment with these drugs could not have commenced more than 72 hours prior to study entry.
• Prophylactic treatment with fluconazole or itraconazole prior to study entry of not more than 200 mg per day p.o. of either drug.
• Age ≥1 month, male or female.
• Written informed consent provided by the patient or parent/legal guardian.
The protocol allowed patients who were participating in another double-blind trial at study entry to be randomized.

Exclusion Criteria
Patients were excluded from the study if they had any of the following:
• Documented systemic fungal infection, other than cryptococcosis, upon study entry
• History of anaphylaxis to amphotericin B
• History of sensitivity to triazole or imidazole compounds
• Serum creatinine concentration greater than twice the upper limit of normal (ULN)
• AST or ALT value greater than 10 times the ULN
• Unwillingness (for sexually active females with childbearing potential) to use adequate birth control methods during the course of the study
• Pregnancy or lactation (nursing)

Study Withdrawal Criteria
Reasons for study discontinuation included failure to meet inclusion/exclusion criteria, toxicity, lack of efficacy, requirement for therapy or prophylaxis of AIDS with a restricted medication, and noncompliance. Patients who withdrew from study therapy for reasons other than ineligibility had efficacy and safety evaluations performed at the time of discontinuation and, when possible, an evaluation of survival, clinical, and CSF status and off-study therapeutic regimen at 10 weeks.

Reviewer's comments: *Inclusion and exclusion criteria were acceptable. AmBisome has been demonstrated to be safe in children, who were included in this study.*

Randomization
Within each investigative site, adult patients who met the selection criteria were stratified by primary and recurrent cases and then randomly assigned within each center (1:1:1) to receive 0.7 mg/kg amphotericin B, 3.0 mg/kg AmBisome, or 6.0 mg/kg AmBisome. Since few pediatric (< 13 years of age) patients were expected to enroll, they were to be randomized (1:1:1) across centers. Patients were not to be enrolled for more than one episode of cryptococcal meningitis.

Reviewer's comments: *It was appropriate to randomize children across centers given the low prevalence of cryptococcal meningitis in this population.*

Treatments

Patients received 3.0 mg/kg or 6.0 mg/kg amphotericin B as AmBisome or 0.7 mg/kg of amphotericin B deoxycholate by intravenous infusion once daily for an 11-21 day induction period. The duration of each daily infusion was 2-4 hours. This infusion time was longer than the recommended 2-hour infusion for AmBisome in order to accommodate the recommended infusion time for amphotericin B. Amphotericin B is commonly used at dosages ranging from 0.5 to 1.0 mg/kg per day in the treatment of cryptococcal meningitis in AIDS patients. The daily dose used in this study, 0.7 mg/kg, is in the middle of that range. The 3 mg/kg per day AmBisome dose was chosen because this regimen was well-tolerated and effective in AIDS patients with cryptococcosis. It was hypothesized that 6 mg/kg per day would result in greater antifungal responses without compromising safety.

Following induction, all patients were switched to oral fluconazole– 400 mg per day for adults and 200 mg per day for patients less than 13 years of age–to complete 10 weeks of protocol-directed therapy. Fluconazole was administered intravenously if the patient was unable to take oral medication.

The targeted induction phase was 14 days of uninterrupted therapy; however, a minimum of 11 days of drug dosing was required and treatment could have continued for up to 21 days of uninterrupted therapy if the patient had minimal or delayed clinical improvement, or was critically ill. Reduction or interruption of daily study drug administration was permitted for reasons such as toxicity (e.g., abnormal liver function test values, increased serum creatinine, hematologic or other Grade III or IV toxicity, or temporary lack of venous access). If study drug dosing was reduced or interrupted, decisions to resume dosing and deliver a minimum desired dose were to be made as if the patient were receiving standard amphotericin B.

Medications for prophylaxis or treatment of infusion-related reactions were permitted throughout the induction phase.

Reviewer's comments: *The duration of the induction phase was acceptable, as was the duration of the maintenance phase with fluconazole.*

Procedures

The following procedures were performed within 72 hours prior to the first dose of study drug:

History and physical exam, assignment of meningitis score, Karnofsky performance status, assessment of neurologic status (patients with focal neurologic signs or seizures were evaluated by computer tomography (CT) or magnetic resonance imaging (MRI) for other CNS diseases), chest X-ray if clinically indicated and laboratory studies that included:

Hemoglobin, leukocyte count (total and differential), platelet count and hematocrit. Serum chemistries and urinalysis. CSF was evaluated for fungal culture,

analysis, cell count and differential, protein and glucose. Blood and sputum (if abnormal chest x-ray) for fungal culture. Serum HIV antibody test, if not known to be positive for HIV or if no prior AIDS diagnosis. Total CD_4 count was to be documented from a CD4 test obtained within the past 12 weeks.
Serial blood samples to obtain a concentration-time profile of amphotericin B were not taken in this study. However, single blood samples for serum amphotericin B concentration measurement were collected within 72 hours prior to the first dose of study drug and at weeks 1 and 2 at unspecified times relative to dosing. Additional blood samples were collected at weeks 5, 6, 9, and 10 in some patients. CSF samples were collected at week 2 for the determination of amphotericin B concentration.

Patients were evaluated at least twice weekly for clinical signs and symptoms and laboratory profile during the induction phase, and at weekly intervals during study weeks 3 and 4, and at biweekly intervals during weeks 5 through 10.

The lumbar puncture (LP) for mycological evaluation of the induction phase was performed on 14 ± 4 days. Clinical assessment for comparison of the induction phase of the three study groups was also performed at 14 ± 4 days. The end of study evaluations was at 10 weeks ± 3 days.

Reviewer's comments: *Safety evaluations were done at appropriate intervals to ensure the safety of subjects. The timing of the follow-up lumbar puncture was also appropriate. An LP done too soon would have underestimated the efficacy of therapy because of slow clearance of the organisms and their antigens.*

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Table 1 Schedule of Procedures

Procedure	Baseline[1]	Induction Phase (weeks 1-2)	Consolidation Phase (weeks 3-10)		End of Study
		Day 1 to Last Day of Infusion Drug Therapy	Day 1 to Last Day of Consolidation Drug Therapy		
			Weeks 3-4	Weeks 5-10	
History	X				
Inclusion/Exclusion Criteria	X				
Pregnancy Test	X				
Physical Exam Karnofsky	X				
Randomization	X				
Efficacy					
Clinical: Neurological Signs/Symptoms	X	2x/week[3,5]	1x/week	Every 2 weeks	X
Laboratory					
HIV	X				
CD4[2]	X				
LP	X	End of Week 2		Week 6	O[4]
Non CSF Culture					
Blood	X	End of Week 1, 2		Week 6	O
Sputum	O	O		O	O
Other	O	O		O	O
Serum Antigen	CL	End of Week 1, 2-CL		Week 6-CL	CL
Serum Ampho B	CL	End of Week 1, 2-CL		-	-
Diagnostic:					
Chest X-Ray	O	O	O	O	O
CT/MRI	O	O	O	O	O
Safety					
Infusion Reaction Monitoring	-	Daily	-	-	-
Adverse Event Monitoring		X	X	X	X
Laboratory:					
Hematology	X	2x/wk[3]	1x/wk	Every 2 wks	X
Serum Chemistry	X	2x/wk[3]	1x/wk	Every 2 wks	X
Urinanalysis	X	Wk 2		Wks 6, 10	X

X= Required; O= If indicated; CL= Central Laboratory

[1] Performed within 72 hours before first dose of study drug

[2] CD4 performed within 12 weeks is acceptable

[3] At least one day apart. The final determination must be on day 14±1

[4] Week 10 LP is required if CSF culture remains positive at wk 6

[5] Additional clinical assessment to be completed at the end of Induction Extension Phase.

