8.3.3.2 Results

The study started in January 1992. According to the protocol, enrollment of 60 evaluable patients was expected by September 1993. However, because of slow enrollment and the large number of nonevaluable patients, the study period was extended and the last patient was enrolled on January 1996. An interim analysis was conducted and reported to the FDA in a presubmission (submitted Oct. 1996). The presubmission did not include all patients included in the final report. The results reviewed below are based on data presented in the final report.

8.3.3.2.1 Patient Disposition

In the final report, 53 patients in the AmBisome group and 55 patients in the amphotericin B group received study drug. The sponsor analyzed for safety all patients who had received at least one dose of study drug. A total of 73 patients discontinued study participation. Reasons for premature discontinuation of study drug, as provided by the applicant, are listed in Table 8.3.12. The most common reason for study discontinuation was the lack of positive fungal cultures at baseline. A larger percentage of patients in the AmBisome group had negative pretreatment cultures.

Table 8.3.12 Disposition of Patients. Reasons for discontinuation of Study Drug

	AmBisome (n=53)	Amphotericin B (n=55)
Infection not responding in 14 days	0	3 (4%)
Adverse event	6 (11%)	6 (11%)
Pretreatment culture negative for fungi	16 (30%)	10 (18%)
Investigator decision	4 (8%)	9 (16%)
Increase in serum creatinine	0	1 (2%)
Death	5 (9%)	6 (11%)
Other	2 (4%)	6 (11%)
Total Discontinued	33 (62%)	40 (73%)

Source: Vol 30.1 page 33 Table 10.1.1.

From the applicant's efficacy analysis, it is apparent that only a minority of patients had confirmed deep fungal infections at baseline. According to the applicant, only 15 and 10 patients had confirmed fungal infections at baseline for the AmBisome and amphotericin B groups, respectively. Differences between the applicant's assessment and FDA's assessment for the number of patients considered to have confirmed

infection are shown in Table 8.3.15 and Appendix B.

There were some Aspergillus species infections that were considered confirmed based on clinical signs and symptoms and a positive sputum culture for Aspergillus species. Threes patient receiving AmBisome and two patients receiving amphotericin B had pulmonary aspergillosis by these criteria. By MSG criteria these cases would be considered possible pulmonary aspergillosis but not definitively confirmed unless the culture was obtained by more invasive means (BAL, lung biopsy).

8.3.3.2.2 Patient Demographics and Pretreatment Characteristics

The demographic characteristics for all randomized patients who received at least one dose of drug (patients included in the safety analysis) were comparable for the two treatment groups. The majority of patients were white males. Mean age was 48 years. The underlying illness in most patients was acute leukemia. For the AmBisome group, 47% had AML and 19% had ALL. For the amphotericin B group 60% had AML and 7% had ALL. The number of days of neutropenia prior to treatment with study drug was similar for both groups.

8.3.3.2.3 Efficacy

Clinical response rates, as reported by investigators, for all patients who received study drug are shown in Table 8.3.13. This analysis included all patients who received drug, regardless of confirmation of fungal infection at baseline.

Table 8.3.13 Investigator's Assessment of Clinical Response for All Patients Suspected and Confirmed

	AmBisome n=53	amphotericin B n=55
Cure	13 (25%)	7 (12%)
Improved	9 (17%)	10 (18%)
Failed	15 (28%)	23 (42%)
Not evaluable	16 (30%)	15 (27%)

Source: NDA 50-740 Vol. 30.1, page 39, Table 11.4.1.

Confirmed Infections

There was a difference between the two treatment groups with respect to the number and types of confirmed fungal infections treated. For the amphotericin B group, there was only one patient with confirmed Candida species infection compared to 6 patients with confirmed Candida species infections for the AmBisome group. Also among patients randomized to amphotericin B there were fungal infections other than those caused by Aspergillus and Candida species, including one case each of Cryptococcus, Fusarium, and Absidia species. Because the type and number of fungal infections for

the two groups were different, the two treatment groups can not be reliably compared for outcome of all fungal infections combined. One might consider comparing treatment group differences for Aspergillus species infections since there were a similar number of infections for each treatment arm. However, the total number of Aspergillus species infections was relatively small (16 patients total). If one does not include possible infections, this number is further reduced to 9.

Clinical outcomes for confirmed fungal infections as assessed by the applicant are listed in Table 8.3.14.

Table 8.3.14 Clinical Outcome of Confirmed Infections (Applicant)

	AmBisome n=15	amphotericin B n=10
Total	15	10
Success	8	1
Improved	2	1
Failed	4	8
Aspergillus	9	7
Success	5	1
Improved	2	0
Failed	2	6
Candida	6*	1
Success	3	0
Improved	0	0
Failed	2	1
Other	0	2
Success	0	0
Improved	0	1
Failed	0	1

Source: NDA 50-740 Vol. 30.1, page 41, Table 11.4.4
One patient was not evaluable

Clinical outcome of confirmed infections as assessed by FDA is listed in Table 8.3.15. Although the applicant and FDA analysis report the same numbers of confirmed fungal infections, there is disagreement regarding which infections were confirmed. See Appendix B for narratives describing these differences. For the FDA analysis, clinical outcome is reported according to type of fungal infection. Since many patients did not have follow-up cultures, we did not re-evaluate patients for a microbiological outcome. Instead, microbiologic outcome is indirectly included in the FDA clinical outcome analysis. For example, if a patient showed clinical improvement but demonstrated a positive follow-up culture, they were considered failures. However, if a patient had a clinical response and no microbiologic follow-up, the clinical response would have been classified as a success.

FDA assessment of clinical outcome is fairly similar to that of the applicant's; however, in the FDA analysis there are fewer cures, more improvements, and two additional failures among patients receiving AmBisome.

Table 8.3.15 Study 104-05 Clinical Efficacy
FDA Evaluation

	AmBisome	amphotericin B
Applicant confirmed	15	10
FDA confirmed	15	10
Fungal Infection (total) Aspergillus Candida Other Cryptococcus Fusarium Absidia	15 9 6 0	10 6 1 3 1 1 1
Clinical Outcome (total) Success Improve Fail	15 5 4 6	10 0 3 8
Clinical Outcome (aspergillus) Success Improve Failure	9 3 4 2	6 0 1 5
Clinical Outcome (Candida) Success Improve Failure	6 2 0 4	1 0 0 1
Clinical Outcome (other) success improve failure	0 0 0 0	3 0 1 2

In addition to the patients with confirmed fungal infections at baseline, there were several patients who appeared to have treatment emergent fungal infections that were not apparent at baseline. There were three possible treatment emergent fungal infection for amphotericin B and one possible treatment emergent fungal infection for AmBisome. These are listed below:

Amphotericin B

#01009. This patient had pulmonary infiltrates at baseline. Pretreatment

bronchoscopy cultures were negative. Three days later he underwent a second bronchoscopy. Cultures were positive for Aspergillus species. He continued treatment with amphotericin B but his condition did not significantly improve and he died secondary to disease progression (leukemia) on study day 17.

#3009 This patient had pulmonary infiltrates and underwent bronchoscopy pretreatment. Cultures were negative. On day 18 the patient underwent another bronchoscopy. Cultures were positive for Aspergillus species and staphylococcus aureus.

#7008 This patient had progressive pulmonary infiltrates. Pretreatment bronchoscopy cultures were negative. The patient died of pulmonary complications after 12 days of treatment. According to the case report form, a few pulmonary vessels showed the presence of fungi at autopsy.

AmBisome

#3001 This patient was enrolled with pulmonary infiltrates. At pretreatment cultures obtained via bronchoscopy were negative. On day 5 this patient had a skin lesion culture which grew Aspergillus species, subsequent skin lesion cultures from other sites were negative.

Concomitant medications

Some patients received antifungal prophylaxis prior to study drug treatment. Patients who failed study drugs were often switched to other antifungal agents. One patient with candidemia, who was randomized to AmBisome, was concomitantly administered itraconazole. Itraconazole was given for thirty days prior to treatment and for 12 days during study. Presumably, if the candidemia arose during treatment with itraconazole, then itraconazole may have been ineffective. This patient was classified as a clinical cure despite the protocol violation. One patient receiving amphotericin B and listed as an improvement received itraconazole on day 12. Other patients who had improved switched to oral itraconazole 3-4 weeks into the study.

Comments:

Concomitant use of other antifungal drugs were protocol violations. There were two patients who were cures or improvements, one on each arm, who received systemic antifungals while receiving study drug.

8.3.3.2.4 Safety

Study Drug Exposure

The mean duration of exposure to study treatment was 14 days and 13 days for patients randomized to AmBisome and amphotericin B, respectively. The mean cumulative dose was 4257 mg for patients receiving AmBisome and 791 mg for those receiving amphotericin B.

Changes in dosing

According to the applicant a change in dosage due to toxicity was required for 9 patients receiving AmBisome (1 renal toxicity and 8 other adverse events) and for 27 patients receiving amphotericin B (16 renal toxicity and 11 other adverse events).

Adverse Events

According to the applicant, 39 (74%) patients receiving AmBisome and 48 (87%) patients receiving amphotericin B experienced an adverse event. The most frequent adverse events, seen in at least two patients in either study group are shown in Table 8.3.16. In effect, this table lists events that occurred in at of patients on either study arm. Adverse events were considered related in 26 patients treated with AmBisome and 42 patients treated with amphotericin B. However comparisons of "drug-related" adverse events in a open-label study should be interpreted with caution. Investigators may have been biased toward the belief that AmBisome was better tolerated.

Adverse events commonly associated with amphotericin B such as fever, rigors, and renal insufficiency appeared to occur less frequently among patients receiving AmBisome. Of note, bronchospasm did not appear to be more frequent among patients receiving AmBisome. In some studies dyspnea and bronchospasm have been observed to occur more frequently among lipid amphotericin B preparations when compared to amphotericin B. In study 104-05, one patient receiving AmBisome was listed as having an anaphylactic, allergic reaction. No patient receiving amphotericin B experienced an anaphylactoid reaction.

