





FDAAA* Provision

"A table...,including the number of patients who dropped out of the clinical trial and the number of patients excluded from the analysis, if any."

[Sec. 282(j)(3)(C)(i)]

*Food and Drug Administration Amendments Act of 2007

4

Description of the Participant Flow Module

- Tabular presentation of progress of research participants through each stage of trial
 - Arms are "copied" from Protocol Section, but may be modified
 - Table may consist of a single Period or multiple Periods, to represent different stages of the trial (e.g., "double-blind period," "open-label period")
 - Each Period must include two Milestones: Number STARTED and Number COMPLETED

5

Flow Diagram ("Figure 1" Format) Enrolled n=143 Randomized to Standard Therapy Randomized to Low-Dose Randomized to High-Dose (AmB) n=47 Combination Therapy (AmB+Fluc400) Combination Therapy (AmB+Fluc800) n=48 n=48 Study Eligible Study Eligible Study Eligible⁴ n=45 (Treated: n=49^b) n=47 n=48 (Treated: n=45 b (Treated: n=47 b) Completed Missed Completed Missed Completed Missed Day 14 Visit Day 14 Visit ^c Day 14 Visit Day 14 Visit Day 14 Visit c Day 14 Visit n=46 n=1 n=44 n=4 n=42 n=3 Completed Completed 70 Days of Completed 70 Days of Discontinued Discontinue Discontinued 70 Days of Therapy Therapy Therapy Therapy n=35 Therapy n=32 Therapy n=12 n=16 n=13 n=32 Missed Completed Completed Missed Completed Missed Day 112 Follow-up n=31 Day 112 Day 112 Day 112 Day 112 Day 112 Follow-up n=36 Follow-up n=11 Follow-up Follow Follo ollow-up n=15 n=14 n=33 6 Pappas PG, Chetchotisakd P, Larsen RA et al. Clin Infect Dis. 2009

Key information releva period and locations	nt to the recruitment process for the overall study, such as date of recruitment
Subjects were screened	and enrolled at 10 sites in the US and 5 sites in Thailand.
Pre-Assignment Det	ails
Significant events and group assignment	approaches for the overall study following participant enrollment, but prior to
No text entered.	
Reporting Groups	
Reporting Groups	Description
Reporting Groups AmphoB Standard	Description Amphotericin B 0.7 mg/kg for 14 day followed by fluconazole 400 mg daily for 8 weeks. For subjects in the standard therapy arm whose Amphotericin B dose is continued beyond 14 days, fluconazole initiation will be delayed.
Reporting Groups AmphoB Standard AmphoB+Fluc400	Description Amphotericin B 0.7 mg/kg for 14 day followed by fluconazole 400 mg daily for 8 weeks. For subjects in the standard therapy arm whose Amphotericin B dose is continued beyond 14 days, fluconazole initiation will be delayed. Amphotericin B 0.7 mg/kg and the randomized dose of fluconazole at 400 mg/day for the first 14 days, then the randomized dose of fluconazole at 400 mg/day respectively for an additional 8 weeks.

	AmphoB Standard	AmphoB+Fluc400	AmphoB +Fluc800
STARTED	47[1]	48[2]	48 ^[3]
COMPLETED	36	33	31
NOT COMPLETED	11	15	17
[3] 47 subjects randomized; 4	49 treated – 3 subjects randoi	mized to AmphoB+Fluc400	rec'd AmphoB+Fluc400 rec'd AmphoB+Fluc800
 [3] 47 subjects randomized; 4 	49 treated – 3 subjects rando	mized to AmphoB+Fluc400	rec'd AmphoB+Fluc800



- Recruitment Details
- Pre-assignment Details
- Arm/Group*
 - Title
 - Description
- Period Title(s)*
 - "Overall Study" (default) if single period

*Required by ClinicalTrials.gov

- Milestones
 - STARTED Data*
 - Comments
 - Milestone Title
 - Data
 Comments
 - COMPLETED Data*
 - Comments
 - Reason Not Completed
 - Type (e.g., Death)
 Data

Basic Informat	ion Needeo	b
	Arm Title*	Arm Title*
	Arm Description	Arm Description
(Period Title, if more than 1 Period)		
STARTED*	# participants	# participants
(Milestone Title)	(# participants)	(# participants)
COMPLETED*	# participants	# participants
Not Completed [calculated]		
Reasons Not Completed		
Adverse Event	(# participants)	(# participants)
Death		
Lack of Efficacy		
Lost to Follow-up		
Physician Decision		
Pregnancy		
Protocol Violation		
Withdrawal by Subject		
Other (Specify)		↓ ↓



