CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-740/SE8-001

STATISTICAL REVIEW(S)

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

Statistical Review

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

Date Submitted: March 26 1999
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Drug Name: AmBisome®

Generic Name: amphotericin B liposome for injection

Applicant: Fujisawa Healthcare, Inc.
Research and Development
Three Parkway North
Deerfield, Illinois 60015

Indication: Empirical Treatment of Febrile Neutropenia

Protocol Number: 97-0-034

Study Initiation Date: 29 October 1997

Study Completion Date: 28 August 1998

Responsible Medical Officer: Donald N. Buell, M.D., Medical Director
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Statistical Reviewer: Andrei Breazna, Ph.D.

Study Design

Study 97-0-034 is a randomized, double-blind study designed to evaluate the safety of AmBisome and Abelcet when administered to neutropenic patients (absolute neutrophil count < 500/mm^3) at least 2 years of age who remained febrile after at least 72 hours of broad-spectrum antibacterial therapy. Study drug was administered once daily. A 120-minute infusion period was used. The duration of therapy was dependent on the patient's clinical response, but was not to exceed 42 days of treatment.

Patients were stratified as "high risk" (baseline use of the immunosuppressants tacrolimus or cyclosporine) or "low risk" (no use of such immunosuppressants) at each investigative center before being randomized (1:1:1 by study center) to a treatment group. The sponsor-provided "demographics" data set does not agree perfectly with their own summary, however the difference does not bring an imbalance to the randomization.

Table1: Patient Demographics

		AmBisome			Abelcet
		3 mg/kg/day	5 mg/kg/day	BOTH	5mg/kg/day
Nr. of neutropenic patients:		85	81	166	78
Sex	Female	34 (40.0%)	43 (53.1%)	77 (46.4%)	37 (47.4%)
	Male	51 (60.0%)	38 (46.9%)	89 (53.6%)	41 (52.6%)
Race	White	71 (83.5%)	71 (87.7%)	142 (85.5%)	70 (89.7%)
	Black	6 (7.1%)	7 (8.6%)	13 (7.9%)	6 (7.7%)
	Other	8 (9.4%)	3 (3.7%)	11 (6.6%)	2 (2.6%)
Age (years)	Mean (SD)	41.4 (20.8)	42.0 (21.2)	41.7 (20.9)	42.8 (19.4)
	Median	45.0	44.0	44.5	47.0
	Range	3-74	2-84	2-84	2-76
	<16 years	15 (17.6%)	14 (17.3%)	29 (17.5%)	13 (16.7%)
	≥16 years	70 (82.4%)	67 (82.7%)	137 (82.5%)	65 (83.3%)
Patients with BMT†		39 (45.9%)	40 (49.4%)	79 (47.6%)	40 (51.3%)
	Autologous	25 (29.4%)	26 (32.1%)	51 (30.7%)	28 (35.9%)
	Allogeneic	13 (15.3%)	13 (16.0%)	26 (15.7%)	12 (15.4%)
	Syngeneic	1 (1.2%)	1 (1.2%)	2 (1.2%)	0
Risk	High risk	15 (17.6%)	11 (13.6%)	26 (15.6%)	13 (16.7%)
	Low risk	70 (82.4%)	70 (86.4%)	141 (83.3%)	65 (83.3%)

† Bone Marrow Transplant.

Adverse events were recorded through the 7-day posttreatment follow-up visit. Infusion related adverse events, defined as adverse events reported during infusion or for up to 1 hour postinfusion, were recorded on a separate CRF.

Analyses

The primary endpoint in this safety study was the incidence of infusion related chills/rigors on Day 1 (the first infusion). The secondary endpoint was the incidence of nephrotoxicity. Other safety assessments included the incidence of other infusion-related reactions on Day 1, all adverse events, hepatotoxicity, hypokalemia, anemia, and drug tolerance. We note that the safety issues have a strong overtone of efficacy. The implication on labeling is that some caution has to be exercised in reporting marginal differences in the context of testing multiplicity.