3.2 Endpoints

Efficacy

The primary efficacy endpoint was the incidence of mycological success, defined as CSF culture conversion, at week 2 (i.e., 14±4 days) among the mycologically evaluable

population (i.e., all randomized patients who received at least one dose of study drug, had a positive baseline culture, and had at least one follow-up culture).
Mycological success at week 10 was also recorded, with deaths and discontinuations prior to week 10 counted as failures.

The secondary efficacy endpoints were:
• Therapeutic success (protocol-defined) at week 10 (i.e., week 10 clinical success plus week 10 mycological success) among the mycologically evaluable patients who completed study treatment or died during weeks 2-10 of study.
• Survival at week 10 among the intent-to-treat population (i.e., all randomized patients who received at least one dose of study drug).
As supplemental information, therapeutic success based on the investigator's judgement, total meningitis scores, lumbar puncture opening pressure, and clinical response at 2 and 10 weeks were tabulated.

A successful clinical outcome at 2 weeks was defined as no increase in the intensity or severity of the individual signs and symptoms of meningitis (i.e., fever, headache, level of consciousness, thought content/awareness, muscle strength, meningeal signs, cranial nerve involvement). At 10 weeks, clinical success was defined as absence of fever and meningeal signs, reduction of headache severity by at least one grade, and stabilization or improvement in the remaining individual parameters. In addition, total meningitis score at week 10 must be < 5 if baseline score was ≤ 9 or must have decreased by 50% if baseline score was ≥ 10. Serum and CSF antigen titers, measured at baseline and weekly intervals throughout the study, were also recorded.

Reviewer's comments: *Primary and secondary efficacy endpoints will all be considered for outcome analyses. Clinical and mycological outcomes were clearly defined in the protocol.*

Safety
All adverse events were recorded. In order to compare treatment groups with respect to outcomes of particular clinical interest, incidence of the following was analyzed:
• Infusion-related reactions (IRR), defined as the appearance, during study drug infusion or during a 1-hour period after completion of infusion, of one or more of the following: fever, chills/rigors, nausea, vomiting, other significant reactions (e.g., cardiovascular events)
• Nephrotoxicity, defined as an increase in serum creatinine to a value above normal and representing a value >50% above baseline (1.5x baseline). The incidence of patients experiencing a 100% increase from baseline (2x baseline) serum creatinine was also compared.
• Hepatotoxicity, defined as significant changes from baseline in serum concentrations of AST (SGOT) or ALT (SGPT). Significant changes were considered to be:
1. an increase to >5x baseline in cases where baseline is <2x ULN.
2. an increase to >3x baseline in cases where baseline is 2-≤5x ULN.
3. an increase to >2x baseline in cases where baseline is >5-10x ULN.

• Drug tolerance, defined as the requirement for a reduction in study drug dose due to toxicity. Drug tolerance was assessed based on the number of days study drug was withheld, whether the toxicity was considered a drug-related adverse event, and the percent difference between the desired cumulative dose and the actual dose administered.

Reviewer's comments: *Definitions of the above adverse events are acceptable. The main adverse events of amphotericin B, namely infusion-related reactions and nephrotoxicity, were compared.*

3.3 Statistical Methods

Populations for Analysis

The study was powered originally for 300 evaluable patients (100 in each treatment arm). However, slow accrual led to an early termination of the trial, and power was recalculated based on a sample size of 180 evaluable patients (60 in each treatment arm). This sample size would allow for a 71% power to detect a difference of 20% in the mycological success rate between the combined AmBisome group (3 mg/kg and 6 mg/kg) and the amphotericin B arm.

Patients were grouped according to the following classifications for data analyses:

- Modified Intent-to-Treat (MITT): All randomized patients who received at least one dose of study drug.
- Mycologically evaluable: All randomized patients who received at least one dose of study drug, had a positive baseline CSF culture, and had at least one follow-up culture.
- Therapeutically evaluable: Mycologically evaluable patients who either completed study therapy or died during weeks 2-10 of study.
- Per–Protocol Evaluable: Patients who met the inclusion/exclusion criteria and were without a major protocol deviation as determined during a blinded patient classification review.

Reviewer's comments: *The above dataset definitions were acceptable.*

Statistical Methodology

The primary efficacy endpoint was the incidence of mycological success (CSF culture conversion) at week 2 (14 ± 4 days) among the mycologically evaluable population. The secondary efficacy endpoints were:

1) protocol-defined therapeutic success at week 10 among the mycologically evaluable patients who completed study treatment or died during weeks 2-10.
2) survival at week 10 among the intent-to-treat population.

Primary outcome was analyzed using a 95% two-sided confidence interval, constructed for the difference (combined AmBisome – amphotericin B) in the week 2 culture conversion rate. If the lower bound of the confidence interval was above -0.20, it was to be concluded that AmBisome was not inferior to amphotericin B. If it was concluded that AmBisome treatment (combined dose groups) was not inferior to amphotericin B, this same testing procedure was applied to the individual AmBisome dose groups

(AmBisome 3.0 mg/kg vs. amphotericin B; AmBisome 6.0 mg/kg vs. amphotericin B). If the non-inferiority claim could not be made for the AmBisome combined-dose versus amphotericin B treatments, no further testing was done. The week 10 therapeutic success rate was analyzed by the same testing procedure as above. Survival at week 10 was determined by the Kaplan-Meier method.

The modified intent-to-treat population was analyzed for safety. Safety was assessed based on the incidence of adverse events (including infusion-related reactions), nephrotoxicity, hepatotoxicity, and drug. All adverse events were mapped to a modified COSTART dictionary. Incidence rates of adverse events and other safety variables were tabulated by treatment group and compared using Fisher's exact test. Kaplan-Meier plots were used in nephrotoxicity evaluations.

Interim Analysis

A Data Safety Monitoring Board (DSMB) of two physicians reviewed unblinded safety data from the ongoing trial in a closed session. The DSMB did not find any evidence of potential risks to the patients and did not recommend any alterations to the conduct of the trial.

4. Results

4.1 Patient Disposition

A total of 275 patients were randomized into the study. Five of the randomized patients did not receive study drug for the following reasons: one patient died prior to first dose of study drug, one patient was transferred to another hospital prior to first dose, 2 patients withdrew consent prior to first dose and a physician withdrew one patient because of misdiagnosis.

Three patients were randomized twice but did not receive drug under the misrandomized numbers.

One patient reenrolled in the study, which was not permitted by the protocol. Only data from this patient's first enrollment are included in the analyses; patient populations in this study are summarized in Table 2.

Table 2: Patient Population

	AmBisome			Ampho B
	3 mg/kg/d	6 mg/kg/d	BOTH	0.7 mg/kg/d
MITT[1]	86	94	180	87
Mycologically evaluable[2]	60	75	135	61
Therapeutically evaluable[3]	40	57	97	53
Per protocol population[4]	44	54	98	40

Ampho B: Amphotericin B

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

2: Mycologically evaluable: all randomized patients who had at least one dose of study drug, a positive baseline culture, and at least one follow-up culture.

3: Therapeutically evaluable: mycologically evaluable patients who either completed treatment or died during weeks 2-10 of study.

4: Per protocol patient population: patients who met the inclusion/exclusion criteria and were without a major protocol violation as determined during a blinded patient classification review.