Table 8.3.16 Study 104-5: Adverse Events

	AmBisome (n=53)	Amphotericin B (n=55)
Any Adverse Event	39 (74%)	48 (87%)
Body as a Whole		
Fever	3 (6%)	6 (11%)
Headache	2 (4%)	0
Pain	1 (2%)	2 (4%)
Rigors	4 (8%)	9 (16%)
Sepsis	5 (9%)	4 (7%)
Digestive Tract		
Diarrhea	1 (2%)	2 (4%)
Hepatitis cholestatic	2 (4%)	1 (2%)
Hepatocelluar damage	0	3 (6%)
Jaundice	2 (4%)	1 (2%)
Vomiting	1 (2%)	2 (4%)
Metabolic and Nutritional		
Alkaline Phosphatase Increased	2 (4%)	1 (2%)
BUN increased	1(2%)	7 (13%)
CPK increased	0	6 (11%)
Edema	3 (6%)	1 (2%)
Hypokalemia	5 (9%)	10 (18%)
LDH increased	2 (4%)	0
Creatinine increased	8 (15%)	15 (27%)
Nervous		
Confusion	2 (4%)	0
Hallucination	2 (4%)	0
Respiratory		
Bronchospasm	0	2 (4%)
Pneumothorax	0	2 (4%)
Pulmonary Infiltrates	2 (4%)	0
Respiratory Insufficiency	5 (9%)	5 (9%)
Respiratory Disorder	1 (2%)	4 (7%)
Skin and Appendages		
Rash erythematous	4 (8%)	5 (9%)
Rash	4 (8%)	1 (2%)
Urogenital		
Hematuria	0	2 (4%)
Nephropathy Toxic	0	10 (18%)
Renal Function Abnormal	3 (4%)	2 (4%)

Source: Vol 30.1 page 45 Table 12.3.1.

Adverse Events Resulting in Premature Discontinuation of Drug
Six patients in the AmBisome group and seven in the amphotericin B group

discontinued drug due to an adverse event. All but one of the individuals who discontinued amphotericin B did so because of nephrotoxicity. Elevated serum creatinine was at least a contributing cause of drug discontinuation in three patients receiving AmBisome. Two patients discontinued drug due to infusion related reactions, one of these was listed as allergic/anaphylactic. The events leading to drug discontinuation are listed below:

AmBisome
abnormal kidney function and pain
arthritis, respiratory insufficiency, mild serum creatinine elevation
elevated serum creatinine, sepsis
allergic/ anaphylactoid reaction
severe cholestatic hepatitis
flushing, hypotension and rigors

Comment:
The patient who developed cholestatic hepatitis was a 38 year old male with ALL and pre-study blood cultures positive for Candida glabrata. The patient was treated for 17 days and discontinued drug because of severe cholestatic hepatitis which lasted 25 days before resolving. The investigator assessed this event as drug-related. SGPT was slightly elevated at baseline; this increased to
Alkaline phosphatase increased to 1144 IU/L. Bilirubin was elevated at baseline (59 umol/L). This increased to 99 umol/L on day 11 but decreased to 48 umol/L while on treatment.

Amphotericin B
renal toxicity
elevated serum creatinine
elevated creatinine and bronchospasm, dyspnea, and rigors
elevated creatinine, hypokalemia, fever
elevated creatinine
increased CPK
elevated creatinine, respiratory insufficiency, hypokalemia, epistaxis, mucositis

Deaths
There were 21 deaths among patients randomized to AmBisome and 19 deaths among patients randomized to amphotericin B. None of the deaths were considered related to study drug. Death was the reason for study drug discontinuation in 5 patients receiving AmBisome and 6 patients receiving amphotericin B.

Serious Adverse Events
Thirteen patients receiving AmBisome experienced 14 serious adverse events and 15 patients receiving amphotericin B experienced 23 serious adverse events. Three and 4

patients receiving AmBisome and amphotericin B, respectively, experienced serious respiratory insufficiency.

Laboratory Abnormalities

The applicant stated that the primary variable for the evaluation of safety was the incidence of renal function impairment, defined as a 100% increase of the baseline serum creatinine at any time during treatment. Table 8.3.17 shows the applicant's and FDA's assessment of changes in creatinine (100% increases in creatinine). The applicant included all randomized patients who had both baseline and end of study laboratory values. FDA assessment includes any patient who had a baseline and at least one follow-up value. Both analyses show substantially less nephrotoxicity for AmBisome compared to amphotericin B.

Table 8.3.17 Comparison of Creatinine Changes from Baseline

	AmBisome	amphotericin B
Applicant (N)	49	55
100% increase	5 (10%)	20 (36%)
FDA (N)	53	55
100% increase	8 (15%)	27 (49%)
50% increase	15 (28%)	43 (78%)

Source: NDA 50-740 Vol. 30.1 page 48, table 12.5.1

Other laboratory changes appeared to be comparable between groups, except for SGPT (ALT). The applicant reported that 27% of individuals receiving AmBisome and 16% of individuals receiving amphotericin B had SGPT levels exceeding 105 IU/L . Changes in bilirubin, alkaline phosphatase and SGOT appeared to be similar between groups. I evaluated two category or greater increases in SGPT. More patients receiving AmBisome as compared to amphotericin B had two category laboratory shifts in SGPT as shown in the table below.

Table 8.3.18. Two category or greater shifts in SGPT

	AmBisome n=47	Amphotericin B n=50
Normal to 3-5 times ULN	3	3
Normal to 5-10 times ULN	2	2
Normal to > 10 times ULN	1	0
< 3 times ULN to 5-10 times ULN	3	1
Total with two category shifts	9 (19%)	6 (12%)

Source: NDA 50-740 vol 30.6, Line listings, table 16.2.8.2.

Three of the largest SGPT shifts (normal to >5 or 10 times normal) resolved during treatment. AmBisome dosing was continued while the SGPT levels returned to baseline. These cases appeared to be unrelated to drug.

8.3.3.3 Overall Conclusions

Conducting comparative clinical trials for the treatment of Aspergillus species and invasive candidiasis (other than esophageal disease) is difficult. An adequately sized, controlled, comparative clinical trial for the treatment of infections caused by Aspergillus species has never been completed for any antifungal drug. Few candidemia trials have been completed or published. Analyses of invasive candidiasis trails are generally difficult to interpret due to problems in establishing confirmed infections and difficulties in deciding whether candidemia is simply a line infection or an invasive infection. It is also difficult to determine when successful treatment of an infection with Candida species has occurred, unless one has followed patients for a prolonged period of time to rule out late sequelae.

8.3.3.3.1 Efficacy

This study was not adequately powered to detect superiority or to demonstrate equivalence. There were too few confirmed fungal infections. In addition there was an imbalance among treatment arms in the number and type of confirmed fungal infections. For example, there was only one Candida species infection among patients receiving amphotericin compared to six among patients receiving AmBisome. There was one case each of Cryptococcus, Fusarium and Absidia species infection among patients randomized to amphotericin B. All of the infections among patients receiving AmBisome were caused by either Aspergillus species or Candida species.

There was an insufficient number of fungal infections due to Candida species to make any comparisons. For Aspergillus species, there were 9 and 6 cases among patients receiving AmBisome and amphotericin B, respectively. Seven of the 9 patients receiving AmBisome appeared to respond (cure or improve) to treatment while only 1 of six patients with Aspergillus species who had received amphotericin improved. Numerically, successful responses for treatment of aspergillosis was higher for the AmBisome group. This trial is supportive of AmBisome's activity against Aspergillus species infections. However, there is not enough data to conclude that AmBisome is equivalent or superior to amphotericin B for this infection.

8.3.3.3.2 Safety

In this study AmBisome was given at doses of 5 mg/kg, a higher dose than all the other studies in this submission. AmBisome appeared to be relatively well tolerated at this dose. As in other studies, AmBisome was less nephrotoxic than amphotericin B.

Rigors were observed but to a lesser extent than with amphotericin B. Infusion of AmBisome was associated with an allergic reaction in one individual. This was not observed with amphotericin B in this study.

One concern is whether higher doses of amphotericin B as administered via AmBisome would increase liver toxicity. There were four more individuals among patients receiving AmBisome as compared to amphotericin B who had a two category increase in SGPT. However three patients with the largest increases had resolution of the lab abnormality while continuing AmBisome. In addition, one patient receiving AmBisome discontinued drug due to cholestatic hepatitis with increased alkaline phosphatase, bilirubin and SGPT. For this individual, bilirubin levels were elevated pretreatment, and fluctuated during treatment, such that later bilirubin values were below baseline levels during continued AmBisome treatment. Although there is no strong suggestion that this dose of AmBisome was associated with increased liver toxicity, studies evaluating AmBisome at doses higher than 5 mg/kg will require evaluation for possible liver toxicity.

APPEARS THIS WAY
ON ORIGINAL

8.3.4 Study 104-19: Randomized Multicenter Trial of 1mg/kg versus 4 mg/kg/day AmBisome in the Treatment of Invasive Aspergillosis

This study was also EORTC (European Organization for Research and Treatment of Cancer) protocol #19923; NexStar provided AmBisome. An interim report of this study was submitted. The applicant had originally planned to submit a final study report with the safety update. They subsequently informed us that a final report of study 104-19 would not be a part of this NDA. The report submitted was an interim analysis. Not all patients who had completed therapy were included since all data had not been entered in the database. The planned sample size of 52 evaluable patients per treatment arm was not achieved due to a substantial number of nonevaluable patients.

The format of the submitted report was an executive summary. Data or line listings were not included. Therefore, this study will be only be briefly summarized. A critical review of this study was not possible.

This study was a multicenter, randomized, open-label, study of two doses of AmBisome for the treatment of invasive aspergillosis in neutropenic patients with malignancies. A total of 104 neutropenic cancer patients with documented invasive aspergillosis were to be randomized to receive either 1 mg/kg of AmBisome (low dose =LD) or 4 mg/kg of AmBisome (high dose = HD). Patients who were considered treatment failures with itraconazole or amphotericin B (and had not received more than 500 mg total dose) were permitted to enroll.

Patients who were randomized to the 4 mg/kg dose and experienced deterioration of renal function were allowed to be dose reduced to 1 mg/kg until renal function improved. Dose was to be titrated back to the randomized dose as tolerated.

