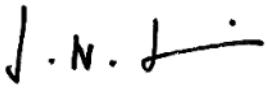
Ambition Trial Coordinating Centre
Private Bag 320, Princess Marina Hospital
Gaborone, Botswana

AMBITION-*cm*
AMBIsome Therapy Induction OptimizatioN

Work Practice Document: 19
Pharmacokinetics and Pharmacodynamics Sub-study

Title of study	High Dose AMBISOME© on a Fluconazole Backbone for Cryptococcal Meningitis Induction Therapy in sub-Saharan Africa: A Phase III Randomized Controlled Non-inferiority Trial		
Acronym	Ambition-cm – AMBIsome Therapy Induction OptimizatioN		
ISRCTN No.:	ISRCTN72509687		
WPD Current version	Version 1.0, 20/07/2017		
Author(s)	David Lawrence Lead Clinician		20/07/2017
	Katharine Stott PK/PD Lead in Blantyre		20/07/2017
Reviewer(s)	Timothée Boyer Chammard Clinical Advisor		20/07/2017
Approved by	Joseph Jarvis CI		20/07/2017

Revision History:		
Version Number	**Effective Date**	**Reason for Change**
1.0		First version

Working Practice Document 19: Pharmacokinetics and pharmacodynamics sub-study

Purpose
This document describes the processes to be followed in Blantyre where the pharmacokinetic (PK) and pharmacodynamics (PD) sub-study will take place.

Scope
This WPD applies to the schedule and timing for the blood and CSF sampling which will take place in Blantyre, Malawi

General

1. The aims of this stub-study are to examine the pharmacology of L-AmB, 5FC and FLU in the blood and CSF.
2. This sub-study will only take place in Blantyre and will only recruit patients in the L-AmB arm
3. There will be 50-60 patients recruited to this sub-study
4. An interim analysis will take place after roughly 10 patients have been sampled and recruitment will continue whilst awaiting the results of this analysis
5. Accurate documentation of the time of drug administration and of blood sampling are key to this process.
6. If doses have been given at the wrong times or omitted, it is crucial that this is accurately documented in the eCRF

Blood PK/PD

1. Blood PK/PD studies will take place on D1 and D7
2. 4ml of blood will be taken for each sample into a green lithium heparin tube
3. Timings of bloods on D1 and D7 are outlined below. Please note that there is a 2-hour window during which blood can be sampled but the exact time of sampling must be recorded
4. The clock starts from the moment the infusion begins and does not change if the infusion is given over more than the recommended two hours
5. Patients who do not receive a full dose of L-AmB will be excluded from this stub-study

Working Practice Document 19: Pharmacokinetics and pharmacodynamics sub-study

Day	Hour	LAmB IVI	FLC PO	5FC PO	Sampling window (hrs since start of IVI)	Blood: PK sample number
1	0*	2 h IVI				
	1					
	2				2-2.5h	1
	3					
	4				4-5	2
	5					
	6					3
	7				7-8	
	8					
	9					
	10					
	11					
	12				12-13	4
	13					
	14					
	15					
	16					
	17					
	18					
	19					
	20					
	21					
	22				22-23.9	5
	23					
	24					
7	-2					
	-1					
	0				0 h (pre-dose)	1
	1					
	2				2-2.5h	2
	3					
	4				4-5	3
	5					
	6					4
	7				7-8	
	8					
	9					
	10					
	11					
	12				12-13	5
	13					
	14					
	15					
	16					
	17					
	18					
	19					
	20					
	21					
	22				22-23.9	6
	23					
	24					

CSF PK

1. 1ml of CSF will be taken from the LPs on D1, D7 and D14 for PD studies
2. In addition, 1ml of CSF will be taken from the LP on D7 and D14 for PK studies.
3. CSF will be sampled into a plain collection bottle.
4. If included patients have LPs at other times for another reason (e.g. deterioration, raised intracranial pressure) 1ml of CSF should be saved for this study, with the time of the LP documented accurately on the sample and eCRF.
5. On D7 patients will be randomized alternately to have their LP either before or after their daily dose of fluconazole.
6. On D14 patients will then switch round and if they had their D7 LP before their fluconazole dose they will have their D14 LP after their fluconazole dose (and vice versa).

Training

Each staff member receives or has direct access to applicable Working Practice Documents (WPDs).

Each staff member reviews the applicable WPDs once a year.

All WPD training is documented and tracked in the WPD training logbook located in the Project Coordinator's office.

New staff is trained on applicable WPDs within 30 days of employment and all WPDs within 90 days of employment.

Staff members whose duties fall within this WPD scope are retrained within 14 days of the approval of each WPD revision.

References

1. Declaration of Helsinki, 2013: https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/ accessed 12th June 2017
2. International Conference on Harmonisation (ICH) Guideline For Good Clinical Practice E6(R1), 1996
3. Integrated Addendum to ICH E6(R1): Guideline For Good Clinical Practice E6(R2), 2016
4. Ambition Trial Protocol

Staff signatures: (signing below indicate that you have read this SOP and understand the material contained in it)

Date	Name (Please print)	Signature