The disposition of the modified intent-to-treat population is shown by treatment group in Table 3. Loss to follow-up was higher in the AmBisome group compared to the amphotericin B group and primarily occurred after the conclusion of induction dosing.

Table 3: Patient Disposition of MITT population

	AmBisome			Ampho B
	3 mg/kg/d n=86	6 mg/kg/d n=94	BOTH n=180	0.7 mg/kg/d n=87
Completed Study	49 (57.0%)	54 (57.4%)	103 (57.2%)	58 (66.7%)
Discontinued				
Death	7 (8.1%)	3 (3.2%)	10 (5.6%)	7 (8.0%)
Adverse event (AE)	4 (4.7%)	6 (6.4%)	10 (5.6%)	5 (5.7%)
AE during induction	3 (3.5%)	2 (2.1%)	5 (2.8%)	5 (5.7%)
Lack of efficacy	8 (9.3%)	9 (9.6%)	17 (9.4%)	6 (6.9%)
Lack of efficacy during induction	7 (8.1%)	5 (5.3%)	12 (6.7%)	5 (5.7%)
Lost to follow-up	7 (8.1%)	4 (4.3%)	11 (6.1%)	1 (1.1%)
Administrative reason[1]	11 (12.8%)	18 (19.1%)	29 (16.1%)	10 (11.5%)
Admin. during induction	4 (4.7%)	6 (6.4%)	10 (5.6%)	5 (5.7%)

Ampho B: Amphotericin B; Admin: Administrative discontinuation

1: Administrative reasons included physician decision, transfer or discharge from hospital, and noncompliance.

Reviewer's comments: *Reviewer agrees with the figures shown in the above tables per the databases. Proportionately more patients in the conventional amphotericin B group completed the study. There were numerically more discontinuations due to death in that group compared with the high dose AmBisome. Discontinuations due to adverse events were similar among all 3 groups. Discontinuations due to lack of efficacy, loss of follow-up and administrative reasons were higher in both AmBisome groups. All but one patient who were lost to follow-up received 2 weeks of therapy with either formulation of amphotericin B.*

Protocol Deviations

Respectively in the low dose AmBisome, high dose AmBisome and amphotericin B arms, there were 52 (60.5%), 64 (68.1%) and 59 (67.8%) protocol deviations. The majority of deviations for all three treatment groups involved missed or mistimed lumbar puncture, laboratory evaluations, or clinical assessments, baseline evaluations not

performed, or missed consolidation dosing. Patients were not excluded from the analyses because of a protocol deviation.

Reviewer's comments: *The most significant protocol deviations were those related to missed or mistimed lumbar punctures. These occurred in 20% and 29% of patients in the low and high dose AmBisome groups respectively, and in 30% of the amphotericin B group.*

Demographics and Other Baseline Characteristics

Demographics and other baseline characteristics are shown in Table 4 and Table 5. There were no statistically significant differences between treatment groups with respect to demographic and baseline characteristics such as age, antifungal history, total CD4 count, baseline laboratory values, incidence of pulmonary involvement, or Karnofsky score. The one pediatric patient (10 years of age) who participated in the study was randomized to amphotericin B.

Table 4: Demographics and Other Baseline Characteristics

		AmBisome			Ampho B	Total
		3 mg/kg/day n=86	6 mg/kg/day n=94	BOTH n=180	0.7 mg/kg/d n=87	n=267
Sex	Female	10 (11.6%)	13 (13.8%)	23 (12.8%)	6 (6.9%)	29 (10.9%)
	Male	76 (88.4%)	81 (86.2%)	157 (87.2%)	81 (93.1%)	238 (89.1%)
Race	Black	42 (48.8%)	53 (56.4%)	95 (52.8%)	51 (58.6%)	146 (54.7%)
	White	19 (22.1%)	26 (27.7%)	45 (25.0%)	19 (21.8%)	64 (24.0%)
	Hispanic	21 (24.4%)	13 (13.8%)	34 (18.9%)	16 (18.4%)	50 (18.7%)
	Other[1]	4 (4.7%)	2 (2.1%)	6 (3.3%)	1 (1.1%)	7 (2.6%)
Age (years)	Mean	38.7	40.1	39.5	38.5	39.2
	SD	9.2	10.0	9.6	8.14	9.2
	Median	37.0	39.0	38.5	39.0	39.0
	Range	22-61	21-68	21-68	10-59[2]	10-68
Primary Disease		81 (94.2%)	86 (91.5%)	167 (92.8%)	85 (97.7%)	252 (94.4%)
Recurrent Disease		5 (5.8%)	8 (8.5%)	13 (7.2%)	2 (2.3%)	15 (5.6%)
Pulmonary Involvement		13 (15.1%)	12 (12.8%)	25 (13.9%)	6 (6.9%)	31 (11.6%)
Total CD4 Count	N	67	70	137	66	203
	Mean	48.9	50.8	49.9	42.1	47.3
	SD	69.7	92.2	81.7	55.4	74.1
	Median	20.0	19.5	20.0	17.5	20.0
	Range					
Positive CSF culture for *C. neoformans*		73	85	158	76	234

Patient population: MITT (all randomized patients who received at least one dose of study drug.)
Ampho B: amphotericin B
1: Other: Asian, Native American (First Nation Ojibway)
2: One pediatric patient, 10 years of age, participated in the study.

Table 5: Baseline Clinical Laboratory Profile

Total number (%) with	AmBisome 3 mg/kg n=86	AmBisome 6 mg/kg n=94	AmBisome BOTH n=180	Ampho B 0.7 mg/kg n=87	Total n=267
Elevated serum creatinine	20 (23.3%)	16 (17.0%)	36 (20.0%)	15 (17.2%)	51 (19.1%)
Elevated AST/SGOT	39 (45.3%)	40 (42.6%)	79 (43.9%)	37 (42.5%)	116 (43.4%)
Elevated ALT/SGPT	31 (36.0%)	31 (33.0%)	62 (34.4%)	32 (36.8%)	94 (35.2%)
Elevated total bilirubin	3 (3.5%)	6 (6.4%)	9 (5.0%)	8 (9.2%)	17 (6.4%)

Patient population: MITT (all randomized patients who received at least one dose of study drug).
Ampho B: Amphotericin B

***Reviewer's comments**: The predominance of males in all 3 arms can be explained by the gender distribution of AIDS at the time this study was conducted. The location of the centers where the study was conducted explains the predominance of black patients.*

Prior and Concomitant Therapies

The majority of randomized patients in each group (approximately 80%) had started antifungal treatment for the current episode of cryptococcal meningitis, primarily amphotericin B, by the time of study entry. The proportions of patients who received conventional amphotericin B were 70.9%, 74.5% and 78.2%, respectively in the AmBisome 3 mg/kg, AmBisome 6 mg/kg and amphotericin B groups. Those who received fluconazole were 15.1%, 19.1% and 11.5% respectively. Approximately one-third of the patients had received antifungal treatment within the 3 months prior to study entry.

As shown in table 6, the proportion of patients in the amphotericin B group who received treatment of infusion-related reactions (IRR) was more than twice that in the AmBisome groups. The proportion of patients administered premedication to prevent IRR was similar across groups. The most common medications for IRRs were acetaminophen, diphenhydramine, pethidine, prochlorperazine, and promethazine. The most common medications for prophylaxis of IRRs were acetaminophen, diphenhydramine, hydrocortisone, and pethidine.

