Medicines Control Authority of Zimbabwe

Clinical Trials Registry

PUBLIC TITLE/ACRONYM	IMAGINE-TBM -A5384
Scientific Title	A Phase II, Randomized, Open-Label Trial of a Six-Month Regimen of High-Dose Rifampicin, High-Dose Isoniazid, Linezolid, and Pyrazinamide versus a Standard Nine-Month Regimen for the Treatment of Adults and Adolescents with Tuberculous Meningitis: Improve

Primary Sponsor Details

Sponsors *	AIDS CLINICAL TRIAL GROUP

Secondary Sponsor Details

Contact for Public Queries

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Countries of Recruitment *

USA, South Africa, Zimbabwe, Mexico , Peru, Malawi, Brazil and Kenya

Source of Funds	AIDS CLINICAL TRIAL GROUP
Health Condition(s) or Problem(s) Studied *	: Tuberculosis meningitis (TBM) treatment
Medicine Name *	Linezolid Rifampicin Isoniazid Pyrazinamide Ethambutol
Quantity of medicine required *	The study drugs will be ordered from the sponsor intermittently as the study progresses. The quantities ordered will be determined by the participant recruitment rate and duration of follow-up .

7.0 PRINCIPAL INCLUSION CRITERIA *

Definite, probable, or possible TBM diagnosis wherein the participant is being committed to a full course of SOC anti-TB treatment for TBM in the setting of routine care. CSF, imaging, laboratory, and other results used to determine definite, probable, or possible TBM can be from testing performed as part of routine care, as long as obtained within 21 days prior to study entry.

Definite TBM is defined by the presence of one or more of the following:

- **Acid-fast bacilli (AFB) seen in the CSF, MTb cultured from CSF, or a CSF Mtb-positive nucleic acid amplification test (e.g., Gene Xpert or Xpert Ultra) from a participant who presents with symptoms or signs suggestive of meningitis;**

OR

- **AFB seen in the context of histological changes consistent with tuberculosis in the brain with suggestive symptoms or signs and CSF changes [Marais 2010]**

Probable and Possible TBM are defined using previously published consensus criteria as shown in Appendix I [Marais, Thwaites et al., 2010].

- **Probable TBM is defined as a total score of ≥12 (see Appendix I). At least two points should either come from CSF or cerebral imaging criteria.**
- **Possible TBM is defined as a total score of 6–11 (see Appendix I).**
- **To determine if a participant meets criteria for probable or possible TBM, CSF appearance, cell count, and differential, glucose and protein must be documented.**

Because culture confirmation is rarely available or often delayed in TBM, participants with probable or possible TBM will be enrolled based on these predefined criteria (see Appendix I), and CSF, if available, should be sent for mycobacterial culture and/or molecular testing. Preference is for this culture and testing to be done at a DAIDS-approved lab but a national/regional TB reference lab is acceptable. Refer to section 14 of the A5384 Manual of Procedures (MOPS).

Persons aged ≥15 years

Absence of HIV-1 infection, as documented by any licensed rapid HIV test or HIV-1 enzyme or chemiluminescence immunoassay (E/CIA) test kit, within 30 days prior to study entry,

OR

HIV-1 infection, documented by any licensed rapid HIV test or HIV-1 E/CIA test kit at any time prior to entry and confirmed by a licensed Western blot or a second antibody test by a method other than the initial rapid HIV and/or E/CIA, or by HIV-1 antigen or plasma HIV-1 RNA viral load. Two or more HIV-1 RNA viral loads of >1,000 copies/mL are also acceptable as documentation of HIV-1 infection, or documentation of HIV diagnosis in the medical record by a healthcare provider.

Note A: The term "licensed" refers to a US FDA-approved kit, which is required for all IND studies, or for sites located in countries other than the United States, a kit that has been certified or licensed by an oversight body within that country and validated internally. Non-US sites are encouraged to use US FDA-approved methods for IND studies.

Note B: WHO and Centers for Disease Control and Prevention (CDC) guidelines mandate that confirmation of the initial test result must use a test that is different from the one used for the initial assessment. A reactive initial rapid test should be confirmed by either another type of rapid assay or an E/CIA that is based on a different antigen preparation and/or different test principle (e.g., indirect versus competitive), or a Western blot or a plasma HIV-1 RNA viral load.

Documentation within 3 days prior to study entry of stage of disease using BMRC TBM grade:

Grade I: Glasgow Coma Score 15, no focal neurological deficits

Grade II: Glasgow Coma Score 11-14 or 15 with focal neurological deficits

Grade III: Glasgow Coma Score ≤10

The following laboratory values obtained within 3 days prior to study entry:

- **Serum creatinine ≤1.8 times upper limit of normal (ULN)**
- **Hemoglobin ≥8.0 g/dL for men, ≥7.5 g/dL for women**
- **Absolute neutrophil count ≥600/mm3**
- **Platelet count ≥60,000/mm3**
- **Alanine aminotransferase (ALT) ≤3 x ULN**
- **Total bilirubin ≤2 x ULN**

For participants of reproductive potential who have not been post-menopausal for at least 24 consecutive months (i.e., no menses within the preceding 24 months), or participants who have not undergone surgical sterilization, hysterectomy, bilateral salpingectomy, bilateral oophorectomy, or tubal ligation, documentation of a serum or urine pregnancy test result (positive or negative; see section 6.3.6 for test sensitivity requirement) within 21 days prior to study entry.