A definitive diagnosis of aspergillosis was made based on disease-related signs and symptoms, a positive culture and radiologic signs of aspergillosis. A presumptive diagnosis was made if only two of these criteria were present. The response was to be assessed weekly and at the end of therapy.

8.3.4.1 Summary of Efficacy

This study was conducted at 18 centers in Europe and Saudi Arabia. The first and last patients were enrolled on March 1993 and October 1995, respectively. There were 119 patients randomized to the study, 59 LD, 60 HD. Several centers were excluded from this analysis because the data had not yet been entered into the computerized database. Of the 119 patients enrolled, 89 patients were evaluable for efficacy (42 LD, 47 HD). Patients were considered clinically evaluable if a positive culture, clinical signs and symptoms, and/or radiological evidence of infection were present at baseline. Patients who had no repeat cultures were excluded form the mycological efficacy

analysis. Clinical efficacy was based on the investigator's subjective assessment.

Overall, there were no statistically significant differences between the two treatment arms. Table 8.3.19 shows clinical and radiological response for the two treatment arms as reported by the applicant. Numerically, there was a slightly higher clinical and radiologic response among patients randomized to the LD as compared to HD. The applicant states that the treatment groups were somewhat unequal for baseline characteristics which may have conferred a worse prognosis for the HD group.

Since this is an interim analysis of an incomplete data set, one is unable to draw conclusions for this study. This study was not submitted in a form that could be reviewed critically. Therefore it cannot be used to support an indication.

Table 8.3.19 Study 104-19 Clinical and Radiological Response, Applicant's

	AmBisome 1 mg/kg	AmBisome 4 mg/kg
Clinical		
Cure	19/42 (45%)	20/47 (43%)
Improve	6/42 (14%)	9/47 (19%)
Fail	12/42 (29%)	16/47 (34%)
Not evaluable	5/42 (12%)	2/47 (4%)
Radiologic Response		
Cure	6/42 (14%)	1/47 (2%)
Improve	18/42 (43%)	22/47 (47%)
Fail	12/42 (29%)	20/47 (43%)
Not done	5/42 (14%)	4/47 (8%)

Source: NDA 50-740, Vol. 13.1 Page 5.

8.3.4.2 Summary of Safety

According to the applicant's summary, the HD was associated with more adverse events than the LD. Overall 15 patients (36%) in the LD and 24 patients (51%) in the HD group reported adverse events. Nephrotoxicity (defined as a doubling of creatinine) was reported in 7% of the low dose patients and 11% of the HD patients. The report was not of sufficient detail to critically comment on safety. Line listings, and baseline values for laboratory tests were not submitted.

The applicant reported that no deaths were considered to be related to treatment with AmBisome in this study. Narratives or case report forms of deaths or discontinuations were not included.

8.4 Indication: Treatment of Cryptococcal Meningitis

8.4.1 Study 104-03: AmBisome for Primary Therapy of Disseminated Cryptococcosis in Patients with HIV Infection.

8.4.1.1 Protocol

8.4.1.1.1 Objectives

To evaluate the safety and efficacy of AmBisome as first-line therapy for a primary episode of HIV-related cryptococcosis, including cryptococcal meningitis.

8.4.1.1.2 Study Design

This was a phase 2/3, multicenter, non-comparative, open-label study of AmBisome (3 mg/kg) in approximately 40 HIV-infected patients. AmBisome was administered at a starting dose of 1 mg/kg/day and dose escalated over three days in 1 mg/kg increments for a final dose of 3 mg/kg.

Maintenance therapy was to be given according to the investigator's discretion. It was not considered a part of the protocol.

8.4.1.1.3 Study Population

To be eligible patients were required to be HIV seropositive and hospitalized for a primary episode of cryptococcosis. Confirmation of cryptococosis was to be established by culture. Patients were allowed to enroll on the basis of microscopic or serologic results while cultures were pending.

Patients younger than age 18 were excluded. Patients who were likely to require 5-FC or any other systemic antifungal drug were also excluded.

Comment:
The study design is typical of a phase 2 study or pilot study. An open label, uncontrolled trial is not a desirable design for a study supporting a drug approval. This protocol was not reviewed by FDA prior to its initiation.

Although it has been difficult to conduct clinical trials for certain fungi such as Aspergillus species and histoplasmosis, it has not been exceedingly difficult to study cryptococcosis in a controlled manner. In the past ten years there have been several sizable controlled studies for the treatment of cryptococcosis.

8.4.1.1.4 Study Procedures

AmBisome was to be administered as 1 hour infusions. The duration of treatment according to the protocol was to be 42 days or less. Treatment was to continue until all

previously positive cultures were negative for two successive weeks.

Vitals signs were to be collected daily; chemistry and hematology laboratory test were to be collected twice weekly. The protocol states that any cultures that were positive prior to treatment were to be repeated on a weekly basis. However, the protocol states that CSF cultures should be performed at least once during treatment, 48 hours post treatment, and at least 7 days after therapy, if possible.

A 3 month post-treatment evaluation was considered optional.

Comment:
The study procedures were not very stringent. The protocol only required one CSF culture on study treatment. The exact timing of this culture was not specified.

8.4.1.1.5 Endpoints
The protocol states that the efficacy of AmBisome will be determined using the investigator's evaluation of the resolution of fungal disease as assessed by resolution of clinical signs and culture results.

Mycological eradication required that all previously positive cultures be negative for two successive weeks.

8.4.1.1.6 Statistical Considerations
Patients who received less than 14 days of drug were not eligible for the efficacy analysis. Patients receiving other systemic antifungal therapy were also not to be included in the efficacy analysis.

Comment:
All patients who receive drug and are culture positive are baseline should be considered evaluable for efficacy. Requiring 14 days of therapy is likely to overestimate the response rate because early treatment failures would be excluded.

8.4.1.2 Results

8.4.1.2.1 Patient Disposition
A total of 24 patients were enrolled for the treatment of 27 episodes of disseminated cryptococcal infection. One patient was treated for three episodes and one patient was treated for two.

Comment:
The re-enrollments were protocol violations; the protocol was designed to evaluate the treatment response for a primary episode of cryptococcosis. Of the 24 patients with

primary episodes, it appears that 2 patients did not have any positive cultures for Cryptoccocus species, either pretreatment or at some time point during treatment.

For the 27 treatment cycles, there were nine premature discontinuations of study treatment. Reasons for discontinuation according to the sponsor were as follows: death (3), negative pretreatment cultures (2), lack of clinical response (1), intercurrent illness (1), disease progression (1). For one episode the reason for premature discontinuation was missing.

8.4.1.2.2 Demographics and Pretreatment Characteristics

All study participants were males between the ages of 21 and 47. The majority of patients were Caucasian. One patient did not have HIV infection confirmed by serology.

Ten patients had received at least one antifungal drug prior to their first study dose of AmBisome. Two of these patients had re-enrolled in the protocol to receive AmBisome more than once. Six patients had received amphotericin B prior to enrollment. Therefore, not all patients who enrolled were being treated for their primary episode of cryptococcosis; some patients had previously failed treatment.

For the 15 patients who had baseline CD4 count measurements, 13 had absolute CD4 counts less than 100 cells/mm^3 .

8.4.1.2.3 Efficacy

Although the protocol required that two consecutive cultures be negative for determination of mycological eradication, the sponsor later determined that one negative follow-up culture would be satisfactory for this determination. This was changed due to the failure of investigators to routinely obtain follow-up cultures (especially CSF) in these patients.

The sponsor did not exclude patients from the efficacy analysis for an inadequate course of therapy (<14 days) or for the use of concomitant antifungal medications as specified in the protocol. Patients with negative cultures at baseline were excluded from the applicant's efficacy analysis.

The applicant reported that 12/16 (75%) of evaluable episodes of cryptococcosis had a clinical cure and 11/16 had (69%) had mycological eradication. For cryptococcal meningitis (which comprised most of the cases), the applicant reported that 9/13 (69%) had a clinical cure and 8/13 (62%) had mycological eradication.

Table 8.4.1 shows FDA evaluation of clinical and mycological response for cryptococcal meningitis. Of the 27 fungal episodes, I excluded from the FDA efficacy analysis the following treatment episodes:

Three patients who had re-enrolled for subsequent doses of AmBisome were excluded (#06003, 13202, 13303). Two patients with negative cultures at baseline were excluded (#07006, 08002).

Three patients who had received prior treatment with conventional amphotericin B for cryptococcal disease and did not have documentation of positive cultures prior to starting AmBisome (#13001, #13004, #14001) were excluded. These patients had positive cultures prior to starting amphotericin B. Two additional patients who had received prior amphotericin B for cryptococcal meningitis and had positive cultures prior to starting AmBisome were included in the FDA efficacy analysis.

Since there were only three cases of disseminated cryptococcosis without meningitis, I did not lump these two categories together. Two of the three cases of disseminated cryptococcosis (blood and/or urine cultures positive for Cryptococcus neoformans) appeared to be asymptomatic. The line listings indicated that these patients were afebrile, and there was no documentation of other symptoms associated with disseminated disease. This left 16 cases of cryptococcal meningitis evaluable for efficacy.

For clinical response, 9/16 (56%) had a clinical cure. For mycological response 8/16 (56%) had eradication of the organism at the end of treatment. However two of these 16 did not have follow-up CSF cultures, therefore, 9/14 (64%) evaluable for mycological response were eradicated. With respect to the combined response (mycological and clinical), 8/16 (50%) patients had a positive outcome. Excluding the two patients who did not have follow-up cultures, 8/14 (57%) had a positive outcome. This is comparable, although somewhat lower than the applicant's estimations of clinical cure and mycological eradication. It should be noted that two patients included in this analysis had received approximately 4 weeks of prior amphotericin B just prior to enrolling in the protocol. These patient could be considered amphotericin B failures. One of these patients responded to AmBisome and the other did not. On further review of patient narratives, it is apparent that other patients may have been treated for cryptococcal meningitis prior to enrollment in this protocol. For example patient #7003 was treated for previous episodes of cryptococcal meningitis over 17 months prior to enrollment. This patient failed to respond to AmBisome. Thus, some of these patients were being treated for relapse and not for their primary episode. It is likely that relapses would confer a worse prognosis.