Table 6: Prophylaxis and Treatment of Infusion Related Reactions (IRR)

	AmBisome			Ampho B
	3 mg/kg n=86	6 mg/kg n=94	BOTH n=180	0.7 mg/kg n=87
Number (%) of patients administered premedication to prevent IRR	54 (62.8%)	67 (71.3%)	121 (67.2%)	63 (72.4%)
Number (%) of patients administered treatment of IRR	20 (23.3%)	21 (22.3%)	41 (22.8%)	46 (52.9%)

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

***Reviewer's comments**: The proportion of patients treated with conventional amphotericin B for the current episode of meningitis was higher in the amphotericin B group compared to AmBisome. The smaller number of patients on AmBisome requiring treatment for IRR suggests a potential role for AmBisome in the treatment of patients intolerant to amphotericin B.*

Treatment Compliance and Study Drug Exposure

Study drug dosing and administration during the induction phase is summarized in Table 7. As shown, the duration of study drug treatment was similar for patients in the AmBisome and amphotericin B groups. These patients received, on average, 88.7% to 93% of their desired cumulative dose.

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Table 7: **Study Drug Dosing and Administration (Induction Phase)**

	AmBisome			Ampho B
	3 mg/kg n = 86	6 mg/kg n = 94	BOTH n = 180	0.7 mg/kg n = 87
Number of days on study drug				
Mean ± SD	13.5±4.0	14.0±3.8	13.8±3.9	13.3±5.5
Median (range)				
Maximum infusion duration				
≤2 hours	1 (1.2%)	0	1 (0.6%)	0
>2 - ≤3 hours	10 (11.6%)	10 (10.6%)	20 (11.1%)	8 (9.2%)
>3 - ≤ 4 hours	40 (46.5%)	39 (41.5%)	79 (43.9%)	33 (37.9%)
>4 hours	33 (38.4%)	44 (46.8%)	77 (42.8%)	46 (52.9%)
Number of infusions per patient				
Mean ± SD	12.9±4.0	13.2±3.6	13.1±3.8	12.3±4.6
Median (range)				
Cumulative dose (mg/kg)				
Mean ± SD	39±14.5	77.3±21.6	59±26.6	8.7±3.5
Median (range)				
Percent of Desired Dose[1]				
Mean ± SD	93±34.6	92.1±25.7	92.5±30.2	88.7±35.3
Median (range)				

Patient population: all randomized patients who received at least one dose of study drug.
Ampho B: Amphotericin B; SD: standard deviation.
1: Percent desired dose defined as cumulative dose (mg/kg) over desired cumulative dose for 14 days x 100.

The number of patients treated with fluconazole during the consolidation phase was 64 (74%) and 77 (82%) in the AmBisome 3.0 mg/kg and 6.0 mg/kg groups, respectively, and 66 (76%) in the amphotericin B group. The mean ± SD duration of fluconazole dosing was 49.2 ± 18.5, 45.6 ± 18.7, and 50.2 ± 17.1 days in the three groups, respectively.

***Reviewer's comments**: The cumulative dose of study drugs that patients received was adequate in the 3 arms, as was the duration of fluconazole dosing.*

Amphotericin B concentration data are summarized in Table 8.
Higher mean serum amphotericin B concentrations were obtained at weeks 1 and 2 with administration of AmBisome compared with the conventional formulation of amphotericin B. By week 10, concentrations declined to barely detectable levels in all treatment groups. Interpatient variability was considerable throughout the study.
Of 46, 58 and 44 patients in AmBisome 3 mg/kg, AmBisome 6mg/kg and amphotericin B groups respectively, who had CSF measurements of amphotericin B levels done at week 2, only six patients demonstrated measurable CSF concentrations of amphotericin B.

Table 8: Mean ±SD Amphotericin B Concentration in Serum and CSF

	AmBisome				Ampho B 0.7 mg/kg	
	3 mg/kg		6 mg/kg			
	n	mg/L	n	mg/L	n	mg/L
Serum Concentration[1]						
Baseline	55	0.2±0.2	69	3.0±12.2	52	0.3±0.3
Week 1	54	12.9±14.9	69	31.6±34.9	52	0.6±0.4
Week 2	49	20.3±26.0	67	39.0±40.8	53	0.5±0.5
Week 9/10	18	0.4±1.0	21	0.2±0.1	21	0.1±0.1
CSF Concentration[2] Week 2	1	85.7	4	13.7±26.4	1	0.1

Ampho B: Amphotericin B

1:Patient population: all randomized patients who received at least one dose of study drug and had serum concentration measurements performed.

2: Patient population: all randomized patients who received at least one dose of study drug and had detectable CSF amphotericin B concentrations.

***Reviewer's comments**: Patients randomized to AmBisome 6mg/kg had mean serum amphotericin B concentrations 10 times higher than those in the conventional amphotericin B arm at baseline, but since samples were drawn at any time within the 72 hours prior to study drug initiation, no firm conclusion can be drawn as to the impact of that difference on efficacy rates . CSF drug levels were mostly undetectable in all 3 arms despite the large number of patients who were tested (46 for AmBisome 3 mg/kg, 58 for AmBisome 6 mg/kg and 44 for amphotericin B). This suggests that penetration of amphotericin B into the CSF may not be necessary to achieve therapeutic efficacy.*

4.2 Efficacy

Primary Efficacy Endpoint: Mycological Success at Week 2

Mycological success as presented by the sponsor is shown in Table 9.

Table 9: Mycological Success Rate (CSF Culture Conversion)

	AmBisome 3 mg/kg	AmBisome 6 mg/kg	BOTH	Ampho B 0.7 mg/kg
Number of mycological evaluable[1] patients	60	75	135	61
Success at Week 2[†]	*35 (58.3%)*	*36 (48.0%)*	*71 (52.6%)*	*29 (47.5%)*
Success at Week 10	36 (60.0%)	53 (70.7%)	89 (65.9%)	48 (78.7%)
Number of mycological evaluable patients with Week 2 culture	55	67	122	54
Success at Week 2	35 (63.6%)	36 (53.7%)	71 (58.2%)	29 (53.7%)
Number of therapeutic evaluable[2] patients	40	57	97	53
Success at Week 10	36 (90.0%)	53 (93.0%)	89 (91.8%)	48 (90.6%)

	AmBisome 3 mg/kg vs. Ampho B	***AmBisome 6 mg/kg vs. Ampho B***	***AmBisome BOTH vs. Ampho B***
[†] Treatment Difference (AmBisome-amphotericin B) and 95% CI for Mycological Success at Week 2	*10.8% (-6.9%, +28.5%)*	*0.5% (-16.4%, +17.3%)*	*5.0% (-10.0%, +20.2%)*

1: Mycologically evaluable: all randomized patients who received at least one dose of study drug, had a positive baseline culture and at least one follow-up culture.
2: Therapeutically evaluable: mycologically evaluable patients who completed therapy or died during weeks 2-10.

The lower bounds of the 95% confidence intervals for the treatment differences (AmBisome minus amphotericin B) were all above –20% , indicating that AmBisome (combined, 3 and 6mg/kg) was as effective as amphotericin B with regards to mycological success at 2 weeks. Week 10 success was higher in the amphotericin B group for the mycologically evaluable population but was similar across groups for the therapeutically evaluable population.