Note: Acceptable documentation of lack of reproductive potential is oral or written documentation from the participant.

Participants with documentation of a positive pregnancy test will be consented using the consent form for pregnant participants (Appendix V).

Participants of reproductive potential with documentation of a negative pregnancy test must agree to use at least one acceptable form of contraception, or abstain from sexual activity that could lead to pregnancy while receiving study treatment and for 30 days after stopping study treatment.

Acceptable forms of contraception include:

- **Condoms (male or female) with or without a spermicidal agent**
- **Diaphragm or cervical cap with spermicide**
- **Non-hormonal IUD**

Participants who are not of reproductive potential or whose partner(s) has documented azoospermia are not required to use contraception. Any statement of self-reported sterility or that of the partner's must be entered in the source documents.

Note: Acceptable documentation of lack of reproductive potential is oral or written documentation from the participant.

Ability and willingness of participant or parent or legally authorized representative (for adolescents or participants unable to provide consent) to provide informed consent/assent.

Ability to comply with the protocol requirements in the opinion of the site investigator.

Exclusion Criteria

More than 14 cumulative days of first-line TB medications, including but not limited to INH, RIF, EMB, and PZA, received within 90 days prior to study entry.

Note: INH used as prophylaxis is allowed.

Known current or previous drug resistant TB infection (i.e., resistance to one or more first-line TB medications, including but not limited to INH, RIF, EMB, LZD and PZA).

Known allergy/sensitivity or any hypersensitivity to components of study TB drugs (INH, RIF, LZD, PZA, and EMB) or their formulation.

For participants who are able to undergo the Brief Peripheral Neuropathy Screen (BPNS) within 21 days prior to study entry, Grade 3 subjective peripheral neuropathy score on the BPNS AND EITHER vibratory loss OR absent ankle jerks.

Note: For participants who are unable to undergo the BPNS (e.g., due to altered mental status), this exclusion criterion can be disregarded.

Expected concomitant use or use up to 21 days prior to study entry of monoamine oxidase inhibitors or selective serotonin reuptake inhibitors, or concomitant use of any other drug with significant interaction with the study drugs (see section 5.4.2).

For participants with HIV and ART-naïve, planned initiation of ART during the first 4 weeks after randomization.

For participants with HIV and on ART that includes a protease inhibitor, nevirapine, or other prohibited ART (see section 5.4.2), contraindication to switching to an acceptable alternative regimen (e.g., efavirenz, high-dose raltegravir or dolutegravir with nucleoside reverse transcriptase inhibitors, as per local SOC) prior to randomization. TB treatment, including study drugs, should be started as soon as possible.

Contraindication to LP at discretion of treating clinician (e.g., unequal pressures between intracranial compartments due to mass lesion, non-communicating hydrocephalus).

Positive cryptococcal antigen, gram stain, bacterial culture, or other test result obtained from a CSF specimen collected within 21 days prior to entry as part of routine care indicating CNS infection with a pathogen other than MTb (e.g.,

cryptococcal meningitis, bacterial meningitis). Refer to section 14 of the A5384 MOPS.

Note: Participants may enroll with pending results. If, after enrollment to study, results are returned which indicate an alternative cause of meningitis, participants would meet criteria for late exclusion (see section 4.3).

7.1 PRINCIPAL EXCLUSION CRITERIA *

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Known allergy/sensitivity or any hypersensitivity to components of study TB drugs (INH, RIF, LZD, PZA, and EMB) or their formulation.

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7.2 PRIMARY END POINTS *

Modified Rankin Scale (6-death, 5-severe disability, 4-moderately severe disability, 3-moderate disability, 2-slight disability, 1-no significant disability, 0-no symptoms) at 48 weeks

9.0 DESIGN OF THE TRIAL

Type of trial *	Opened
If controlled	
Randomised	Yes
Single Blind	
Double Blind	
Parallel group	
Cross over	
Other	
If yes to other, specify	This will be an international, multicenter, Phase II randomized, open-label trial to compare a 6-month regimen of high-dose rifampicin (RIF), high-dose isoniazid (INH), linezolid (LZD), and pyrazinamide (PZA) to the World Health Organization (WHO) 9-month
If controlled, specify the comparator	World Health Organization (WHO) 9-month standard of care (SOC) regimen for the treatment of tuberculous meningitis (TBM)
Other medicinal product(s)	
Placebo	No
Other	
If yes to other, specify	
Other	

Expected Number of participants in Zimbabwe *	15
Total enrolment in each site: (if competitive enrolment, state minimum and maximum number per site.) *	15
Total participants worldwide *	330

Time period for the trial *	72 weeks