	Edit Participant Flow
	Help Definitions
Recruitment Details:	Subjects were screened and enrolled at 10 sites in the US and 5 sites in Thailand.
^o re-assignment Details:	Edit
Recruitment L Definition: Key and types of lo	Details (Optional) information relevant to the recruitment process for the overall study, such as dates of the recruitment period cation (e.g., medical clinic), to provide context.
Recruitment I Definition: Key and types of lo	Details (Optional) information relevant to the recruitment process for the overall study, such as dates of the recruitment period cation (e.g., medical clinic), to provide context. Characters remaining: 268
Recruitment I Definition: Key and types of lo Arm/G Subjects were	Details (Optional) information relevant to the recruitment process for the overall study, such as dates of the recruitment period ccation (e.g., medical clinic), to provide context. Characters remaining: 268 screened and enrolled at 10 sites in the US and 5 sites in Thailand.
Recruitment Definition: Key and types of lo	Details (Optional) information relevant to the recruitment process for the overall study, such as dates of the recruitment cation (e.g., medical clinic), to provide context.

Armo/Groups (2)							
Arms/Groups (3)	+ Add Ar	m/Group	record		-		
the loss Till	Edit) 	Edit	DI DI DI DI DI DI	Edit	Angel B I Electron	
Arm/Group Description:	Ampho day fol	otericin B 0.7 mg/kg for 14 I	Amphot random	tericin B 0.7 mg/kg and the i	Ampl rando	notericin B 0.7 mg/kg and the	e
	× Delete	Move -	× Delete	Move Move	× Delete	- Mov	
* Period Title:	Overall S	Study				Protocol E	nrollment: 1
* Period Title:	Overall S	Study	۵	AmphoB+Fluc400		Protocol E AmphoB + Fluc800	Total f
* Period Title:	Overall S	Study mphoB standard	48	AmphoB+Fluc400	48	Protocol El AmphoB + Fluc800	Total fi (Not pub
* Period Title:	Overall S A 47	Study mphoB standard	48 48 sub	AmphoB+Fluc400	48 48 s	Protocol Ei AmphoB + Fluc800 Edit Comment ubjects randomized; 49	Total 9 (Not pub
* Period Title: * Started:	Overall S A 47 47 su subje	Itudy ImphoB standard Edit Comment bjects randomized; 45 cts treated	48 48 sub subject random Ampho	AmphoB+Fluc400 Edit Comment jects randomized; 47 ts treated-2 subjects mized to AmphoB rec'd oB+Fluc400	48 48 s trea to A Amp	AmphoB + Fluc800 Edit Comment ubjects randomized; 49 ted-3 subjects randomized mphoB+Fluc800 rec'd ohoB+Fluc800	Total 9 (Not pub)
Period Title: Started: Add Milestone	Overall S A 47 47 su subje	Itudy ImphoB standard Edit Comment bjects randomized; 45 cts treated	48 48 sub subjec randon Ampho	AmphoB+Fluc400 Edit Comment jects randomized; 47 ts treated-2 subjects nized to AmphoB rec'd bB+Fluc400	48 48 s trea to A Amp	AmphoB + Fluc800 Edit Comment ubjects randomized; 49 ted-3 subjects randomized mphoB+Fluc800 rec'd ohoB+Fluc800	Total s (Not pub)
* Period Title: * Started: * Add Milestone * Completed:	Overall S A 47 47 su subje	Edit Comment Edit Comment bjects randomized; 45 cts treated	48 48 sub subjec random Ampho	AmphoB+Fluc400 Edit Comment jects randomized; 47 ts treated-2 subjects nized to AmphoB rec'd bB+Fluc400	48 48 s trea to A Amp 31	AmphoB + Fluc800 Edit Comment ubjects randomized; 49 ted-3 subjects randomized mphoB+Fluc400 rec'd ohoB+Fluc800	Total 9 (Not pub) 143 100
* Period Title: * Started: * Add Milestone * Completed: (Started - Completed)	Overall S A 47 47 subje 36 11	Bitudy mphoB standard Edit Comment bjects randomized; 45 cts treated Add Comment	48 48 subjec randon Ampho 33 15	AmphoB+Fluc400 Edit Comment jects randomized; 47 ts treated-2 subjects mized to AmphoB rec'd B+Fluc400 Add Comment	48 48 s trea to A Amp 31 17	AmphoB + Fluc800 Edit Comment ubjects randomized; 49 ted-3 subjects randomized mphoB+Fluc800 Add Comment	Total S (Not pub 143 100
* Period Title: * Started: * Add Milestone * Completed: (Started - Completed) Reason Not Completed	Overall S 47 47 su subje 36 11	Bitudy ImphoB standard Edit Comment bjects randomized; 45 cts treated Add Comment	A 48 48 subjec randon Ampho 33 15	AmphoB+Fluc400 Edit Comment j jects randomized; 47 ts treated-2 subjects mized to AmphoB rec'd B+Fluc400 Add Comment	48 48 s trea to A Amp 31 17	Protocol El AmphoB + Fluc800 Edit Comment ubjects randomized; 49 ted-3 subjects randomized mphoB+Fluc400 rec'd ohoB+Fluc800 Add Comment	Total 9 (Not publ 143 100