***Reviewer's comments**: Mycological success in the above table is based solely on a negative CSF culture result, performed at or prior to week 2 for week 2 results, and at or prior to week 10 for week 10 results. Very few patients had a lumbar puncture done at week 10, which means that most week 10 mycological successes were carried forward from weeks 2 and 6. This makes interpretation of week 10 myclogical success rates very difficult. A better way to examine week 10 mycological success rates is by considering as successes only those negative cultures performed at week 10 or, for patients without a week 10 culture, requiring that they have a negative culture available from an earlier lumbar puncture and be clinical successes at week 10. Such a definition was agreed upon with the sponsor prior to unblinding the study. Results of such an analysis are shown in Table 9a:*

Table 9a: Mycological Success Rates at week 10

	AmBisome 3 mg/kg	AmBisome 6 mg/kg	AmBisome BOTH	Ampho B 0.7 mg/kg
Number of therapeutically evaluable patients	40	57	97	53
Success at week 10	27 (67.5%)	42 (73.7%)	69 (71.1%)	40 (75.5%)
Treatment difference AmBisome-amphotericin B and 95% CI	-8.0% -26.5%; +10.5%	-1.8% -18.1%; +14.5%	-4.3% -19%; +10.3%	

Since for some patients week 2 culture results were carried forward from week 1, a separate analysis is shown in Table 9 with success rates for only those subjects with a week 2 culture. Ninety-five percent CI for this group are shown below:

AmBisome 3mg/kg - amphotericin B: -8.5% to 28%
AmBisome 6mg/kg - amphotericin B: -18% to 18%
AmBisome BOTH - amphotericin B: -11% to 20%

Secondary Efficacy Endpoints

Therapeutic Success at Week 10

Therapeutic success at week 10 is summarized in Table 10. The lower bound of the 95% confidence interval for the treatment difference in week 10 therapeutic success (AmBisome minus amphotericin B) was above –20% but was not above zero, for the AmBisome combined dose and 6 mg/kg groups. The lower bound of the 95% confidence interval for the treatment difference (AmBisome minus amphotericin B) was –26.5% for the AmBisome 3 mg/kg group.

Based on the investigators' evaluation, therapy was successful in 85% (34/40) and 93% (53/57) of the 3 mg/kg and 6 mg/kg AmBisome groups, respectively, and 94% (50/53) of the amphotericin B group.

Table 10: Therapeutic Success Rates (Therapeutically evaluable Population)

	AmBisome 3 mg/kg	AmBisome 6 mg/kg	AmBisome BOTH	Amphotericin B 0.7 mg/kg
Number of therapeutically evaluable patients	40	57	97	53
Success at week 10	27 (67.5%)	42 (73.7%)	69 (71.1%)	40 (75.5%)
Treatment difference AmBisome-amphotericin B and 95% CI	-8.0% -26.5%; +10.5%	-1.8% -18.1%; +14.5%	-4.3% -19%; +10.3%	

***Reviewer's comments**: Note that the above results are identical to those in Table 9a. This is due to the fact that no patients with negative week 10 cultures were clinical failures at week 10. AmBisome at 3 mg/kg was inferior to conventional amphotericin B at week 10 in terms of therapeutic success rates as evidenced by the*

lower limit of the CI (-26.5%). The results were also marginal for AmBisome 6 mg/kg with a lower limit of –18.1%.

By the investigators' assessment, therapeutic success rates were higher for the 3 groups. Ninety-five % CI calculated by the FDA for those rates were:

AmBisome 3mg/kg - amphotericin B: -22% to +3%
AmBisome 6mg/kg - amphotericin B: -10% to +8%
AmBisome BOTH - amphotericin B: -13% to +4%

Again AmBisome at 3 mg/kg was inferior to conventional amphotericin B.

FDA also performed additional analyses of therapeutic success rates at week 10 among patients with positive baseline CSF culture who received at least one dose of study drug, as shown in table 10a (this population would be called MITT by FDA's definition):

Table 10a: Therapeutic Success Rates (MITT by FDA's definition)

	AmBisome 3 mg/kg	AmBisome 6 mg/kg	Ampho B 0.7 mg/kg
Number of patients	73	85	76
Success at week 10	27 (37%)	42 (49%)	40 (53%)
Treatment difference AmBisome-amphotericin B and 95% CI	-16% -32.8%; +1.5%	-4% -19.9%; +13.5%	

CI limit was below -20% for AmBisome 3 mg/kg and marginally above –20% for AmBisome 6 mg/kg.

Patient Survival at Week 10

Kaplan-Meier estimates of patient survival through week 10 were similar between AmBisome- and amphotericin B-treated patients (p=0.619, Wilcoxon test). Kaplan-Meier estimates at week 10 were 83.6% (95% CI: 75.7%, 91.6%) for the combined AmBisome group and 87.0% (95% CI: 79.5%, 94.6%) for the amphotericin B group.

Reviewer's comments: *Actual survival rates were 86% for AmBisome 3 mg/kg, 90% for AmBisome 6 mg/kg, 88% for AmBisome BOTH, and 88% for conventional amphotericin B. The differences were not significant.*

Additional Efficacy Endpoints

Clinical Success

Clinical success is summarized in Table 11.

Table 11: Clinical Success Rates

	AmBisome 3 mg/kg	AmBisome 6 mg/kg	BOTH	Ampho B 0.7 mg/kg
Number of evaluable[1] patients	73	85	158	76
Success at Week 2	48 (65.8%)	64 (75.3%)	112 (70.9%)	50 (65.8%)
Number of evaluable[2] patients	44	59	103	54
Success at Week 10	31 (70.5%)	43 (72.9%)	74 (71.8%)	44 (81.5%)

Ampho B: Amphotericin B

1: Clinically evaluable: All randomized patients who received at least one dose of study drug and had a positive baseline culture

2: Clinically evaluable patient who completed therapy or died during weeks 2-10.

Reviewer's comments: *Week 10 clinical success rates were higher for conventional amphotericin B than for either AmBisome group. Ninety-five percent CI for the difference in success rates at week 10 were as follows:*

AmBisome 3mg/kg - amphotericin B: -28.3% to +6.3%

AmBisome 6mg/kg - amphotericin B: -24.3% to +7.1%

AmBisome BOTH - amphotericin B: -23.5% to +3.9%

These CI suggest that both doses of AmBisome were inferior to amphotericin B in terms of clinical success at week 10.

FDA performed an additional analysis among patients with positive baseline CSF culture who received at least one dose of study drug, as shown in table 11a. CI limits are again below –20%.

Table 11b: Clinical Success Rates (MITT by FDA's definition)

	AmBisome 3 mg/kg	AmBisome 6 mg/kg	Ampho B 0.7 mg/kg
Number of patients	73	85	76
Success at week 10	31 (42%)	43 (51%)	44 (58%)
Treatment difference AmBisome-amphotericin B and 95% CI	-16% -32.6%; +1.8%	-7% -23.9%; +9.3%	

4.3 Safety

Adverse Events

Summary of Adverse Events

Week 1-4 adverse events for which a significant difference between AmBisome and amphotericin B was detected are presented in Table 12. Adverse events after week 4 occurred at too low an incidence to demonstrate significance between the different arms. Nearly all patients experienced at least one adverse event during the study. During weeks 1-4, the overall incidence of adverse events was significantly lower in the 3 mg/kg AmBisome group compared with the amphotericin B group. Adverse events that

occurred with a significantly lower frequency with AmBisome 3 mg/kg compared with amphotericin B were fever, chills, phlebitis, anemia, increased creatinine, bilirubinemia, hypokalemia and hiccups (Table 12). The AmBisome 6 mg/kg group had significantly less fever, chills, phlebitis, increased cough and hiccups. There were no adverse events that occurred with significantly lower frequency in the amphotericin B group during weeks 1-4. It was noted that the week 1-4 overall incidence of hemic and lymphatic system adverse events (37.2% vs. 55.3%, p=0.017) was significantly higher in the AmBisome 6 mg/kg group compared with the 3 mg/kg group. Individual adverse events that occurred with significantly higher incidence in the 6 mg/kg group during weeks 1-4 were anemia (26.7% vs. 47.9%, p=0.005), hypokalemia (31.4% vs. 51.1%, p=0.010), hypomagnesemia (29.1% vs. 48.9%, p=0.009), creatinine increased (18.6% vs. 39.4%, p=0.003), and bilirubinemia (0 vs. 8.5%, p=0.007). There were no significant differences between AmBisome groups for fever (16.3% vs. 13.8%, p>0.05) or chills (7.0% vs. 11.7%, p>0.05) during weeks 1-4. (P-values are from Fisher's exact test).