In addition to safety assessments, the comparative efficacy of AmBisome and Abelcet was also evaluated. Fungal infection status was assessed weekly through the 7-day posttreatment follow-up visit. At the 7-day posttreatment follow-up visit, the physician evaluated the treatment as either being a success (became afebrile [≤ 38°C or 100.4°F] while neutropenic and remained afebrile for 24 hours; did not meet any failure criterion) or a failure (persistent fever; progression or persistence of a proven baseline infection such as a persistent positive blood culture or other determinations; treatment emergent development of a probable or proven systemic fungal infection; a requirement for treatment with an alternative systemic antifungal agent for a presumed, probable, or proven fungal infection; discontinuation of study drug due to toxicity; or death with fungal infection as a primary or contributing factor).

Table 2:Patient Disposition (randomized and received at least one dose of study drug)

	AmBisome		BOTH	Abelcet
	3 mg/kg/day	5 mg/kg/day		5mg/kg/day
Nr. of patients:	85	81	166	78
Completed treatment	61 (71.8%)	59 (72.8%)	120 (72.3%)	41 (52.6%)
Discontinued	24 (28.2%)	22 (27.2%)	46 (27.7%)	37 (47.4%)
p-value*	0.015	0.009	0.003	-
Adverse event	11 (12.9%)	10 (12.3%)	21 (12.7%)	25 (32.1%)
p-value*	<0.001	<0.001	<0.001	-
Lack of efficacy	3 (3.5%)	5 (6.2%)	8 (4.8%)	2 (2.6%)
Administrative reason†	10 (11.8%)	7 (8.6%)	17 (10.2%)	6 (7.7%)
Death-on study drug‡	0	0	0	4 (5.1%)

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

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

* Fisher's exact test comparing discontinuation rates relative to the Ablacet arm.

Safety

a) Chills/Rigors

There was a significantly lower incidence of infusion related chills/rigors on Day 1 for patients administered AmBisome (individual dose groups and combined) compared with those administered Abelcet;

Table 3: Infusion Related Chills/Rigors on Day 1

	AmBisome			Abelcet
	3 mg/kg/day	5 mg/kg/day	BOTH	5mg/kg/day
Number of patients	85	81	166	78
Chills/Rigors (Day 1)	16 (18.8%)	19 (23.5%)	35 (21.1%)	62 (79.5%)
p-value*	<0.001	<0.001	<0.001	-
By Age				
<16 years	4/15 (26.7%)	3/14 (21.4%)	7/29 (24.1%)	8/13 (61.5%)
p-value*	0.125	0.054	0.035	-
≥16 years	12/70 (17.1%)	16/67 (23.9%)	28/137 (20.4%)	54/65 (83.1%)
p-value*	<0.001	<0.001	<0.001	-
By Gender				
Male	9/51 (17.6%)	11/38 (28.9%)	20/89 (22.5%)	29/41 (70.7%)
p-value*	<0.001	<0.001	<0.001	-
Female	7/34 (20.6%)	8/43 (18.6%)	15/77 (19.5%)	33/37 (89.2%)
p-value*	<0.001	<0.001	<0.001	-
By BMT				
Without BMT	10/46 (21.7%)	8/41 (19.5%)	18/87 (20.7%)	30/38 (78.9%)
p-value*	<0.001	<0.001	<0.001	-
With BMT	6/39 (15.4%)	11/40 (27.5%)	17/79 (21.5%)	32/40 (80.0%)
p-value*	<0.001	<0.001	<0.001	-
Autologous	2/25 (8.0%)	8/26 (30.8%)	10/51 (19.6%)	22/28 (78.6%)
Allogeneic	3/13 (23.1%)	3/13 (23.1%)	6/26 (23.1%)	10/12 (83.3%)
Syngeneic	1/1 (100%)	0/1	1/2 (50.0%)	0/0

* Fisher's exact test for comparing proportions with the Ablacet arm.

b) Nephrotoxicity

As presented in Table 4, the incidence of nephrotoxicity by all measures was significantly ($p \leq 0.001$) lower for patients administered AmBisome (individual dose groups and combined) compared with Abelcet.