Table 8.4.1 Clinical and Mycological Response: FDA evaluation

Clinical Response	Mycological Response			Total
	Eradication	Persistent	Not evaluable	
Cure	8 (50%)	1	-	9 (56%)
Improved	-	2	-	2
Fail	1	2	2	5
Total	9 (56%)	5	2	16

8.4.1.2.4 Safety Considerations

Extent of Exposure

Twenty-four patients received AmBisome for 27 episodes of infection. All 27 treatment cycles are included in the safety analysis. To simplify the safety review, the 27 fungal episodes are sometimes treated as separate patients, even though this is technically incorrect.

The mean duration of AmBisome treatment was 27 days
Approximately two-thirds of the patients remained on treatment for greater than 3 weeks. The mean cumulative dose received was 4273 mg.

Adverse Events

Fourteen of the 24 patients (58%) experienced at least one adverse event. Thirteen of the 14 experienced at least one event that was considered to be related to drug. No patient discontinued drug due to an adverse event. Table 8.4.2 lists the number of patients experiencing adverse events by body system

Table 8.4.2 Study 104-03, Adverse Events

CoStart Body System	Adverse Event	Number
Body as a Whole	Headache Fungal Infection Rigors	1 3 1
Cardiovascular	Thrombophlebitis	1
Digestive	Constipation Nausea Vomiting	1 2 2
Hemic and Lymphatic	Anemia Leukopenia Thrombocytopenia	1 1 1
Metabolic and Nutritional	Hyperuricemia Hypokalemia Creatinine increased SGOT increased SGPT increased	1 3 2 1 2
Musculoskeletal	Tendon disorder	1
Nervous	Agitation Coma	1 1

Source: Vol 10.1 Page 57, Table 14.3.3

Serious Adverse Events and Deaths

Progressive fungal infection was considered a serious adverse event leading to death in three patients (12.5%), these patients died while receiving AmBisome therapy. An additional two deaths occurred after AmBisome had been discontinued. Therefore, five deaths (21%) occurred during treatment or within 30 days after the discontinuation of treatment. Four of the five deaths were considered unrelated to AmBisome and related to cryptococcal disease progression or another intercurrent AIDS-related illness. One of the patients who died had been treated for cryptococcal meningitis several times with fluconazole and amphotericin B prior to enrolling in this protocol. One death was considered to be possibly treatment-related. For this individual the investigator could not exclude study drug toxicity or drug-induced hypokalemia leading to a possible cardiovascular event as the cause of death. However, this patient had a pretreatment potassium of 2.9 mmol/L and no further potassium values were reported.

Laboratory Abnormalities

A doubling of serum creatinine was observed in 2/21 evaluable patient episodes (evaluable meaning baseline and follow-up creatinine levels were obtained). Several other patients had increases in creatinine levels temporally related to AmBisome

administration but not exceeding two times pretreatment values. Increases in AST and ALT levels (defined as levels greater than 105 IU/L) were seen in 2 (8%) and 3 (14%) of evaluable patients, respectively. Two of the patients with ALT elevations had isolated values greater 105 IU/L. One individual had several values above the range of normal. Bilirubin levels were not routinely measured.

8.4.1.3 Overall Conclusions

The major weaknesses of this trial include its uncontrolled design, small number of patients, and protocol violations. Although there were clearly clinical responses and mycological clearing of CSF cultures, it is not possible to evaluate the efficacy of AmBisome 3 mg/kg/day relative to other commonly used treatments (amphotericin B, fluconazole, itraconazole). The success rate of treatment appeared to be

The protocol inclusion criteria required the enrollment of patients with a primary episode of cryptococcal disease. However, there were several protocol violations for this criteria. Several patients had enrolled with one or more relapses of cryptococcal meningitis. The inclusion of relapsed patients was likely to lower the expected response rate, in that many of these individuals had refractory and advanced disease. Therefore, the reported clinical response rate may be an underestimate for patients experiencing a primary episode of cryptococcal meningitis.

In this protocol, patients were to be treated for up to 42 days. More recent study designs treat patients with intravenous amphotericin, conventional or liposomal, for a 2 week induction period and then treat with fluconazole 400 mg qd for a consolidation period. Thus, it is difficult to compare the response rate from this study with other cryptococcal studies.

With respect to safety, AmBisome appeared to be generally well tolerated. The deaths and serious adverse events appeared to be related to underlying disease. There were several patients who experienced amphoterin B associated toxicities such as increased creatinine and rigors. The frequency of nephrotoxicity, defined as a doubling of baseline creatinine levels was estimated as 9.5%. This is probably lower than that observed with conventional amphotericin B. There were no reported cases of allergic reaction, dyspnea or liver failure. However, a few patients had isolated or transient increases in transaminase levels.

8.4.2 Study 104-09: AmBisome vs. amphotericin B in HIV-Infected Patients with Cryptococcal Meningitis (CM).

8.4.2.1 Protocol

APPEARS THIS WAY
ON ORIGINAL

8.4.2.1.1 Objectives

To compare the efficacy and safety of AmBisome with conventional amphotericin B in the primary therapy of CM in patients with HIV infection.

Comment:
Amphotericin B is currently the drug of choice for initial treatment of CM. The applicant stated that this study was designed to determine if higher doses of amphotericin B, as provided by AmBisome, can reduce the eradication time of Cryptoccocus species in the CSF.

8.4.2.1.2 Study Design

The study was designed as an open-label, randomized, multicenter trial comparing AmBisome (4 mg/kg) with amphotericin B (0.7 mg/kg) for the treatment of primary episodes of CM in HIV-infected patients. Patients were to receive daily doses of study drug for 3 weeks followed by fluconazole 400 mg qd for 7 weeks.

Patients were stratified by center.

8.4.2.1.3 Study Population

HIV-infected patients hospitalized with a primary episode of CM were eligible to participate. A patient could be enrolled on the basis of a positive India ink test or cryptococcal antigen test of CSF while cultures were pending.

Patients were excluded from participating if they were less than 18 years old, if their cryptococcal infection had already been treated with another systemic antifungal drug, if there was some indication that another systemic antifungal would be needed in addition to the assigned study drugs, or if serum creatinine levels were > 250 µmol\L.

8.4.2.1.4 Study Procedures

AmBisome was infused at a dose of 4 mg/kg over 45 minutes. After a test dose and dose titration, amphotericin B was infused at a dose of 0.7 mg/kg over 6 hours.

According to protocol, repeat lumbar punctures and CSF cultures were to be obtained on days 7, 14, and 21 of therapy and also on day 28, if day 21 was the first culture-negative time point. In addition CSF cultures were to be obtained at week 10. Other positive pretreatment cultures were to be repeated on days 7, 14, and 21.

At baseline and periodically during the study, each patient's overall condition was to be assessed by the degree of headache, Glasgow coma scale, Karnofsky status, meningeal symptoms, and signs of infection.

8.4.2.1.5 Endpoints

Efficacy

The primary efficacy endpoint was mycological response at three weeks. Originally the protocol required two negative cultures to classify treatment as a success; however, due to the lack of repeat cultures in all patients mycological success was later defined as one single negative culture by 21 days.

Secondary efficacy parameters included: time to early clinical success, incidence of failure after 3 weeks of treatment, rate of clinical relapse, rate of cures after 10 weeks of therapy, rate of mycological relapse, and rate of fall in CSF and serum cryptococcal antigen titers.

Early clinical success was defined in the protocol as the elimination of pretreatment signs and symptoms of CM at the conclusion of the initial 3 week period. Early clinical relapse was defined as recurrence of disease during week 3-10. Late clinical relapse was defined as recurrence of CM during post-treatment follow-up (after 10 weeks).

Safety

According to the protocol, the primary safety endpoint was the incidence of renal function impairment defined as the number of patients with a 50% increase in serum creatinine over baseline.

8.4.2.1.6 Statistical Considerations

Only patients with positive CSF cryptococcal titers were evaluable for efficacy.

Sample Size

The sample size of 15 evaluable patients per arm was based on showing a culture conversion rate of 90% for AmBisome and 40% for conventional amphotericin B (power 80%, $\alpha = 0.05$). The protocol stated that this sample size would also be sufficient to demonstrate a difference in renal function impairment of 80% versus 20% for amphotericin B and AmBisome, respectively.

Comment:

This study had sufficient statistical power to detect only very large treatment differences. Smaller differences in treatment success and nephrotoxicity would be of interest.

Protocol Amendments
No protocol amendments were included in the study report.

8.4.2.2 Results
This study was conducted from 1992-1995.

8.4.2.2.1 Patient Disposition
Thirty (30) patients were enrolled in the study; 16 patients were randomized to AmBisome and 14 patients to amphotericin B. One patient randomized to amphotericin B was found to have negative cultures. This patient never received drug. Table 8.4.3 shows reasons for drug discontinuation.

Table 8.4.3 Reasons for drug discontinuation

Reason for discontinuation	AmBisome n=16	Amphotericin B n=14
Baseline culture negative	---	1
Adverse events	1	3
Condition deteriorated	4	3
Study completed	11	7

Source: Vol. 29.1 page 29 Table 10.1.1

8.4.2.2.2 Demographics, comparability
Most of the patients who enrolled were male (27/29, 93%). Among the two female patients, both were randomized to AmBisome. Homosexuality was the most frequent risk factor for HIV. Mean age was approximately 39 and was similar for both groups. One patient randomized to AmBisome was comatose at entry and died on study.

None of the patients had received prior systemic antifungal drug for their primary episode of CM.

Numerically more patients in the AmBisome group had CM that was classified as severe (see table 8.4.4).