FRJ.			III/Group		
			Edit Participant Flow		
	Help	Definitions			
Recruitment Details:	Edit	jects were screene	d and enrolled at 10 sites in the US and 5 sites in Thailand.		
Pre-assignment Details:	Edit				
* Arm/Group Title: Arm/Group Description:	Al da	r Arm/Group Title: Arm/Group Description:	AmphoB standard Characters remaining: 778 Amphotericin B 0.7 mg/kg for 14 day followed by fluconazole 400 mg daily for 8 weeks. For subjects in the standard therapy arm whose Amphotericin B dose is continued beyond 14 days, fluconazole initiation will be delayed.	800 /kg and the	
Periods (1)				Protocol Enr	ollment:
* Period Title:	Ove				
		OK Cancel	78	800	Total (Not pu

Periods (1)					Protocol En	rollment: 14
* Period Title:	Overall Study					
	AmphoB standard		AmphoB+Fluc400		AmphoB + Fluc800	Total ≅
		48	Edit Comment	48	Edit Comment	()
* Started:	47 Edit Comment 47 subjects randomized; 45 subjects treated	48 sub rand Amj	subjects randomized; 47 jects treated-2 subjects domized to AmphoB rec'd phoB+Fluc400	48 s trea to A Am	subjects randomized; 49 tted-3 subjects randomized \mphoB+Fluc400 rec'd phoB+Fluc800	143
+ Add Milestone						
* Completed:	36 Add Comment	33	Add Comment	31	Add Comment	100
Not Completed: (Started - Completed)	11	15		17		
Reason Not Completed						
+ Add Reason Not Completed						





- Overall structure of Arms and Periods makes sense
 - Can follow "flow" of participants in study
- Consistent with Protocol Section
 - Arm and Intervention information
 - Actual Enrollment is same as Total STARTED (or discrepancy explained)

