Oral Administration of Amphotericin B (CAmB) in Humans: a Phase I Study of Tolerability and Pharmacokinetics

Biederdorf FA[1], Breithaupt I[2], Mannino R, Blum DE

(1) CEDRA Corporation, 8609 Cross Park Drive, Austin, TX 78754

Abstract

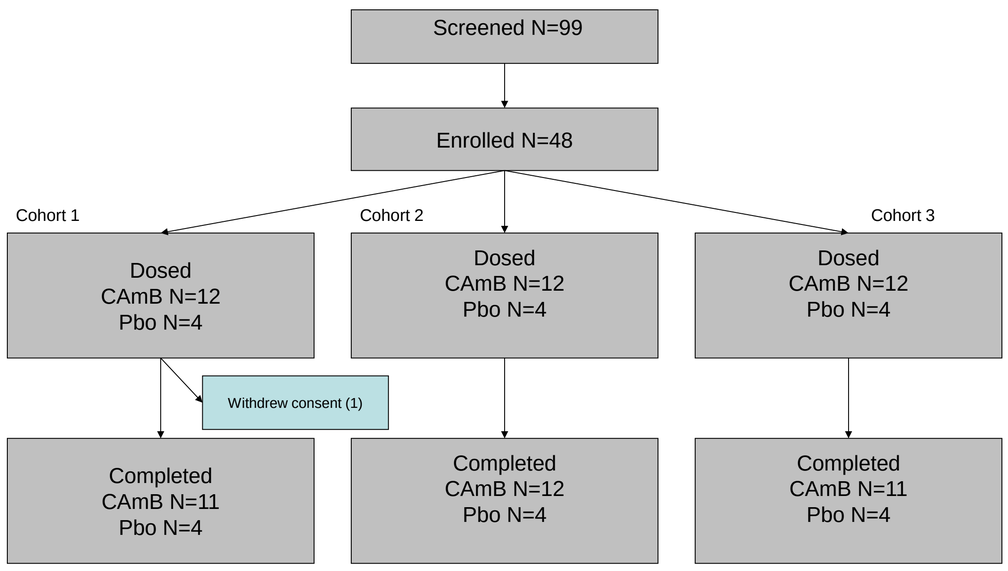
Purpose of study: Cochleates are solid particles of lipid bilayers arranged in spirals, which encapsulate drug without covalently bonding, and may facilitate oral absorption. Encochleated amphotericin B (CAmB) is a suspension of amphotericin B carried in cochleates. CAmB has previoiusly demonstrated activity following oral administration in mouse models of systemic candidiasis[1] and aspergillosis[2]. A Phase I study was conducted to evaluate the safety, tolerability and pharmacokinetics of CAmB in healthy volunteers.
Description of study: CAmB or volume-matched cochleate placebo (delivery vehicle without amphotericin B) was administered orally in double-blind fashion following overnight fast. Each subject was given a single dose. Safety and pharmacokinetic evaluations were conducted for 2 weeks after administration. Subjects were recruited in 3 cohorts given escalating doses of 200, 400, and 800 mg.
Results: 16 subjects were recruited for each cohort (12 CAmB, 4 placebo empty cochleate vehicle). CAmB was well-tolerated at doses of 200 and 400 mg. Adverse events are reported for the full cohort of 16 subjects. Gastrointestinal adverse events were seen in 6%, 38% and 56% of subjects at 200, 400 and 800 mg respectively, and all were mild at doses of 200 and 400 mg. The most common AE was nausea, seen in 6% of subjects taking 200 mg and 19% of subjects taking 400 mg, and were of mild severity in all cases at those dose levels. One subject became pregnant and underwent elective termination. There were no abnormalities in clinical laboratory testing of blood or urine. Pharmacokinetic evaluation of amphotericin was conducted.
Conclusions: This study demonstrates the feasibility of oral administration of encochleated amphotericin B in humans in single doses of 200 and 400 mg. Next steps in development include a multi-dose pharmacokinetic study and Phase II trials in humans.

(1) Santangelo et al, 2000. Antimicrob Agents Chemother. v44(9):2356-60
(2) Delmas et al, 2002. Antimicrob Agents Chemother. v46(8):2704-7.

Methods

- This was a single-dose, double-blind, dose-escalating, pharmacokinetic (PK) study in healthy volunteers, designed to determine the safety, tolerability, and PK profile of amphotericin B and to estimate relative bioavailability with cross-study comparison to other amphotericin formulations.
- A total of 48 subjects were planned for participation in this study, across 3 cohorts, 16 per treatment cohort. Within each treatment cohort, 12 subjects received active drug and 4 received placebo. Subjects checked into the clinic on Day 0 and were randomized to active treatment (200, 400, or 800 mg CAmB depending on cohort) or placebo.
- Blood samples for PK analysis were collected predose (0 hours), and postdose on Day 0 (1, 2, 4, 8, and 12 hours) and Day 1 (24 hours). Subjects checked out of the clinic when all scheduled procedures were completed. Additional blood samples were collected on an outpatient basis on Days 2, 3, 4, 8, 9, and 14 (48, 72, 96, 192, 216, and 336 hours).
- Safety was evaluated by monitoring adverse events (AEs), concomitant medication, physical examination and medical history, and clinical laboratory and vital sign measurements.