Table 8.4.4 Pretreatment characteristics

Reason for discontinuation	AmBisome n=16	Amphotericin B n=13
Infection Status		
Mild	2 (12.5%)	8 (61.5%)
Moderate	9 (56.3%)	5 (38.5%)
Severe	5 (31.3%)	
Clinical Condition		
Fair	8 (50%)	6 (46%)
Good	4 (25%)	6 (46%)
Poor	4 (25%)	1 (8%)
Opening Pressure		
0-29	9 (56.3%)	6 (46.2%)
>30	7 (43.8%)	4 (30.8%)
missing		3 (23.1%)

Source: Vol. 29.1 page 51 table 14.3

8.4.2.2.3 Efficacy

Some study participants refused weekly lumbar punctures. This resulted in the absence of a confirmatory culture one week after conversion from positive to negative in some patients.

Tables 8.4.5 and 8.4.6 show the frequency of treatment successes, both mycological and clinical, as evaluated by the applicant and FDA, respectively. According to the applicant's evaluation, mycological cure at 3 weeks was 10/16 (63%) in the AmBisome group and 3/13 (23%) in the amphotericin B group. However, there were more patients who were not evaluable at 3 weeks in the amphotericin B group due to lack of CSF cultures. The imbalance in nonevaluable patients among treatment arms makes comparing the mycological success rate at 3 weeks problematic. FDA assessment of three-week mycological cures are listed in table 8.4.6 below. For the FDA assessment, two patients who were classified as nonevaluable by the applicant were considered evaluable.

According to the applicant's evaluation, the 3-week, "early clinical success" outcome was similar for the two treatment arms, 10/15 (67%) patients randomized to AmBisome had clinical success at 3 weeks compared to 8/12 (67%) in the amphotericin B group. Two patients, one in each treatment arm, were considered nonevaluable for clinical success. FDA agrees with the applicant's assessment of clinical response at 3 weeks.

According to the applicant, the frequency of therapeutic success at 10 weeks, combining clinical and mycological endpoints, was 12/16 (75%) for patients randomized to AmBisome compared to 7/13 (54%) for those patients randomized to amphotericin B.

Table 8.4.5 Efficacy: Applicant's Evaluation

Endpoint	AmBisome n=16	Amphotericin B n=13
3- Week Mycological		
Cure	10/16 (62.5%)	3/13 (23%)
Fail	5/16 (31%)	5/13 (38%)
Nonevaluable	1/16 (6%)	5/13 (38%)
3-Week Mycological (excluding nonevaluable) Cure	10/15 (67%)	3/8 (38%)
10-Week Combined Response	12/16 (75%)	7/13 (54%)

Source: Vol. 29.5

Table 8.4.6 Efficacy: FDA Evaluation

Endpoint	AmBisome n=16	Amphotericin B n=13
3- Week Mycological		
At least 1 Negative Culture	10/16 (62.5%)	5/13 (38.5%)
Excluding nonevaluable	10/15 (66.7%)	5/10 (50%)
All nonevaluable = Cures	11/16 (68.8%)	8/13 (61.5%)
At least 2 Negative Cultures (protocol)	9/16 (56.3%)	2/13 (15.4%)
Excluding Nonevaluable	9/14 (64.3%)	2/7 (28.6%)
10-Week Combined Response	10/16 (62.5%)	7/13 (53.8%)
Excluding nonevaluable	--	7/11 (63.6%)

Source: Vol. 29.5, patient listings

Because of the small number of patients and the large proportion of nonevalable patients for the amphotericin B arm, 3 week success rates vary substantially depending on how the nonevaluble patients are analyzed.

APPEARS THIS WAY
ON ORIGINAL

8.4.2.2.4 Safety Considerations

Drug Exposure

The median duration of study drug exposure was 21 and 20 days for AmBisome and amphotericin B, respectively. The median cumulative dose was substantially different however. For AmBisome the median cumulative dose of amphotericin B was 5250 mg; for conventional amphotericin B it was 800 mg.

Adverse Events

Table 8.4.7, as excerpted from the applicant's report, shows the frequency of adverse events occurring during or post treatment. This table was modified to show only events occurring with a frequency of at least 10%. Thus, specific adverse events experienced by only one patient per treatment arm are not listed. Numerically, more

patients receiving AmBisome experienced an adverse event compared to those receiving amphotericin B.

APPEARS THIS WAY
ON ORIGINAL

Comment:
There is an obvious inconsistency in the applicant's recording of adverse events. Two patients receiving AmBisome vs. zero for amphotericin B were listed as having abnormal renal function in the applicant's clinical adverse event table. Yet, one patient discontinued amphotericin B due to nephrotoxicity and no patient discontinued AmBisome secondary to nephrotoxicity. In the same table under the category "creatinine increased", there were 5 and 4 patients for the AmBisome and amphotericin B treatment arms, respectively.

APPEARS THIS WAY
ON ORIGINAL

Table 8.4.7 Adverse Events During or Post-Treatment (>10% on any treatment arm)

	AmBisome n=16	Amphotericin B n=13
All Systems		
Any Adverse event	15 (94%)	11 (85%)
Metabolic and Nutritional		
Creatinine increased	5 (31%)	4 (31%)
Hypokalemia	5 (31%)	2 (15%)
BUN increased	2 (13%)	1 (8%)
Hypomagnesemia	2 (13%)	0
Body as a Whole		
CMV infection	2 (13%)	1 (8%)
Rigors	1 (6%)	2 (15%)
Sepsis	2 (13%)	0
Hemic and Lymphatic		
Anemia	2 (13%)	5 (39%)
Leukopenia	2 (13%)	2 (15%)
Skin		
Rash	1 (6%)	2 (15%)
Cardiovascular		
Tachycardia	2 (13%)	0
Urogenital		
Renal Function Abnormal	2 (13%)	0

Source: Vol. 29.1 page 54 Table 14.5.1.

Unlike other studies, there did not appear to be a significant reduction in the number of adverse events for patients receiving AmBisome compared to amphotericin B. One explanation may be that more patients randomized to AmBisome had severe infection

at baseline. Also the AmBisome infusion rate of 45 minutes was shorter in this study. This may have decreased the tolerability of AmBisome.

This review has focused on adverse events relating to anaphylactoid reactions, dyspnea, bronchospasm, hypoxia, hypotension and hepatic toxicity. The following is a list of patients receiving AmBisome with adverse events of interest.

Respiratory Problems/ Anaphylactoid response

#1005 Respiratory Insufficiency. This patient had pneumonia and was comatose at baseline and throughout the study. She died after nine days secondary to respiratory insufficiency. The death was considered to be unrelated to AmBisome.

#4001 This patient experienced coughing in conjunction with flushing, hypertension, and tachycardia. These symptoms were considered to be related to study drug and were of moderate severity. The patient had dose reduction and the symptoms resolved. This appears to be an infusion reaction related to AmBisome.

#6003 Dyspnea was listed with other adverse events including tachycardia, fever and rigors. The dyspnea was mild but considered related to drug, the patient recovered. No dose adjustments were required.

#7005 This patient, receiving amphotericin B, had mild dyspnea, considered unrelated to drug.

Two patients receiving AmBisome had adverse events terms referring to liver toxicity. These will be described under laboratory abnormalities.

Discontinuations due to Adverse Events

No patients randomized to AmBisome discontinued drug secondary to drug toxicity. One patient (#2003) randomized to amphotericin B discontinued drug during the first 3 weeks secondary to renal dysfunction.

Serious Adverse Events

Four of sixteen (25%) of patients receiving AmBisome experienced a total of 10 serious adverse events and 2/13 (15%) of patients receiving amphotericin B experienced a total of 10 serious adverse events. Most of the serious adverse events were not considered related to either study drug.

Of the serious adverse events that were considered to be related, one patient on each treatment had increases in creatinine. In addition one patient receiving

AmBisome was reported as having nephropathy and one patient receiving amphotericin B was reported as having anemia.

Deaths

There were three deaths during the 10 week study period and an additional two deaths within 30 days after this study period. Two deaths were among patients randomized to AmBisome and three were among those randomized to amphotericin B. One death (on amphotericin B) was considered possibly related to drug. The other deaths were considered to be not related. Patients who died on study or within 30 days of the 10 week study period are listed in table 8.4.8.

Table 8.4.8 Patient Deaths

	Day	Cause of Death	Relationship to Drug
AmBisome			
Patient 01005	10	Respiratory Insufficiency of unknown reason	Not Related
Patient 07002	94	Disease Related Complication	Not Related
Amphotericin B			
Patient 02003	45	Hepatic failure, Chronic Hep. B	Possibly Related
Patient 06001	70	Disease Related Complication	Not Related
Patient 07003	79	Intercurrent/Unrelated Event	Not Related

Source: Vol. 29.5 page 854, app. 16.2.37

The one death during the initial 3 week treatment period occurred in a patient randomized to AmBisome. This patient was comatose prior to treatment and never regained consciousness. She died of respiratory insufficiency of unknown etiology. Pulmonary cryptococcosis was not found on autopsy.

The only death that was considered possibly related to drug occurred in patient 02003, randomized to amphotericin B. This patient discontinued amphotericin B on study day 14 and died of hepatic failure on day 45. According to the case report form, the patient had chronic hepatitis C. Transaminases were elevated the upper limit of normal prior to treatment. The patient discontinued amphotericin B on week 2 secondary to nephrotoxicity. The patient became jaundiced on week 3 and subsequently died on day 45.

Laboratory Abnormalities

The primary protocol specified safety endpoint was the incidence of renal function impairment defined as the number of patients with a 50% increase in serum creatinine compared to baseline. The applicant did not report this degree of creatinine increase but instead reported the percentage of patients experiencing a 100% increase (2-fold increase) in serum creatinine over baseline. According to

the applicant's evaluation, when nephrotoxicity was defined as an increase in creatinine to greater than 2 times baseline occurring during or within three weeks of completing randomized therapy, 6/13 (46%) of patients receiving amphotericin B and 4/16 (25%) patients receiving AmBisome experienced nephrotoxicity. For BUN, 9/11 (82%) patients receiving amphotericin B vs. 3/15 (20%) patients receiving AmBisome, respectively, had a doubling of baseline values. Table 8.4.9 compares the sponsors nephrotoxicity assessment with those calculated by FDA. Although the FDA analysis shows a higher frequency of nephrotoxicity for both arms, both analyses show that AmBisome was associated with less nephrotoxicity than amphotericin B.