- Pre-assignment and Recruitment Details
 - Content is relevant to data element



Started 47 11 48 12 48 13 143 Completed 36 33 31 100	Started 47 [1] 48 [2] 48 [3] 143 Completed 36 33 31 100 Not Completed 11 15 17 43 11 47 subjects randomized; 45 subjects treated 21 48 subjects randomized; 47 subjects treated-2 subjects randomized to AmphoB rec'd AmphoB+Fluc400 31 48 subjects randomized; 49 treated-3 subjects randomized to AmphoB+Fluc400 rec'd AmphoB+Fluc800	 Arm/Group Description 	Amphotericin B 0.7 mg/kg for 14 day	Amphotericin B 0.7 mg/kg and the ra	Amphotericin B 0.7 mg/kg and the ra	(Not public)
Started 47 ^[1] 48 ^[2] 48 ^[3] 143 Completed 36 33 31 100 Not Completed 11 15 17 43 11 47 subjects randomized; 45 subjects treated-2 subjects randomized; 47 subjects treated-2 subjects randomized; 40 mphoB rec'd AmphoB+Fluc400 48 subjects randomized; 47 subjects treated-2 subjects randomized to AmphoB rec'd AmphoB+Fluc400 48 subjects randomized; 40 mphoB+Fluc400	Started Completed 47 ^[1] 48 ^[2] 48 ^[3] 143 100 Not Completed 36 33 31 100 Not Completed 11 15 17 43 11 47 subjects randomized; 45 subjects treated-2 subjects randomized to AmphoB rec'd AmphoB+Fluc400 8 9 9 21 48 subjects randomized; 49 treated-3 subjects randomized to AmphoB+Fluc400 rec'd AmphoB+Fluc800 9 9 9	eriod Title: Overall St	udy			
Completed 36 33 31 100 Not Completed 11 15 17 43 [1] 47 subjects randomized; 45 subjects treated-2 subjects randomized to AmphoB rec'd AmphoB+Fluc400 100 100 [2] 48 subjects randomized; 47 subjects treated-2 subjects randomized to AmphoB rec'd AmphoB+Fluc400 100 100	Completed363331100Not Completed11151743[1] 47 subjects randomized; 45 subjects treated-[2] 48 subjects randomized; 47 subjects treated-2 subjects randomized to AmphoB rec'd AmphoB+Fluc400[3] 48 subjects randomized; 49 treated-3 subjects randomized to AmphoB+Fluc400 rec'd AmphoB+Fluc800	Started	47 [1]	48 [2]	48 ^[3]	143
Not Completed 11 15 17 43 [1] 47 subjects randomized; 45 subjects treated - - - - - [2] 48 subjects randomized; 47 subjects treated-2 subjects randomized to AmphoB rec'd AmphoB+Fluc400 - - - - [1] 48 subjects randomized; 47 subjects treated - 2 subjects randomized to AmphoB rec'd AmphoB+Fluc400 - - - -	Not Completed 11 15 17 43 [1] 47 subjects randomized; 45 subjects treated- [4] 48 subjects randomized; 47 subjects treated-2 subjects randomized to AmphoB rec'd AmphoB+Fluc400 [3] 48 subjects randomized; 49 treated-3 subjects randomized to AmphoB+Fluc400 rec'd AmphoB+Fluc800 [4] 48 subjects randomized; 49 treated-3 subjects randomized to AmphoB+Fluc400 rec'd AmphoB+Fluc800 [5] 48 subjects randomized; 49 treated-3 subjects randomized to AmphoB+Fluc400 rec'd AmphoB+Fluc800 [6] 48 subjects randomized; 49 treated-3 subjects randomized to AmphoB+Fluc400 rec'd AmphoB+Fluc800 [6] 48 subjects randomized; 49 treated-3 subjects randomized to AmphoB+Fluc400 rec'd AmphoB+Fluc800 [6] 48 subjects randomized; 49 treated-3 subjects randomized to AmphoB+Fluc400 rec'd AmphoB+Fluc800 [6] 48 subjects randomized; 49 treated-3 subjects randomized to AmphoB+Fluc400 rec'd AmphoB+Fluc800 [6] 48 subjects randomized; 49 treated-3 subjects randomized to AmphoB+Fluc400 rec'd AmphoB+Fluc800 [6] 48 subjects randomized; 49 treated-3 subjects randomized to AmphoB+Fluc400 rec'd AmphoB+Fluc800 [6] 48 subjects randomized; 49 treated-3 subjects randomized to AmphoB+Fluc400 rec'd AmphoB+Fluc800 [6] 48 subjects randomized; 49 treated-3 subjects randomized to AmphoB+Fluc400 rec'd AmphoB+Fluc800 [6] 48 subjects randomized; 49 treated-3 subjects randomized; 40 treated-3 subject	Completed	36	33	31	100
 [1] 47 subjects randomized; 45 subjects treated [2] 48 subjects randomized; 47 subjects treated-2 subjects randomized to AmphoB rec'd AmphoB+Fluc400 [3] 48 subjects randomized; 40 treated 3 subjects randomized to AmphoB+Flue400 racid AmphoB+Flue800 	 [1] 47 subjects randomized; 45 subjects treated [2] 48 subjects randomized; 47 subjects treated-2 subjects randomized to AmphoB rec'd AmphoB+Fluc400 [3] 48 subjects randomized; 49 treated-3 subjects randomized to AmphoB+Fluc400 rec'd AmphoB+Fluc800 	Not Completed	11	15	17	43
		 [2] 48 subjects random [3] 48 subjects random 	nized; 47 subjects treate nized; 47 subjects treate nized; 49 treated-3 subjects	ed-2 subjects randomized ects randomized to Amp	d to AmphoB rec'd Amph hoB+Fluc400 rec'd Ampl	noB+Fluc400 hoB+Fluc800

Protocol Section	(selected conte	nt)		
Study Type: Interventi	onal			
Study Design: Treatme	ent, Parallel Assignme	ent, Open Label, Ran	domized, Safety/Effica	cy Study
Official Litle: A Phase	I Randomized Trial o	f Amphotericin B Alor	he or Combined With F	luconazole in the
realment of AIDS-ASS	ocialed Cryptococca	Imeninglus		
Enrollment: 146				
Study Start Date: May	2005			
Study Completion Date	e: April 2008			
Primary Completion Data	ate: April 2008			
Results Section	- Participant Flo	ow		
	•			
Recruitment Details	Subjects were screened	d and enrolled at 10 site	s in the US and 5 sites in	Thailand.
Pre-Assignment Details				
Arm/Group Title	AmphoB Standard	AmphoB+Fluc400	AmphoB + Fluc800	Total
Arm/Group	Amphotericin B 0.7	Amphotericin B 0.7	Amphotericin B 0.7	(Not public)
Description	mg/kg for 14 day	mg/kg and the ra	mg/kg and the ra	
Period Title: Overall Stu	dy			
Started	47 [1]	48 [2]	48 [3]	143
Completed	36	33	31	100
Not Completed	11	15	17	43
[1] 47 subjects randomi	zed; 45 subjects treated			
[2] 48 subjects randomi	zed; 47 subjects treated			
(

