# SUMMARY EVALUATION REPORT TEMPLATE

**Study Title: "** Optimizing the Dose of Flucytosine for the Treatment of Cryptococcal Meningitis "

**NDA CTA Number:** 0259

**Protocol No.** NA

**Version No.** 1.1 **Date:** 14 August 2023

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**Institution /Trial Site:** Infectious Diseases Institute/Kiruddu National Referral Hospital & Mbarara Regional Referral Hospital

**Sponsor:** Makerere University Lung Institute-MakNCD Program

**REC of Record:** IDI REC **REC Reference number:** IDI-REC-2022-32

**UNCST Reference Number:** HS2940ES

**NDA date of Approval:** 19th March 2024

## Study background and Rationale

CM has emerged as one of the most frequent and deadly opportunistic infections in HIV patients with a global burden estimated at nearly 1 million cases annually. 5-FC is essential in reducing fungal burden in the first week of therapy but access remains limited in settings with CM incidence.

In a randomized clinical trial using a higher dose of amphotericin (0.7mg/kg/day) with or without 5-FC (100mg/kg/day), addition of 5FC resulted in higher rates of CSF sterilization and lower mortality rates and no difference in toxicity between groups. The dose was selected as an attempt to mitigate toxicity and maximize therapeutic effects and not based on systematic analysis.

Preliminary modelling based on AMBITION Pharmacokinetics demonstrated that 5-FC may reach concentrations above MIC for Cryptococcus even at lower and less frequent dosing.

Data suggests the dose of 5-FC can be safely adjusted for optimization while maintaining the mortality benefit of CM induction therapy.

Studies have shown that 5-FC can be used effectively at 100mg/kg/day, no studies have shown if lower doses might be effective and this can have an impact on access by reducing the cost and supplies needed for CM patients.

## General objective / Study aims

The randomized controlled trial will determine if oral penicillin is non-inferior to IM penicillin prophylaxis in preventing latent RHD progression

## Primary Objectives and Outcome Measures

To demonstrate the reduced dose of 5-FC, when combined with IV AMB for induction therapy of CM is non-inferior compared to traditional dosing of 5-FC in reducing fungal burden of *Cryptococcus*

**Primary endpoint**.

- CSF early fungicidal activity (EFA) during induction treatment: as measured in the change in log10 CFU/mL of CSF/day and as assessed with general linear models. EFA from the intervention group will be compared to historical controls of fluconazole monotherapy, of fluconazole + flucytosine, of IV amphotericin + fluconazole, and of IV liposomal amphotericin (single-dose) + flucytosine (100 mg/kg/day) + fluconazole (1200 mg/day) or IV deoxycholate amphotericin + flucytosine (100 mg/kg/day).
- Laboratory anomalies (Grade 2-5 adverse events) and Clinical Adverse Reactions (Grade 3-5) as per the NIAID DAIDS toxicity grading table will be separately compared between the flucytosine group and the historical controls for the frequency of having at least one event and the mean number of events with linear and logistic regression models.

## Secondary Objectives and Outcome Measures

1. To determine if there remains a mortality benefit to 5-FC for induction therapy at reduced dosing.
2. To assess the overall safety and tolerability of 5-FC at reduced dosing

**Secondary endpoints**

Desirability of Outcome Response (DOOR) as ordinal ranked maximum score tested by Win Ratio.

1. 18-week Survival with CSF sterility by 2-weeks
2. 18-week survival with CSF culture positivity beyond 2 weeks
3. Grade 3 hematological adverse event by 2 weeks
4. Grade 4 hematological adverse event by 2 weeks
5. Lost to follow up before 18-weeks
6. Serious Adverse Event through 18 weeks (e.g. all-cause re-hospitalization, permanent neurologic deficit)
7. Death by 18-weeks
8. CSF culture sterility cumulative incidence over 18 weeks
9. 18-week survival time

**Study Design**

It's a prospective, adaptive, non-inferiority, open-label, trial to compare the efficacy and safety of reduced dosing of 5-FC induction therapy for the treatment of cryptococcal meningitis in combination with IV AMB to standard of care, with EFA as the primary endpoint

**Study Population**

Participants >18 years with Cerebrospinal Fluid cryptococcal antigen (CrAg) positive meningitis.

**Eligibility Criteria**

**Inclusion Criteria:**

1. CSF cryptococcal antigen (CrAg) positive meningitis Ability and willingness to provide informed consent.

Willing to receive protocol-specified lumbar punctures

**Exclusion criteria:**

- Age < 18 years
- Inability to take enteral (oral or nasogastric) medicine
- Cannot or unlikely to attend regular clinic visits
- Receiving chemotherapy or corticosteroids
- Suspected paradoxical immune reconstitution inflammatory syndrome (IRIS)
- Pregnancy or breastfeeding (tested on screening)
- CrCl < 20 mL/minute
- White blood cell count < 1.5 cells/μL
- Patients with prior 5-flucytosine exposure >3 days in the prior year
- Any condition for which participation would not be in the best interest of the participant or that could limit protocol specified assessments.

**Study Duration**

12 months

**Investigational Medicinal Product**

Oral flucytosine 60mg/kg/day three times a day for 10 days

**Study Arms**

- The investigational cohort will receive 60mg/kg/day of Flucytosine divided into 3 doses per day for 10 days, n=36 CSF culture positive.
- The control group will consist of matched historical participants in the AMBITION trial
- All participants will receive liposomal Amphotericin B 10 mg/kg, single-dose infusion, if available.
- If liposomal Amphotericin is unavailable, participants will receive IV amphotericin deoxycholate 0.7-1.0 mg/kg/day for 7 days.

**Sample size**

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|---|
| 50 participants |

**Evaluator's Risk/Benefit Assessment**:

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| The current information provided on the investigational product is sufficient to justify the proposed clinical trial. The potential benefits of conducting the trial are considered to outweigh the risks involved, provided that the study is carried out in accordance with the approved protocol, applicable local regulatory standards, ethical standards derived from the Declaration of Helsinki and the principles of Good Clinical Practice |