Table 8.4.9 Efficacy: Applicant vs. FDA Evaluation

	AmBisome n=16	Amphotericin B n=13
Applicant		
Creatinine (> 100% increase)	4/16 (25%)	6/13 (46%)
BUN (>100% increase)	3/15 (20%)	9/11 (82%)
FDA		
Creatinine (≥ 100% increase)	6/16 (38%)	7/13 (54%)
Creatinine (≥ 50% increase)	10/16 (63%)	12/13 (92%)
BUN (≥ 100% increase)	6/15 (40%)	10/12 (83%)

Source: Vol. 29.5, patient listings

Changes in other laboratory parameters appeared to be similar for the two treatment regimens. Two patients receiving AmBisome had transaminase elevations between 2 and 3 times the upper limit of normal. In both patients subsequent results showed values decreasing toward the normal range. A few patients receiving amphotericin B also showed transaminase elevations over baseline values. One of these patients experienced jaundice by week 3 and died with liver failure several weeks later.

8.4.2.3 Study 104-09: Overall Conclusions

The 3-week mycological eradication rate and 10-week therapeutic success rate was 63% (10/16 patients) for patients treated with AmBisome. Cryptococcal meningitis in HIV does not resolve spontaneously so it is reasonable to conclude that AmBisome is active in the treatment of cryptococcal meningitis. However, from this small study it is not possible to define, with statistical rigor, whether AmBisome was superior or equivalent to amphotericin B. There appeared to be a higher number of mycological cures at 3 weeks for AmBisome compared to amphotericin B, however, there were 3/13 patients on the amphotericin B arm who were not evaluable. The frequency of mycological eradication would be similar if these nonevaluable patients on the amphotericin B arm were actually mycological cures. The early clinical cure rate (at 3

weeks) was very similar for AmBisome and amphotericin B.

The 10 week therapeutic success rate was similar for the two treatments, with a slightly higher success rate for AmBisome. There was only one nonevaluable patient for the 10 week success rate. The lower 95% C.I. bounds for differences in success rates are not within 20% for any treatment comparison. In conclusion, AmBisome appears to have activity for CM but equivalence with amphotericin B has not been established.

There appeared to be a slight imbalance between treatment arms for the severity of infection at baseline, favoring amphotericin B. Five patients randomized to AmBisome arm versus zero patients randomized to amphotericin B had severe infection according to the investigators. Three of the five patients with severe infections were 3 and 10 week failures. Therefore the severity of infection appeared to be an important factor. Despite the fact that the AmBisome arm had a greater severity of infection, the response rates appeared to be at least as good as that for amphotericin B.

There was a similar number of adverse events for both treatments; however, a smaller percentage of patients receiving AmBisome experienced nephrotoxicity, defined as a 100% increase above baseline; 38% vs. 54% of patients on AmBisome and amphotericin B, respectively, experienced this degree of creatinine increase. A substantial percentage of patients receiving either regimen had abnormalities in serum creatinine. Nearly two-thirds (63%) of patients receiving AmBisome had a 50% increase in creatinine over baseline (the definition of nephrotoxicity specified in the protocol). No patient discontinued AmBisome secondary to nephrotoxicity.

There were two possible cases of infusion associated dyspnea among patients receiving AmBisome. This has been previously described for AmBisome as well as other lipid formulations of amphotericin B. None of the episodes in this study were severe or required treatment discontinuation.

9 Overview of Efficacy - Comparative results between studies

9.1 Efficacy of AmBisome for Treatment of Fungal Infections

Treatment studies with AmBisome provide evidence of antifungal activity of AmBisome and are therefore supportive evidence for an empirical antifungal therapy indication. Table 9.1.1 summarizes five studies that evaluated AmBisome for the treatment of invasive fungal infections. Two of these studies evaluated only cryptococcal infections. The other three studies evaluated AmBisome for the treatment of any deep fungal infection, comprised mostly of infections caused by Aspergillus species or Candida species.

All treatment trials submitted to FDA were open-label, European studies. Three were comparative studies with conventional amphotericin B; two were uncontrolled. Study 104-10, a comparative study, contained a febrile neutropenic (empirical therapy) stratum and a confirmed mycosis stratum.

Table 9.1.1 Summary of Design of Treatment Protocols

Protocol	Design	Patient Population	Treatment Arms (N)	Treatment Duration (mean days)
104-05	Controlled Randomized Open-label	Age > 16	AmBisome 5 mg/kg (53)	14 days 13 days
104-00	Uncontrolled, compassionate use	Age 2-87	AmBisome	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
104-09	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
104-03	uncontrolled, open-label	HIV infected adults with cryptococcosis	AmBisome 3 mg/kg (24)	27 days

* numbers of patients included in the confirmed stratum only.

Table 9.1.2 shows selected comparisons demonstrating the efficacy of AmBisome compared to amphotericin B for the treatment of Aspergillus species and Cryptoccocus species. Due to difficulty confirming invasive Candida species

infections, there were no clear examples directly illustrating the comparative efficacy of AmBisome vs. conventional amphotericin B for the treatment of infections with Candida species. However, approximately 60% of patients who received AmBisome in Study 104-00 (compassionate use) for the treatment of an invasive infection with Candida species had a successful treatment outcome. Most of these patients had either not responded to a prior course of amphotericin B or had developed dose-limiting toxicity with conventional amphotericin B.

Table 9.1.2 Examples of the Comparative Efficacy of AmBisome vs. Conventional Amphotericin B.

	AmBisome	amphotericin B
Study 104-05 **Clinical Outcome for Aspergillus Infections** Total number with confirmed infection Success Improve Failure	 9 3 4 2	 6 0 1 5
Study 104-09 **Mycological Outcome for Cryptococcal Meningitis (at 3 weeks)** Total number of confirmed infections Cure Fail Nonevaluable	 16 10/16 (62.5%) 5/16 (31%) 1/16 (6%)	 13 3/13 (23%) 5/13 (38%) 5/13 (38%)
Study 104-09 **Clinical + Mycological Outcome for Cryptococcal Meningitis (10 weeks)**	10/16 (62.5%)	7/13 (53.8%)

The treatment studies demonstrated clinical and mycological activity when AmBisome was administered for the treatment of invasive fungal infections with Aspergillus, Candida, or Cryptococcus species. However, there were too few definitively confirmed and evaluable fungal infections to determine the relative efficacy of AmBisome compared to conventional amphotericin B.

The cryptococcal meningitis studies are particularly supportive of AmBisome's antifungal activity, since this infection does not resolve spontaneously in HIV-infected patients. The untreated outcome of this infection is death. This is less clear for infections with Candida species which sometimes resolve with removal of an infected line or device.

In conclusion, the collection of treatment studies demonstrated that AmBisome had similar antifungal activity to amphotericin B with improved tolerability. Overall, these

study data are reasonably supportive of a "second-line" indication for AmBisome for the treatment of Candida, Aspergillus or Cryptococcus species in patients who have not responded or are unable to tolerate conventional amphotericin B. However, the comparative data was not sufficient to determine the relative efficacy of AmBisome compared to conventional amphotericin B to support a "first-line" treatment indication. Similar types of data were used to grant "second-line" treatment indications for other lipid amphotericin B preparations.

9.2 Efficacy of AmBisome for Empirical Therapy of Febrile Neutropenic Patients

Empirical antifungal therapy with amphotericin B, in the presence of continued fever after 3-5 days of antibiotic therapy is the clinical standard of care. Amphotericin B is not approved specifically for this indication; however, it is accepted as an appropriate active control arm for the study of such an indication. Since no other antifungal agent is approved for this indication. Concern regarding distribution differences between amphotericin B and the liposomal amphotericin B (AmBisome) product resulted in the requirement for a well designed clinical trail for this indication, as well as, data supporting the clinical efficacy for treatment of fungal infections, as discussed in the section above.

AmBisome was studied in three randomized controlled studies for empirical therapy (Table 9.2.1). Two studies were conducted in Europe, and were not blinded. The largest study was conducted in the United States, and was conducted as a double-blind study. Pediatric patients were studied exclusively in one European study, and were allowed in the U.S. study.

Table 9.1.2 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	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 Empirical Therapy Indication

Empirical therapy includes treating patients who may not have subclinical fungal infections. There is uncertainty in the field as to the percentage of patients subclinically infected; however, it may be on the order of of patients enrolled. Originally, the primary endpoint viewed by the investigators as "appropriate" was failure due to fungal infection; however, it was felt that this endpoint would result in a prohibitively large sample size. Thus, the outcome variable proposed by the investigators was resolution of fever. It was widely recognized that there were inherent flaws in this approach, including the imprecision and non-specificity of this measure. The studies were designed to include assessments of fever resolution, failure due to fungal infections, and safety (nephrotoxicity). The impact of these decisions on the approach to analysis and interpretation of efficacy was discussed at an advisory committee meeting July 16, 1997.

The double-blind study (92-0-002) was key in the demonstration of efficacy for this indication and studies 104-14 and 104-10 were viewed as supportive of the indication.

The two smaller studies (14, 10) were found to contain several design and implementation problems which limited their usefulness: open-label; data quality issues; inadequacy of sample size for efficacy evaluation; small number of proven fungal infections; retrospective application of outcome definitions; and one way cross-overs to AmBisome.

In contrast, Study -002 was considered by the Advisory Committee to be the best study of empirical fungal therapy completed to date. Study design strengths include: double-blind administration of treatment; clear and precise definitions for fungal infection; clear protocols for timing and measurement of fever; adequate sample size for the composite endpoint. Although this study was designed with power to show equivalence with respect to a composite endpoint which included fever resolution, this study demonstrated that an adequate number of fungal endpoints could be obtained providing for adequate statistical analysis supporting efficacy.

A comparison of the efficacy of AmBisome across studies is listed below (Table 9.2.2)

TABLE 9.2.2 Empirical Therapy Trials: Confidence Intervals for Differences in Success Rates

Study	Drug/Dosage	Success Rates	Confidence Intervals* (Lower/Upper)
92-0-002	AmBisome 3 m/kg	50% (171/343)	-7%, 8%
	Amphotericin B 0.6 mg/kg	49% (169/344)	
104-14	AmBisome 1 mg/kg	63% (44/70)	-6%, 23%
	AmBisome 3 mg/kg	63% (45/71)	-12%, 21%
	Amphotericin B 1 mg/kg	52% (33/64)	
104-10	AmBisome 1 mg/kg	45% (21/47)	-29%, 13%
	AmBisome 3 mg/kg	63% (29/46)	-10%, 32%
	Amphotericin B 1 mg/kg	55% (22/40)	

*See statistical review for methodology.