Disposition and Exposure to Study Drug



- Cohort 2 was dosed after all safety parameters from Cohort 1 were reviewed.
- Cohort 3 was dosed after all safety parameters from Cohort 2 were reviewed.

Demographics

	COHORT 1		COHORT 2		COHORT 3		TOTAL
	Placebo (N=4)	200 mg (N=12)	Placebo (N=4)	400 mg (N=12)	Placebo (N=4)	800 mg (N=12)	(N=48)
Age (years)							
Mean (SD)	36 (9.27)	31.8 (10.7)	36.8 (11.93)	36.7 (11.66)	33 (9.13)	31 (8.27)	33.7 (10.04)
Median	36.5	31	37	32.5	31.5	29	30.5
Range	27 - 44	19 - 52	25 - 48	21 - 54	25 - 44	21 - 49	19 - 54
Gender, n (%)							
Male	3 (75.0)	4 (33.3)	0	5 (41.7)	2 (50.0)	6 (50.0)	20 (41.7)
Female	1 (25.0)	8 (66.7)	4 (100.0)	7 (58.3)	2 (50.0)	6 (50.0)	28 (58.3)
Height (in.)							
Mean (SD)	68 (1.41)	67 (4.37)	63.3 (2.06)	68.5 (3.34)	67.5 (3)	67 (4.18)	67.2 (3.74)
Median	67.5	65.5	63	68	67	67.5	67
Range	67 - 70	61 - 75	61 - 66	63 - 74	65 - 71	60 - 73	60 - 75
Weight (lbs.)							
Mean (SD)	164 (19.6)	157 (31.3)	136 (16.7)	156 (29.8)	150 (24.1)	144. (22.9)	152 (26.5)
Median	171.45	147.6	136.25	143.75	146.6	133	146.6
Range	135.5 - 179	120 - 220	120 - 151.7	119 - 202.7	128 - 180	116.2 - 184.2	116.2 - 220
Ethnicity, n (%)							
Hispanic or Latino	2 (50.0)	2 (16.7)	3 (75.0)	6 (50.0)	2 (50.0)	6 (50.0)	21 (43.8)
Not Hispanic or Latino	2 (50.0)	10 (83.3)	1 (25.0)	6 (50.0)	2 (50.0)	6 (50.0)	27 (56.3)
Race, n (%)							
American Indian or Alaska Native	1 (25.0)	0	0	0	0	0	1 (2.1)
Asian	0	1 (8.3)	0	0	0	0	1 (2.1)
Black or African American	0	3 (25.0)	2 (50.0)	2 (16.7)	0	1 (8.3)	8 (16.7)
White	3 (75.0)	8 (66.7)	2 (50.0)	9 (75.0)	3 (75.0)	11 (91.7)	36 (75.0)
Native Hawaiian or Other Pacific Islander	0	0	0	1 (8.3)	0	0	1 (2.1)
Other	0	0	0	0	1 (25.0)	0	1 (2.1)

Safety

All Treatment-Emergent Adverse Events (TEAEs) Occurring in at Least 2 Subjects in Any Treatment Group

	COHORT 1		COHORT 2		COHORT 3	
	Placebo (N=4) n (%)	200 mg (N=12) n (%)	Placebo (N=4) n (%)	400 mg (N=12) n (%)	Placebo (N=4) n (%)	800 mg (N=12) n (%)
Any TEAE	1 (25.0)	3 (25.0)	1 (25.0)	6 (50.0)	3 (75.0)	8 (66.7)
Gastrointestinal Disorders	0	1 (8.3)	1 (25.0)	5 (41.7)	3 (75.0)	7 (58.3)
Abdominal pain	0	0	0	2 (16.7)	1 (25.0)	3 (25.0)
Aerophagia	0	0	0	0	1 (25.0)	2 (16.7)
Diarrhoea	0	0	0	2 (16.7)	1 (25.0)	3 (25.0)
Nausea	0	1 (8.3)	0	3 (25.0)	1 (25.0)	6 (50.0)
Vomiting	0	0	0	0	1 (25.0)	2 (16.7)

- All TEAEs were mild except 1 instance of “upper respiratory tract infection” which was moderate in a patient taking 800 mg of CAmB in Cohort 3.
- No TEAE led to withdrawal and there were no serious AEs.
- There was one pregnancy (subsequently determined that the conception date was 1-2 days prior to dosing) resulting in elective termination.