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Table 12: Incidence of Adverse Events Including Infusion-Related Reactions (Week 1-4):

	Incidence and *p*-Value (Fisher's Exact Test)		
	AmB Both (n=180) vs. Ampho B (n=87)	**AmB 3 mg/kg (n=86) vs. Ampho B (n=87)**	**AmB 6 mg/kg (n=94) vs. Ampho B (n=87)**
Overall	93.3% vs. 97.7% *p* = 0.156	89.5% vs. 97.7% *p* = 0.032	96.8% vs 97.7% *p* > 0.999
Body as a Whole Any AE	57.2% vs. 74.7% *p* = 0.007	57.0% vs 74.7% *p* = 0.016	57.4% vs 74.7% *p* = 0.019
Fever	15.0% vs. 37.9% *p* = <0.001	16.3% vs 37.9% *p* = 0.002	13.8% vs 37.9% *p*<0.001
Chills	9.4% vs. 48.3% *p* = <0.001	7.0% vs 48.3% *p*<0.001	11.7% vs 48.3% *p*<0.001
Cardiovascular System Any AE	29.4% vs. 50.6% *p* = 0.001	27.9% vs 50.6% *p* = 0.003	30.9% vs 50.6% *p* = 0.010
Phlebitis	10.0% vs. 25.3% *p* = 0.002	9.3% vs 25.3% *p* = 0.008	10.6% vs 25.3% *p* = 0.011
Hemic and Lymphatic System Any AE	46.7% vs. 54.0% *p* = 0.297	37.2% vs 54.0% *p*=0.033	55.3% vs 54.0% *p*=0.882
Anemia	37.8% vs. 43.7% *p* = 0.423	26.7% vs 43.7% *p* = 0.026	47.9% vs 43.7% *p* = 0.655
Metabolic and Nutritional Disorder Hypokalemia	41.7% vs. 48.3% *p* = 0.357	31.4% vs. 48.3% *p* = 0.030	51.1% vs 48.3% *p* = 0.767
Increased Creatinine	29.4% vs. 43.7% *p* = 0.027	18.6% vs 43.7% *p*=0.001	39.4% vs 43.7% *p* = 0.651
Bilirubinemia	4.4% vs. 12.6% *p* = 0.021	0 vs 12.6% *p*=0.001	8.5% vs 12.6% *p* = 0.468
Respiratory System Any AE	28.9% vs. 42.5% *p* = 0.037	33.7% vs 42.5% *p* = 0.274	24.5% vs 42.5% *p* = 0.012
Cough Increased	5.0% vs. 10.3% *p* = 0.121	8.1% vs 10.3% *p* = 0.794	2.1% vs 10.3% *p* = 0.028
Hiccup	0 vs. 6.9% *p* = 0.001	0 vs 6.9% *p* = 0.029	0 vs 6.9% *p* = 0.011

Patient population: all randomized patients who received at least one dose of study drug.
AmB: AmBisome; Ampho B: amphotericin B.
There were no statistically significant treatment differences (AmBisome vs. amphotericin B) for adverse events not represented in the table.

Infusion-Related Reactions

The incidence of infusion-related reactions (IRR) are summarized in Table 13. The overall incidence of IRRs, as well as the incidences of individual IRRs (except nausea and vomiting), were significantly lower for patients administered either dose of AmBisome compared with amphotericin B. Fever, chills/rigors, and infusion-related respiratory events overall were also significantly lower in both AmBisome groups compared with the amphotericin B group.

Table 13: Incidence of Infusion-Related Reactions

COSTART Term	AmBisome 3 mg/kg n = 86	AmBisome 6 mg/kg n = 94	Ampho B 0.7 mg/kg n = 87	*(Fisher's exact test)*	
				AmBisome 3 mg/kg vs Ampho B	*AmBisome 6 mg/kg vs Ampho B*
Overall	27 (31.4%)	35 (37.2%)	58 (66.7%)	*p<0.001*	*p<0.001*
Body as a Whole (Any AE)	15 (17.4%)	19 (20.2%)	50 (57.5%)	*p<0.001*	*p<0.001*
Fever:					
Increase in temp of ≥0.3°C	9 (10.5%)	12 (12.8%)	31 (35.6%)	*p<0.001*	*p<0.001*
Increase in temp of ≥0.6°C	8 (9.3%)	12 (12.8%)	29 (33.3%)	*p<0.001*	*p=0.001*
Increase in temp of ≥1.0°C	6 (7.0%)	8 (8.5%)	24 (27.6%)	*p<0.001*	*p=0.001*
Chills/rigors	5 (5.8%)	8 (8.5%)	42 (48.3%)	*p<0.001*	*p<0.001*
Nausea	11 (12.8%)	13 (13.8%)	18 (20.7%)	*p=0.222*	*p=0.241*
Vomiting	14 (16.3%)	13 (13.8%)	16 (18.4%)	*p=0.841*	*p=0.425*
Respiratory System (Any AE)	0	1 (1.1%)	8 (9.2%)	*p=0.007*	*p=0.015*

Premedication for infusion-related reactions was permitted throughout the study.
Ampho B: Amphotericin B; Temp: Temperature
There were no statistically significant treatment differences for IRRs not represented in the table.

Reviewer's comments: *These results confirm what was already shown in other studies to be a better tolerability profile of AmBisome over amphotericin B. Despite the fact that the 6 mg/kg dose is higher than the maximum approved dose, this dose still shows a lower incidence of infusion-related and other adverse events.*

Deaths

A total of 31 patients died during the course of the study. The primary causes of death during weeks 1-4 are listed in Table 14. Only two of the deaths, both in the AmBisome 3 mg/kg group, were considered possibly related to study drug (sepsis and meningoencephalitis with multisystem organ failure); One death in the amphotericin B group (metabolic acidosis) was considered probably related to study drug. None of the deaths was considered related to fluconazole.

Table 14: Primary Causes of Death During Weeks 1-4

AmBisome 3 mg/kg Group	
Number of Deaths/Number of Patients – Weeks 1-10	12/86 (14.0%)
Number of Deaths/Number of Patients – Weeks 1-4	8/86 (9.3%)
Patient Number	**Cause of Death (Weeks 1-4)**
94112	Systemic cryptococcosis
96103	Cardiac arrest
99101	Sepsis
102118	Metastatic non-small cell carcinoma
102130	Gram negative sepsis (*E. coli*)
103106[1]	Sepsis
109105[1]	Meningoencephalitis with multisystem organ failure
116102	Respiratory failure
AmBisome 6 mg/kg	
Number of Deaths/Number of Patients – Weeks 1-10	9/94 (9.6%)
Number of Deaths/Number of Patients – Weeks 1-4	5/94 (5.3%)
Patient Number	**Cause of Death (Weeks 1-4)**
33123	Cryptococcosis
94109	Systemic Kaposi's sarcoma
94111	Acute respiratory failure
102106	Progressive disseminated cryptococcal disease
123101	Cryptococcal meningitis
Amphotericin B 0.7 mg/kg	
Number of Deaths/Number of Patients – Weeks 1-10	10/87 (11.5%)
Number of Deaths/Number of Patients – Weeks 1-4	9/87 (10.3%)
Patient Number	**Cause of Death (Weeks 1-4)**
33103[2]	Metabolic acidosis
33106	Meningitis
33107	Respiratory arrest
33112	Cryptomeningitis
33114	Sepsis
99105	Hydrocephalus
109106	Increased intracranial pressure
119107	PCP pneumonia
137101	Cryptococcal disease

Patient population: all randomized patients who received at least one dose of study drug.
1: Death was possibly related to study drug.
2: Death was probably related to study drug.