PRS Review Commo	ents
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Period Title: Overall Study							
Started 47 ^[1] 48 ^[2] 48 ^[3] 143							
Completed 36 33 31 100							
Not Completed 11 15 17 43							
[1] 47 subjects rand	lomized; 45 subjects	treated					
[2] 48 subjects randomized; 47 subjects treated							
[3] 48 subjects randomized; 45 were study eligible and 49 were treated							
Comments:							
The Enrollment number in the Protocol Section (146) conflicts with the number of participants Started (143) in the Participant Flow module. Please verify and correct either or both of these data elements, as necessary.							
Please provide an explanation for the last footnote. Specifically, it is not clear how the number of participants treated was greater than the number of participants randomized (Started).							
				20			

Specific Review Criteria

- Milestone
 - Number achieving Milestone is greater than or equal to Number COMPLETED the Period
 - Number STARTED is greater than or equal to Number COMPLETED
 - If multiple Milestones, generally Number for subsequent Milestone is not greater than the Number for the previous Milestone

Example					
Participant F	-low: Overall S	Study			
		5-FU/FA	Irinotecan + 5-FU/FA		
STARTED		160	161		
Treated		153	153		
COMPLETED)	125 ^[1]	115 ^[1]		
NOT COMPLI	ETED	35	46		
Adverse Eve	ent	3	8		
Death		1	0		
Withdrawal	by Subject	3	12		
Relapse		15	7		
Protocol Vi	olation	2	2		
Specified by	/ site	4	9		
Randomized	Not Treated	7	8		
[1] Received n	naximum number of	cycles.		:	22



- Period Titles are informative
- Number STARTED in a subsequent Period is the same as the Number COMPLETED in the previous Period
 - If not the same, discrepancy is explained in Comment data element

Example – Poter	Example – Potential Error		
Period 1: Weeks 0 - 16			
	Placebo	Drug X	
STARTED	301	299	
COMPLETED	291	290	
NOT COMPLETED	10	9	
Period 2: Weeks 17 – 32	2		
	Placebo	Drug X	
STARTED	291	285	
COMPLETED	288	278	
NOT COMPLETED	3	7	
		·	
			24

eriod 1: Weeks 0 - 16		
	Placebo	Drug X
TARTED	301	299
OMPLETED	291	290
NOT COMPLETED	10	9
eriod 2: Weeks 17 – 3	2 Placebo	Drug)
TARTED	291	285
COMPLETED	288	278
IOT COMPLETED	3	7
1 5 participants did not enter	Period 2 (4 ineffective tre	eatment; 1 pos

Example – Cross-over Design

	Description
Placebo First, then Drug A	Placebo twice daily in first intervention period and Drug A 25 mg twice daily in second intervention period (after washout period).
Drug A First, then Placebo	Drug A 25 mg twice daily in first intervention period and Placebo twice daily in second intervention period (after washout period).

Period: First Intervention

	Placebo First, then Drug A	Drug A First, then Placebo
STARTED	65	63
Received at Least 1 Dose of Drug	65	64
COMPLETED	65	63
NOT COMPLETED	0	2
Neutropenia	0	1
Withdrawal by Subject	0	1

13

Exam	ple – Cross-over	Design
(cont'	d)	

Period: Washout Period of 2 Weeks

	Placebo First, then Drug A	Drug A First, then Placebo
STARTED	65	63
COMPLETED	63	62
NOT COMPLETED	0	2
Disease Relapse	2	1

Period: Second Intervention

	Placebo First, then Drug A	Drug A First, then Placebo
STARTED	63	62
COMPLETED	60	62
NOT COMPLETED	3	0
Adverse Event	2	0
Lost to Follow-up	1	0

27

Additional Information General ClinicalTrials.gov information: <u>http://clinicaltrials.gov</u> FDAAA-related information (see Submit Studies): <u>http://clinicaltrials.gov/manage-recs/fdaaa</u> Office of Extramural Research: <u>http://grants.nih.gov/Clinicaltrials_fdaaa/</u> Questions? <u>register@clinicaltrials.gov</u>