Laboratory Parameters

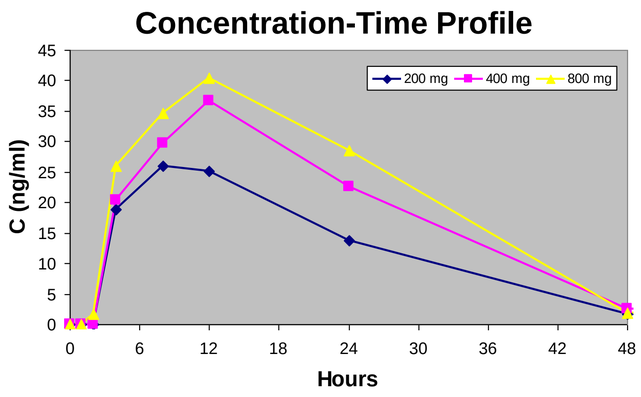
	COHORT 1		COHORT 2		COHORT 3	
	Placebo (N=4)	200mg (N=12)	Placebo (N=4)	400mg (N=12)	Placebo (N=4)	800mg (N=12)
Parameter/Visit	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**
Blood Urea Nitrogen (mg/dL)						
Screening	13.3 (1.89)	10.7 (4.31)	11.3 (4.79)	12.3 (3.77)	12.3 (3.10)	13.3 (5.82)
Day 14/ET	13.8 (3.86)	10.1 (4.81)	14.0 (5.60)	12.8 (4.76)	14.5 (3.70)	13.6 (4.64)
Creatinine (mg/dL)						
Screening	0.83 (0.050)	0.78 (0.221)	0.70 (0.082)	0.86 (0.162)	0.83 (0.150)	1.09 (0.804)
Day 14/ET	0.90 (0.141)	0.80 (0.191)	0.80 (0.000)	0.87 (0.161)	0.85 (0.129)	0.86 (0.124)

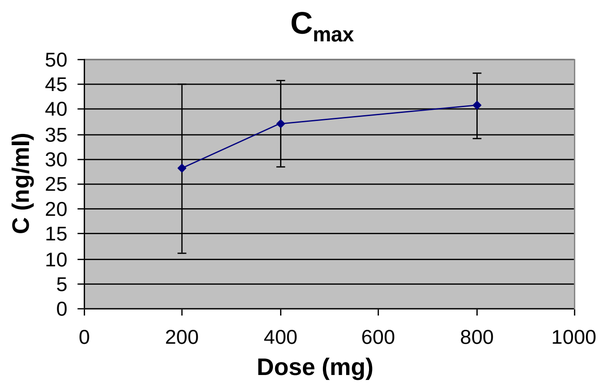
- There were no meaningful changes in any laboratory safety parameter.

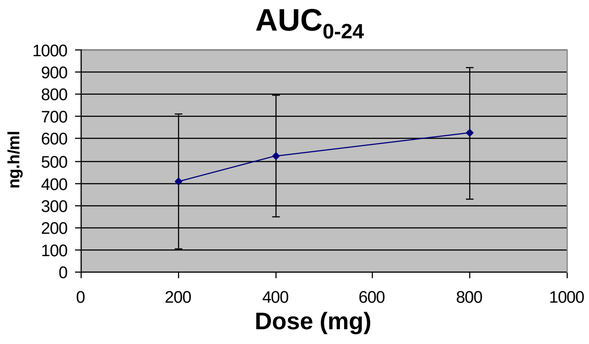
Preliminary Pharmacokinetics

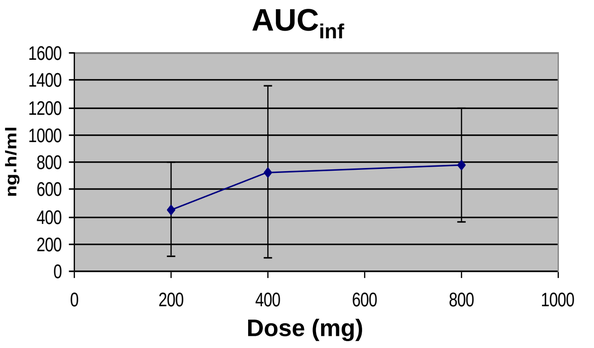
	200 mg	400 mg	800 mg
C_{max} (ng/ml)			
Mean	28.11	37.09	40.76
SD	17.06	8.66	6.48
Median	30.8	40.1	39.45
Range	0 - 48.2	22.2 - 45.9	29.8 - 53.1
AUC_{0-24} (ng.h/ml)			
Mean	407.4	522.9	624.5
SD	302.3	274.0	294.9
Median	396.1	609.2	636.7
Range	0 - 853	0 - 816	0 - 1092
T_{max} (h)			
Median	8	12	12

- Preliminary pharmacokinetic assessment indicated increases in C_{max} and AUC with increasing dose.
- Preliminary C_{max} and AUC_{0-24} are compatible with prior results from animal toxicology studies.









- Increase in dose was associated with increases in C_{max} and AUC.

Conclusions

- Encochleated Amphotericin B was well-tolerated at single oral doses of 200 and 400 mg.
- Plasma concentrations of amphotericin were obtained from this oral dosage form and are comparable to prior results from animal toxicology studies.
- Adverse events primarily affected the gastrointestinal tract and were mild in all cases at the 200 and 400 mg dose levels. There were no serious adverse events and no withdrawals due to adverse events.
- No abnormalities in laboratory or other safety testing were observed, including those associated with renal function.
- This study provides support for multi-dose pharmacokinetic studies and Phase II efficacy studies for oral administration of Encochleated Amphotericin B.