The definition of success varied among studies. Success was defined in studies #14 and # 10 as afebrile for the last three days without use of another anti-fungal and absence of a confirmed fungal infection. Study #-002 defined success as survived 7 days after discontinuation of therapy, fever resolution, baseline infection cured, now new fungal infection, and no severe toxicity.

Confidence intervals narrow enough to be consistent with clinical equivalence up to ± 20% were found in these trials; however, a delta of 10% was felt to be clinically meaningful. Clearly, the confidence interval for success was narrowest (between ± 10%, a prespecified condition for an equivalence claim) in study -002. In study # 10, AmBisome 1 mg/kg was possibly inferior to amphotericin B.

While, the studies listed appear to demonstrate equivalence for the composite endpoint, further investigation of efficacy was performed based upon mycologic outcome (fungal infection). As was noted above, neither study #14 or #10 specified definitions for confirmed fungal infections in the protocol. In addition, serology for Candida species was considered to be evidence for a fungal infection by the investigators, but not by the FDA. This test is not approved in the US, and is not specific. Table 9.2.3 demonstrates the fungal infection rates for each trial.

Table 9.2.3 Fungal Infections by Study

Study	AmBisome 1mg/kg	AmBisome 3 mg/kg	Amphotericin B	Pooled Rate
92-0-002				
proven		11/343	27/344	5.5%
presumed +proven		44/343	41/344	12.3%
104-14	3/70	2/71	1/64	2.9%
104-10	3/47	1/46	1/40	3.7%
FDA reclassification	3/47	3/46	3/40	2.9%

The small sample sizes of studies #14 and #10 gave a power of 20% and 15%, respectively, to detect differences in the emergence of new fungal infections, and therefore, could not be expected to yield statistically significant and clinically meaningful results for this endpoint. Study 002 is therefore more instructive than the other studies when evaluating emergence of fungal infections as an outcome.

Fungal endpoints in study 002 were defined prior to the initiation of the study. Criteria for a "proven" fungal infection were well-defined and similar to Mycosis Study Group definitions. The presumed infections were more loosely defined, and included clinical suspicion. This presented problems for the analysis since it would be difficult for an investigator to distinguish infection from other causes, eg., progression of underlying malignancy. The difficulty with the evaluation of these two definitions can be readily derived from Table 9.2.3. There were more presumed fungal infections in the AmBisome arm compared to the amphotericin B arm (33 vs 14 fungal infections). On the other hand, there were more proven fungal infections in the amphotericin B arm. Each difference was statistically significantly different. This was of concern since the differences went in the opposite direction.

Review of the presumed category revealed that the majority of infections were diagnosed as pulmonary. Without culture results, the investigators were attributing the process to either Candida species or Aspergillus species. Again, there is a difficulty, without culture, in distinguishing fungal infection from progression of malignancy based upon chest x-ray alone.

The clinical significance of the presumed infections may be judged upon 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.

Table 9.2. 4. Mortality Rates for Applicant Classification of Proven and Presumed Emergent Fungal Infection (EFI)

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

Statistical testing of confirmed (proven) infection rates are seen below (Table 9.2.5). The Advisory Committee discussed the issue of proven and presumed infections in study 002 and concluded that the overall fungal infection rate be utilized in judging efficacy, since there were problems with the definition of presumed fungal infection. A comparison based on presumed and proven infections detected no statistically significant difference. Therefore, the data do not support superiority of AmBisome compared to amphotericin B for the indication, however, they do support equivalence.

Table 9.2.5 Confirmed Infection Rates by Study

	Amphotericin B	AmBisome 3 mg/kg	Difference 95% CI
94-0-002	27/344	11/343	4.6% (1.2%, 8.0%)
104-14	1/64	2/71	-1.3% (-6.2%, 3.6%)
104-10	1/40	1/40	0.3% (-6.1%, 6.7%)

The emergence of adverse events was a secondary endpoint of clinical importance. The study investigators defined two events as being clinically meaningful: infusion related reactions and kidney dysfunction. These are discussed in the safety summary below.

In conclusion, the evidence presented by the applicant, reviewed by the FDA and the Advisory Committee, support clinical equivalence of AmBisome with amphotericin B for the empirical treatment of febrile neutropenic patients, leading to its approval for this indication.

9.3 Prophylactic Treatment Against Fungal Infection in Immunocompromised Patients

The applicant provided two studies for this indication (see Table 9.3.1). One for chemotherapy/ bone marrow transplant recipients and one for liver transplant recipients. Both studies were conducted in Europe. The report submitted for the liver transplant patients was based on a journal article alone. Each study will be considered separately.

Table 9.3.1 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

The result of the liver transplant study was statistically significant as it was reported in the journal article (table 9.3.2). The journal article reported no fungal infections in the AmBisome group and 14% (6/43) in the placebo group. However, because of the nature of the surgical procedure, which includes bile-duct-stents or T-tubes with the potential for contamination not representative of true infection, additional data was sought from the applicant regarding the specifics of each of these infections. Three failure patients in the placebo group were listed as positive Candida species from T-tube drainage, which may not represent true infection. In addition, there was one patient in the AmBisome group who had a positive T-tube culture and was not counted as an infection by the investigators. Re-classification of the fungal infection outcomes by the FDA (infection/no infection), results in no statistically significant difference between the two treatments. This study does not provide definitive evidence of superiority over placebo for the prophylaxis indication.

Table 9.3.2 Fungal Infections Failures in Liver Transplant Study

	AmBisome (N=43) % (# Infections)	Placebo (N=43) % (# Infections)	Fisher Exact p-Value
Applicants Result	0% (0)	14% (6)	< 0.01
FDA- proven	0% (0)	7% (3)	< 0.02
FDA-proven + presumed	2% (1)	14% (6)	0.11

The bone marrow transplant study suffered from lack of prespecified endpoints. The applicant included endpoints of proven fungal infection, use of additional systemic antifungal therapies, continued fever and death as failures. Overall there were 45% (34/75) and 44% (39/88) failures for AmBisome and amphotericin B, respectively. Fungal infections and colonizations were reported by the applicant as shown in the following table (Table 9.3.3).

Table 9.3.3 Number of Patents with Fungal Infections and Colonizations in Study # 104-13.

	Placebo (N = 88)	AmBisome (N = 75)	P value
All fungal isolates	30 (34.1%)	11 (14.7%)	0.01
Proven fungal infections	4 (4.5%)	1 (1.3%)	NS
Colonizations	18 (20.5%)	10 (13.3%)	0.29
Urinary Infection	7 (8.0%)	0	0.013
Stool Infection	8 (9.1%)	6 (8.0%)	NS
Concomitant Systemic Antifungal Treatment	21 (23.9%)	21 (28.0%)	NS
Fever of Unknown Origin	11 (12.5%)	3 (4.0%)	NS

Although the "all fungal isolates" category appears to be significant, "proven fungal infections" were not statistically significantly different between the two treatment groups. The only other significant category was "urinary infections", which was based on positive urine cultures which could represent colonization and not true infection. Therefore, although statistically significant, it is not a clinically meaningful difference. (Note that the p-values given above were not adjusted for multiple comparisons)

In summary, neither of the studies presented by the applicant provided sufficient data to demonstrate superiority over placebo. Therefore, data do not support the approval of AmBisome for use as antifungal prophylaxis in either bone marrow recipients or liver transplant recipients.

10 Overview of Safety

The safety of AmBisome has been described in uncontrolled trials, compassionate use programs and controlled trials with amphotericin B as the comparator. The applicant has also included data from the post-marketing experience of AmBisome outside the U.S. The applicant states that the incorporation of amphotericin B into a phospholipid membrane allows for escalation of dosage and reduced toxicity. It is true that higher doses of amphotericin B can be administered as a liposomal formulation. The

Fungizone label states that "under no circumstances" should doses greater than 1.5 mg/kg be exceeded. An important question is whether equipotent doses of AmBisome is associated with less toxicity compared to conventional amphotericin B.

10.1 Infusion Related Toxicity
In study -002, Day 1 infusion related events occurred less frequently in the AmBisome group than the amphotericin B group. AmBisome-treated patients had a lower incidence of infusion related fever (17% vs 44%), chills/rigors (18% vs 54%) and vomiting (6 vs 7%). Cardiorespiratory events, except for vasodilatation (flushing), during all study drug infusions were more frequent in amphotericin B-treated patients. There have been a few reports of flushing, back pain with or without chest tightness, and chest pain associated with AmBisome administration; on occasion this has been severe. Where these symptoms were noted, the reaction developed within a few minutes after the start of infusion and disappeared rapidly when the infusion was stopped. The symptoms do not occur with every dose and in some cases do not recur on subsequent administrations when the infusion rate is slowed.

10.2 Kidney Function
The mean change in creatinine from baseline over time was plotted in study 002. The graph demonstrates smaller increases in creatinine for patients receiving AmBisome compared to those receiving amphotericin B. The difference in these changes was statistically significantly different. Similar results were seen for the other controlled studies. In general, it was felt that the nephrotoxicity profile, while still present in AmBisome, was an improvement over amphotericin B.

10.3 Liver and Pulmonary Function
These toxicities were specifically reviewed because of concerns of potential toxicity in preclinical and early clinical studies. Overall, liver function abnormalities occurred infrequently and at rates that were comparable to the amphotericin B control arm.

Pulmonary function, especially dyspnea related to infusion was seen infrequently. Dyspnea resolved upon stopping the infusions. When the infusion time of AmBisome was lengthened from 1 to 2 hours in these patients, dyspnea did not recur.

