Reviewer's report

Title: AMBITION-cm. Intermittent High Dose AmBisome on a High Dose Fluconazole Backbone for Cryptococcal Meningitis Induction Therapy in sub-Saharan Africa: Study Protocol for a Randomized Controlled Trial

Version: 3
Date: 8 May 2015

Reviewer: Ayodele Odutayo

Reviewer's report:

The enclosed manuscript is a clinical trial protocol for a multicentre adaptive open-label phase II/III randomised non-inferiority trial comparing alternative short course AmBisome regimens for the treatment of HIV-associated cryptococcal meningitis. The study has received ethics approval and is registered in a WHO primary registry.

The protocol is clear and well written. Specific comments are included below.

Major compulsory revisions

1. No details regarding the statistical analyses planned for the study are provided. At a minimum, can the authors please identify the main analysis for the primary outcome (Step 1 and Step 2), including analysis methods for statistical comparisons. Can the authors also provide information on effect measures and significance levels. Finally, the authors should also detail how missing data will be handled and any subgroup analyses that are planned.

2. Primary outcome of step 1: In the outcomes section, can the authors clearly specify the time point at which the EFA measurement will be taken. Based on other sections in the protocol, it seems that it will be based on the second LP.

3. Recruitment: No details are provided regarding recruitment into the study. Can the authors clarify expected recruitment rates, estimates for eligible patients and the estimated duration of the recruitment period and any plans to monitor recruitment during the trial.

4. The study is funded by a Gilead investigator initiated award. Can the authors clarify the role of the sponsor in the study, if any.

Minor essential revisions

1. The authors clearly state the method of random sequence generation and allocation concealment. However, the allocation ratio was not specified although it seems to be 1:1. Can the authors add this information.

2. The study is stated as being open-label and unblinded. Does this also mean that outcome assessors are unblinded? It would be helpful if the authors can specify this detail.
Discretionary revisions

1. For clarity, the paragraph heading “screening” should be changed to “inclusion and exclusion criteria” or “eligibility criteria”.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

No competing interests