Table 4:Nephrotoxicity

	AmBisome			Abelcet
	3 mg/kg/day	5 mg/kg/day	BOTH	5mg/kg/day
Total number of patients	**85**	**81**	**166**	**78**
Nephrotoxicity 1.5X	25 (29.4%)	21 (25.9%)	46 (27.7%)	49 (62.8%)
Nephrotoxicity 2X	12 (14.1%)	12 (14.8%)	24 (14.5%)	33 (42.3%)
Peak Creatinine Mean ± SD Median (range)	1.3 ± 1.0	1.2 ± 0.6	1.2 ± 0.8	1.8 ± 1.2
Change from baseline to peak serum creatinine value (mg/dL) Mean ± SD Median (range)	0.5 ± 0.8	0.4 ± 0.4	0.5 ± 0.7	1.0 ± 1.0

c) Infusion Related Reactions Other Than Chills/Rigors

On Day 1, AmBisome was associated with a significantly reduced overall incidence of infusion related reactions.

Table 5:Infusion Related Reactions on Day 1 (more than 10% of patients in one or more arms)

	AmBisome		Abelcet 5 mg/kg/day
	3 mg/kg/day	5 mg/kg/day	
Total number of patients	85	81	78
Total number with IRR p-value*	58 (68.2%) ! <0.001	56 (69.1%) ! <0.001	69 (88.5%) -
Chills/rigors p-value*	16 (18.8%) <0.001	19 (23.5%) <0.001	62 (79.5%) -
Fever p-value*	47 (55.3%) <0.001	44 (54.3%) <0.001	64 (82.1%) -
Hypertension p-value*	4(4.7%) 0.033	7(8.64%) 0.226	12(15.38) -
Hypoxia p-value*	0 <0.001	1 (1.2%) <0.001	9 (11.5%) -
Nausea p-value*	9 (10.6%) 1	7 (8.6%) 0.6	9 (11.5%) -
Tachicardia p-value*	2(2.35%) <0.001	8(9.9%) 0.171	14(17.9%) -
Vomiting p-value*	5 (5.9%) 0.078	5 (6.2%) 0.117	11 (14.1%) -
Dyspnea p-value*	4(4.7%) 0.233	8(9.9%) 1	8(10.3%) -

! disagreement with sponsor's summary.

* Fisher's exact test for difference of proportions relative to the Ablacet arm.

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

IRR: Infusion related reaction. Patients could be included in more than one category.

d) Adverse Events

Table 6 includes the infusion-related events and the events recorded after one hour post infusion.

Table 6: Adverse events (more than 10% of patients in one or more arms).

	AmBisome		Abelcet
	3 mg/kg/day	5 mg/kg/day	5mg/kg/day
Total number of patients	85	81	78
Abdominal Pain	11	8	9
p-value*	0.816	0.801	-
Alkaline Phosph. Incr	6	7	10
p-value*	0.293	0.449	-
Anxiety	9	6	7
p-value*	0.797	0.778	-
Asthenia	7	5	9
p-value*	0.600	0.272	-
Bilirubinamia	14	9	9
p-value*	0.500	1.000	-
Bun Incr.	17	15	22
p-value*	0.271	0.189	-
Chest Pain	7	9	5
p-value*	0.768	0.403	-
Chills/rigors	34	39	70
p-value*	<0.001	<0.001	-
Confusion	11	7	3
p-value*	0.050	0.329	-
Creatinine Inc.	17	15	38
p-value*	<0.001	<0.001	-
Diarrhea	13	14	11
p-value*	1.000	0.665	-
Dyspnea	15	18	18
p-value*	0.438	1.000	-
Edema	11	10	10
p-value*	1.000	1.000	-
Epistaxis	9	7	11
p-value*	0.634	0.323	-
Fever	74	69	73
p-value*	0.194	0.123	-
Headache	8	14	8
p-value*	1.000	0.253	-
Hyperglycemia	7	7	11
p-value*	0.318	0.323	-
Hypertension	9	16	18
p-value*	0.037	0.700	-
Hypervolemia	7	9	11
p-value*	0.318	0.637	-
Hypocalcemia	9	4	4
p-value*	0.253	1.000	-
Hypokalemia	32	35	31
p-value*	0.872	0.748	-
Hypomagneesemia	13	21	12
p-value*	1.000	0.120	-
Hypotension	9	6	15
p-value*	0.129	0.035	-
Hypoxia	6	5	16
p-value*	0.020	<0.001	-
Liver function tests abnormal p-value*	9	6	9
	1.000	0.425	-
Lung Disorder	12	11	12
p-value*	0.829	0.823	-
Nausea	22	24	29
p-value*	0.131	0.319	-