Reviewer's comments: *Information on survival was obtained on all patients in the MITT population, i.e. including those who were lost to follow-up or discontinued for various reasons. Differences in death rates between the 3 arms were not statistically significant.*

Severe/Life-Threatening (Grade III or IV) Adverse Events

A significantly greater percentage of patients in the amphotericin B group experienced at least one severe/life-threatening event during weeks 1-4 compared with the AmBisome 3 mg/kg group (50.6% vs. 31.4%, p=0.013; Table 15). The incidence in the amphotericin B group relative to the AmBisome 6 mg/kg group was numerically but not significantly higher (50.6% vs. 40.4%, p=0.182). By body system, the incidence of severe/life-threatening adverse events in the body as a whole during weeks 1-4 was significantly higher in the amphotericin B group relative to the AmBisome 3 mg/kg (17.2% vs. 3.5%, p=0.005) and 6 mg/kg (17.2% vs. 6.4%, p=0.035) groups. When infections were included in the analysis, the overall incidence of severe/life threatening adverse events during weeks 1-4 remained significantly higher with amphotericin B relative to the 3 mg/kg AmBisome group (51.7% vs. 34.9%, p=0.032). There were no individual severe/life-threatening adverse events that occurred with high incidence, regardless of the inclusion of concomitant infections in the analysis.

The only individual event for which there was a significant difference between amphotericin B and AmBisome was dyspnea, which occurred in five patients in the amphotericin B group but none in the AmBisome groups.

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Table 15: Incidence of Common Severe/Life-threatening Adverse Events (Weeks 1-4)

COSTART Body System	Term	AmBisome 3 mg/kg	AmBisome 6 mg/kg	Ampho B 0.7 mg/kg
Total number of patients		86	94	87
Overall Number with any adverse event		27 (31.4%)	38 (40.4%)	44 (50.6%)
Body as a whole	Overall (Any AE)	3 (3.5%)	6 (6.4%)	15 (17.2%)
	Fever	2 (2.3%)	1 (1.1%)	6 (6.9%)
	Chills	0	1 (1.1%)	4 (4.6%)
Cardiovascular	Overall (Any AE)	3 (3.5%)	3 (3.2%)	8 (9.2%)
	Tachycardia	0	1 (1.1%)	3 (3.4%)
Digestive	Overall (Any AE)	4 (4.7%)	6 (6.4%)	6 (6.9%)
	Nausea	0	0	3 (3.4%)
Hemic/Lymphatic	Overall (Any AE)	11 (12.8%)	22 (23.4%)	20 (23.0%)
	Anemia	8 (9.3%)	21 (22.3%)	17 (19.5%)
	Leukopenia	4 (4.7%)	1 (1.1%)	3 (3.4%)
	Thrombocytopenia	2 (2.3%)	4 (4.3%)	0
Metabolic/Nutritional	Overall (Any AE)	10 (11.6%)	18 (19.1%)	15 (17.2%)
	Hypokalemia	2 (2.3%)	8 (8.5%)	3 (3.4%)
	Hypomagnesemia	2 (2.3%)	2 (2.1%)	3 (3.4%)
	Hyperglycemia	2 (2.3%)	1 (1.1%)	4 (4.6%)
Nervous	Overall (Any AE)	6 (7.0%)	7 (7.4%)	9 (10.3%)
	Headache	4 (4.7%)	4 (4.3%)	4 (4.6%)
	Convulsion	1 (1.2%)	3 (3.2%)	0
Respiratory	Overall (Any AE)	2 (2.3%)	2 (2.1%)	5 (5.7%)
	Dyspnea	0	0	5 (5.7%)

	p-Values (Fisher's Exact Test)	
	AmB 3 vs. Ampho B	***AmB 6 vs. Ampho B***
Number of patients with any event	*p=0.013*	*p=0.182*
Body as a Whole Overall (Any AE)	*p=0.005*	*p=0.035*
Respiratory Dyspnea	*p=0.059*	*p=0.024*

AmB: AmBisome; Ampho B: Amphotericin B
Patient population: all randomized patients who received at least one dose of study drug.
Adverse events include infusion- related reactions; concomitant infections are not included.
Common: experienced by at least 3 patients in any treatment group.
All statistically significant treatment differences are shown.

Serious Adverse Events

The overall incidence of serious adverse events was similar across groups. The only significant treatment differences were a significantly lower incidence of serious respiratory adverse events in the AmBisome 3 mg/kg group (1.2% vs. 9.2%; p=0.034) and a significantly lower incidence of serious episodes of dyspnea in the AmBisome 6 mg/kg group (0% vs. 5.7%; p=0.024) relative to amphotericin B.

Adverse Events Resulting in Discontinuation

The incidence of adverse events resulting in discontinuation of study are summarized in Table 16. There were no trends in individual adverse events leading to discontinuation.

Table 16: Common Adverse Events Leading to Discontinuation of Study Drug

COSTART Body System Term	AmBisome 3 mg/kg n=86	AmBisome 6 mg/kg n=94	Ampho B 0.7 mg/kg n=87
Overall (Any AE)	4 (4.7%)	3 (3.2%)	6 (6.9%)[1]
Cardiovascular System (Any AE)	0	0	3 (3.4%)
Metabolic and Nutritional (Any AE)	3 (3.5%)	1 (1.1%)	4 (4.6%)
Creatinine Increased	3 (3.5%)	1 (1.1%)	3 (3.4%)
Nervous System (Any AE)	0	0	3 (3.4%)

Patient population: all randomized patients who received at least one dose of study drug.
Adverse events include infusion-related reactions.
Common: experienced by at least 3 patients in any treatment group.
1: One patient, randomized to amphotericin B, discontinued study drug (induction) because of an adverse event after receiving 8 doses over 10 days; however, this patient transitioned to the consolidation phase after receiving permission from the Sponsor and was considered to have completed the study.

Nephrotoxicity

As shown in Table 17, the incidence of nephrotoxicity and the mean increase from baseline in serum creatinine concentration were significantly lower in the AmBisome 3 mg/kg and combined dose groups compared with amphotericin B. In addition, the mean and median time to nephrotoxicity (1.5 times the baseline value and > 1.2 mg/dl) tended to be longer with AmBisome 3 mg/kg than with amphotericin B. The incidence of nephrotoxicity was numerically lower in the AmBisome 6 mg/kg group compared with the amphotericin B group (59.8% vs. 46.8%, p=0.072 for creatinine increased 1.5 times baseline; 33.3% vs. 21.3%, p=0.066 for creatinine increased 2 times baseline).