10.4 Deaths: Upon review of all death summaries, no deaths could be attributed to study drug.

11 Labeling Review: (please refer to the final printed label and telecon minutes regarding labeling negotiations).

11.1 Description: It was agreed that AmBisome was a true single bilayer liposomal drug delivery system. This is in contrast to other liposomal amphotericin products which form ribbon or disk-like structures.

11.2 Indications and Usage:

Empirical therapy for presumed fungal infection in febrile, neutropenic patients.

Treatment of patients with Aspergillus species, Candida species and/or Cryptococcus species infections refractory to traditional amphotericin B, or in patients where renal impairment of unacceptable toxicity precludes the use of traditional amphotericin B.

Treatment of visceral leishmaniasis.

Several important issues were discussed with regard to the label and these indications. First, for empirical therapy, it was important to the applicant to include the confirmed and presumed infection data, which FDA permitted. However, the overall claim centered on the equilavance of AmBisome to amphotericin B based on the composite endpoint. Second, for treatment of Aspergillus species, Candida species and/or Cryptococcus species infection, because a reliable estimate of treatment effect could not be determined the label states that " a clinical response occurred in some patients". Finally, with regard to visceral leishmaniasis, it is unknown whether subsequent treatment after initial therapy would be of clinical benefit in cases of failure or relapse.

11.3 Contraindications, Warnings, General Precautions: Patients with known hypersensitivity to traditional amphotericin B should not be given AmBisome. During the initial dosing period, patients should be under close clinical observation. While AmBisome is less toxic than traditional amphotericin B, adverse events may still occur. During patient management laboratory evaluation of renal, hepatic and hematopoietic function and serum electrolytes (particularly magnesium and potassium) should be performed.

11.4 Drug interactions: No formal clinical studies of drug interactions have been conducted with AmBisome. However it is assumed that the drugs known to interact with amphotericin B may interact with AmBisome (liposomal amphotericin B).

11.5 Carcinogenesis, mutagenesis, impairment of fertility: No long-term animal studies have been performed to evaluate carcinogenic potential of AmBisome.

11.6 Pregnancy, Nursing mothers: No adequate and well-controlled studies of AmBisome in pregnant women with systemic fungal infections have been preformed. It

is not known whether AmBisome is excreted in human milk.

11.7 Pediatric use: The pharmacokinetics of amphotericin B after administration of AmBisome in pediatric patients has not been studied, however, pediatric patients were included in several clinical trials (see clinical trial section).

11.7 Adverse Reactions: The adverse reaction profile for AmBisome is similar to that of amphotericin B; however, events related to decreased kidney function are somewhat fewer in frequency. It also appears that AmBisome is associated with fewer infusion related reactions than amphotericin B. This was particularly so when the administration time of AmBisome was 2 hours.

11.8 Drug Abuse and Dependence: not applicable

11.9 Overdosage: Toxicity of AmBisome due to overdose has not been defined. Repeated daily doses up to 7.5 mg/kg have been administered in clinical trials with no reported dose-related toxicity.

11.10 Dosage and Administration: AmBisome should be administered by intravenous infusion, using a controlled infusion device, over a period of approximately 120 minutes. Infusion time may be reduced to approximately 60 minutes in patients in whom the treatment is well-tolerated. If the patient experiences discomfort during infusion, the duration of infusion may be increased.

Recommended doses: 3 mg/kg/day for Empirical therapy, and 3-5 mg/kg/day for the treatment of systemic fungal infections (Aspergillus, Candida, Cryptococcus). Visceral Leishmaniasis in immunocompetent patients should be treated with AmBisome 3 mg/kg/day on days 1-5 and days 14 and 21. For Immunocompromised patients 4.0 mg/kg/day of AmBisome should be given on days 1-5 and 10, 17, 24, 31, and 38.

13 Recommendations

13.1 Approval

On August 11,1997 AmBisome was approved for the following indications:

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

2) treatment of patients with Aspergillus species, Candida species and/or Cryptococcus species infections refractory to amphotericin B deoxycholate, or in patients where renal impairment or unacceptable toxicity precludes the use of amphotericin B deoxycholate;

3) treatment of visceral leishmaniasis.

Concurrence: /S/

Mark Goldberger, MD, MPH
Division Director
Special Pathogens and Immunologic Drug Products

/S/

Jeffrey Murray, MD, MPH
Medical Reviewer, Acting Team Leader

/S/

Joyce Korvick, MD
Medical Reviewer, Acting Team Leader

45001 Applicant classified outcome as eradicated, FDA NE.

APPEARS THIS WAY
ON ORIGINAL

Appendix A-1: Study 104-00

Aspergillus species Infections

1. Changes in Cases considered to be Definitive Diagnoses

Aspergillus species infections considered definitive by applicant but not by FDA

01008 Only one sputum culture positive for Aspergillus species, no confirmation with bronchoscopy specimen or other invasive procedures.

02001 Biopsy specimen obtained more than 30 days prior to start of treatment.

03015 Culture was from abdominal wound. May have represented colonization, no documentation of invasive infection.

27003 Pre-treatment BAL culture done 109 days prior to treatment, no documentation of other cultures.

27201 Re-enrolled, last BAL culture prior to treatment was 111 days.

Aspergillus species infections considered definitive by FDA but not by applicant

27002 Aspergillus species periorbital cellulitis and sinusitis, CT confirmed, pos. nasal Aspergillus species. An Autopsy showed hyphael elements in cerebral abscess

2. Disagreement for Outcome Assessment

Clinical

06004 Nonevaluable (NE) by applicant; FDA classified as failed. The patient died after one dose.

08002 Investigator classified as improved; FDA classified as failed

40001 NE by applicant; FDA classified as failed; Patient received only two doses.

27002 NE by applicant; FDA classified as failed. Hyphae were found in a cerebral lesion at necropsy according to CRF

Mycological

01004 NE by applicant; FDA classified outcome as persisted. This patient died after one dose.

06004 NE by applicant, FDA classified outcome as persisted. This patient died.

22001 Applicant classified outcome as eradicated (implied) , FDA classified as NE.

33001 Applicant classified as eradicated (implied) , FDA classified as NE.

40001 NE by applicant, FDA classified as persisted.

Appendix A-2: Study 104-00 Candida species infections

1. Disagreement in Cases considered to be Definitive

Candida species infections not considered definitively diagnosed by FDA

03011 Patient had Candida species in BAL which is considered a presumptive diagnosis.

09005 Only mucosal cultures positive.

27004 Pretreatment cultures of mucosal surfaces.

28001 Pretreatment culture of CSF obtained 35 days prior to study start.

01009 Candida Glabrata esophagitis, this should be classified as torulopsis glabrata under other category.

Candida species Infections considered to be definitive according to FDA but not by applicant

01205 Listed in Table 14.2.1 as C. pseudotropicalis in stool, however C. krusei was present in blood at pretreeatment day -4.

05002 Patient had Candida species in BAL which is considered a presumptive diagnosis, however, also had ocular Candida lesions which could be considered definitive.

2. Changes in Outcome Assessment

Clinical

03004 Investigator classified as cured; FDA classified outcome as failed. This patient died.

03013 Investigator classified as NE; FDA classified as failed due to positive cultures

03014 Investigator classified as NE; FDA classified outcome as failed because the patient died.

01007 Investigator's classification of outcome was missing, FDA classified as cured. The patient had negative liver aspiration cultures near end of therapy.

17001 Investigator classified as improved, FDA classified as failed because the patient died (day 5).

Mycological

01007 Applicant classified as NE; FDA as eradicated

03001 Applicant classified as eradication (implied); FDA NE

03003 Applicant classified as eradication (implied); FDA NE

04008 Applicant classified as eradication; FDA NE. Liver biopsy 6 days prior to treatment, negative one after therapy

07008 Applicant classified as eradication (implied); FDA NE

09001 Applicant classified as eradication (implied); FDA NE
13001 sponsor NE; FDA persisted died of septic shock

Appendix A-2 (continued)

16001 Applicant classified as eradication (implied); FDA NE
27005 Applicant classified as eradication (implied); FDA NE

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

Appendix A-3: Study 104-00 Cryptococcal infections

Included as definitive diagnosis by FDA but not by applicant

38001 BAL culture done 24 days prior to treatment, however presence of positive microscopy one day prior to treatment.

Changes in outcome assessment

Clinical

25004 investigator NE, FDA failed
32002 investigator NE, FDA failed
38001 investigator cured, FDA NE

Mycological

No changes

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

Appendix B Study 104-05

Difference in FDA and applicant's assessment of confirmed fungal infection

AmBisome

#5006 Confirmed Aspergillus species according to applicant, presumed by FDA analysis. Patient had mold visualized on microscopy from BAL material. There were no positive cultures at baseline or throughout treatment.

Amphotericin B

#3004 Confirmed Aspergillus species according to applicant, presumed by FDA analysis. Patient had mold visualized on microscopy from BAL material. There were no positive cultures.

#13005 The applicant did not include this patient because baseline cultures were not positive. FDA included this patient because cultures after two days of treatment were positive and the patient eventually succumbed to fungal infection with absidia, which was proven at autopsy. This patient had gum and nose swab cultures on day 2 positive for Absidia. This was also confirmed by gum biopsy. This patient died, absidia was confirmed in gum and lung specimens post mortem.

Difference between FDA and applicant for assessment of clinical outcome

AmBisome

03013 Applicant classified as Nonevaluable, because patient died on day 2 of study. FDA reclassified as failure. Patient received two doses of drug and apparently died of Candida species sepsis.

07001 Applicant classified patient as a success. FDA reclassified patient as failure. This patient had Candida species in blood cultures at baseline. Fever persisted through 29 days.

24002 Applicant classified this patient as a success. FDA reclassified this patient as a failure. Patient had confirmed pulmonary aspergillosis by bronchoscopy. Patient had no follow-up cultures. Patient was afebrile on days 17-24 but had fever on days 25-31.

amphotericin B

02007 Investigator/applicant classified clinical outcome as improved. Patient remained febrile through treatment and through day 18. FDA classified as failed

07016 Investigator/applicant classified outcome as failed. FDA classified as improved, patient survived past 28 days. Sputum cultures for Aspergillus species were positive at baseline and negative at 7 days. Patient became afebrile by days 13 and 14.