Rash p-value*	20 0.162	18 0.220	11 -
Sepsis p-value*	11 0.816	6 0.425	9 -
Tachycardia p-value*	8 0.020	15 0.559	18 -
Transfusion Reaction p-value*	9 0.253	7 0.535	4 -
Vomiting p-value*	19 0.286	21 0.598	24 -

*Fisher's exact test for difference of proportions relative to the Ablacet arm.

Due to multiplicity (number of type of events and number of AmBisome arms) the marginal p-values (around 0.05) show no real significance. They may be accepted as exploratory analyses unless the condition was considered of interest a priori. The sponsor put in the proposed label adverse events with incidences under 10% in all arms and marginal significance.

Efficacy

Table 7:Success Rate

	AmBisome			Abelcet
	3 mg/kg/day	5 mg/kg/day	BOTH	5mg/kg/day
Nr. of patients	85	81	166	78
Success	34 (40.0%)	34 (42.0%)	68 (41.0%)	26 (33.3%)
Failure	51 (60.0%)	47 (58.0%)	98 (59.0%)	52 (66.7%)
Treatment difference*	6.7%	8.6%	7.6%	-
95% CI**	(-8.1%, +21.4%)	(-6.4%, +23.6%)	(-5.2%, +20.5%)	-

Patient population: all randomized patients who received at least one dose of study drug.
* Proportion of success in the current arm - proportion of success in the Ablacet arm.
** Confidence intervals of the difference of proportions *, normal approximation.

The AmBisome arms appear to pass a numeric non-inferiority test when compared to Ablacet. However this may be due to the fact that there is a significant (Table1) difference in treatment completion between any of the AmBisome treatment arms and the Ablacet arm. This reinforces the argument that, in this trial, safety became a component of efficacy, so it should be treated quite conservatively.

Comments

We agree with the core ~~of~~ the sponsor's analyses. However we caution against stating in the label that significant differences in the incidence of specific adverse events occurred, unless the p-value(s) is/are very small, or there is a major safety concern with regard to the adverse event. We also object to quoting the p-values in the label. P-values are not effect size estimators.

We did not note a difference in the efficacy or adverse reactions profile between the two doses of AmBisome.

We suggest that we replace the table on page 17 of the proposed label with Table 6 from this analysis with the p-values removed. This is consistent with the label before the addition of this trial.

In the table "Incidence of Day 1..." page 20 of proposed label we could not reproduce/understand the line "Patients with other significant reactions: 16(18.8%) 21(25.9%) 37(22.3%) 32(41.0%)". The other lines within the same row of the table correctly summarize the presented data.

/S/

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DOB III

Concurrence:

/S/

Michael Elashoff, Ph.D.
Acting Teamk Leader, DOB III

cc:
NDA 50-740 Division File
HFD-590/Dir/Goldberger
HFD-590/MTL/Cavaillé-Coll
HFD-590/MO/Akl
HFD-590/CSO/Bacho
HFD-725/Dr. Huque
HFD-725/Dr. Elashoff
HFD-725/Dr. Breazna

This review contains 8 pages.