Table 17: Nephrotoxicity (Weeks 1-4)

	AmBisome			Ampho B
	3 mg/kg n=86	6 mg/kg n=94	Both n=180	0.7 mg/kg n=87
Number with nephrotoxicity[1]				
1.5x BL and >1.2 mg/dL	30 (34.9%)	44 (46.8%)	74 (41.1%)	52 (59.8%)
2x BL and > 1.2 mg/dL	12 (14.0%)	20 (21.3%)	32 (17.8%)	29 (33.3%)
Peak Creatinine (mg/dL)				
N	85	94	179	85
Mean ± SD	1.7 ± 1.3	1.7 ± 0.8	1.7±1.0	1.9±0.9
Median (range)				
Change from baseline to peak serum creatinine value (mg/dL)				
N	85	93	178	85
Mean ± SD	0.6 ± 0.9	0.7 ± 0.7	0.6 ± 0.8	0.9 ± 0.7
Median (range)				
	p-Value (Fisher's exact test for discrete variables; generalized linear models for continuous variables)			
	AmBisome BOTH vs. Ampho B	*AmBisome 3 mg/kg vs. Ampho B*	*AmBisome 6 mg/kg vs. Ampho B*	
Number of patients 1.5x BL	*p=0.004*	*p=0.001*	*p=0.072*	
Number of patients 2x BL	*p=0.005*	*p=0.004*	*p=0.066*	
Peak Creatinine	*p=0.163*	*p=0.266*	*p=0.188*	
Change from baseline to peak serum creatinine	*p=0.024*	*p=0.023*	*p=0.099*	

Nephrotoxicity: adults (≥ 16 years of age), serum creatinine > 1.2 mg/dL and either > 1.5 times or >2 times baseline value (1.5x or 2x); pediatric patients (<16 years of age), serum creatinine > 1.5 times or >2 times baseline value (1.5x or 2x). The one patient < 16 years of age who participated in this study did not experience nephrotoxicity.

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

SD: standard deviation; BL: baseline

Reviewer's comments: *Although the 6 mg/kg AmBisome group had numerically less nephrotoxicity, only the 3 mg/kg group showed a statistically significant difference with amphotericin B.*

Other toxicity parameters

The incidence of hepatotoxicity was similar among groups. Mean total bilirubin was significantly lower in the 3 mg/kg and the combined AmBisome groups compared to amphotericin B, but there were no other significant treatment differences with respect to hepatotoxicity.

The incidence of hypokalemia defined as serum potassium < 3 mmol/L and anemia were both significantly lower with 3 mg/kg AmBisome relative to amphotericin B. There was no statistically significant difference between treatments for hypokalemia defined as serum potassium of <2.5 mmol/L. There were no significant differences between AmBisome 6 mg/kg and amphotericin B for either parameter.

Drug Tolerance

The incidence of dose reduction or discontinuation during the induction phase is shown in Table 18. Drug tolerance was evaluated based on the proportion of patients who did not require dose reduction or discontinuation because of infusion-related reactions or other adverse events. No AmBisome-treated patients required dose reduction or discontinuation because of IRRs compared with 6.9% and 3.4%, respectively, in the amphotericin B group. Overall, a numerically higher proportion of AmBisome-treated patients compared with amphotericin B-treated patients did not require a dose reduction due to toxicity; 90.6% vs. 72.4%, respectively. There appeared to be a dose relationship between the two AmBisome doses and the incidence of dose reduction for adverse events; however, there was no apparent relationship between AmBisome dose and incidence of study drug discontinuation.

Table 19: Drug Intolerance – Incidence of Dose Reduction or Discontinuation During the Induction Phase

	AmBisome			Ampho B
	3 mg/kg n=86	6 mg/kg n=94	Both n=180	0.7 mg/kg n=87
Dose reduction for: Toxicity[1]	4 (4.7%)	13 (13.8%)	17 (9.4%)	24 (27.6%)
Adverse Event	4 (4.7%)	13 (13.8%)	17 (9.4%)	18 (20.7%)
IRR	0	0	0	6 (6.9%)
Discontinued for: Adverse Event	3 (3.5%)	2 (2.1%)	5 (2.8%)	4 (4.6%)[1]
IRR	0	0	0	3 (3.4%)[1]
Infection	1 (1.2%)	1 (1.1%)	2 (1.1%)	0

Patient population: all randomized patients who received at least one dose of study drug.
1: Toxicity is defined as non-infusion adverse events plus infusion-related adverse events.
Ampho B: Amphotericin B; IRR: Infusion-related reaction

Reviewer's comments: *Overall, the proportion of patients who required dose adjustment or discontinuation because of intolerance was as follows:*

AmBisome 3 mg/kg: 9.4%
AmBisome 6 mg/kg: 17%
amphotericin B: 35.6%

These results indicate that AmBisome is better tolerated than amphotericin B, even at higher than the maximum recommended dose of 5 mg/kg.

Safety Conclusions

Patients administered AmBisome for the treatment of cryptococcal meningitis presented a better safety profile than did those administered amphotericin B. During weeks 1-4, the overall incidence of adverse events was significantly lower in the 3 mg/kg AmBisome group compared with the amphotericin B group. AmBisome was associated with a significantly lower incidence of infusion-related fever, chills and rigors (combined, 3, and 6 mg/kg), and a significantly lower incidence of non-infusion-related phlebitis (combined, 3, and 6 mg/kg), anemia (3 mg/kg), hypokalemia (3 mg/kg), elevated creatinine (combined, 3 mg/kg), bilirubinemia (combined, 3 mg/kg), cough (6 mg/kg), and hiccup (combined, 3, and 6 mg/kg). Although premedication was allowed

throughout the study, the overall incidence of infusion-related reactions with amphotericin B and the proportion of patients in the amphotericin B group who required medication for the treatment of infusion-related reactions was more than twice that in the AmBisome groups. Significantly fewer patients administered 3 mg/kg AmBisome experienced a severe/life-threatening event during the course of the study than did those in the amphotericin B group. As noted in previous comparative trials, the incidence of nephrotoxicity was significantly lower for AmBisome-treated patients (combined, 3 mg/kg).

5. Conclusion

In this study, AmBisome was shown to be equivalent to conventional amphotericin B in terms of CSF sterilization at week 2. At week 10, mycologic, therapeutic and clinical success rates as defined previously were unsatisfactory for AmBisome given at 3 mg/kg as suggested by the 95% confidence intervals, and marginal at best for AmBisome at 6 mg/kg. It is noteworthy to add that had the sample size that was initially sought been reached, the confidence intervals would have been smaller and their upper limits would have possibly dropped below zero.
On the other hand, the following should be noted:
Cryptococcal meningitis carries a high mortality rate when left untreated (see Heyderman *et al.* Clin Inf Dis 1998; 26: 284-9) and the current armamentarium of therapy is narrow;
CSF sterilization rates at week 2 were close to 50% for AmBisome 6 mg/kg/day and equivalent to those seen with conventional amphotericin B;
Survival rates at week 10 were equivalent to that of amphotericin B;
AmBisome clearly offered several advantages in terms of safety, tolerability, less frequent need for dose adjustments, and less frequent use of medications to treat infusion-related reactions;

Given the above, it is this reviewer's opinion that AmBisome should be approved for use in HIV infected patients at the higher dose of 6 mg/kg.

Financial Disclosure:

The applicant certified that based on information obtained from participating clinical investigators, the latter did not participate in any financial arrangement with the sponsor whereby the value of compensation to the investigators for conducting the study could be affected by the outcome of the study, had no proprietary interest in this product or significant equity interest in the sponsor of the study, and were not the recipients of significant payments of other sorts.

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