

ALTER Protocol

STUDY TITLE: Pharmacokinetics and tolerability of **Adjunctive Linezolid** for the **Treatment** of tub**ER**culous meningitis (**ALTER**): a Phase II trial, open-label, randomized trial

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Pharmacokinetics and tolerability of **Adjunctive Linezolid** for the **Treatment of tubERCulous meningitis**
(ALTER): a Phase II trial, open-label, randomized trial

SIGNATURE PAGE

I will conduct the study in accordance with the provisions of this protocol and all applicable protocol-related documents. I agree to conduct this study in compliance with the standards of the International Conference on Harmonization Guideline for Good Clinical Practice (E6); Institutional Review Board/Ethics Committee determinations; all applicable in-country, state, and local laws and regulations; and other applicable requirements and institutional policies.

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Signed: _____ Date: _____

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PARTICIPATING SITES

ALTER will recruit 60 participants from Masaka Regional Referral Hospital in Masaka, Uganda over approximately 1.5 years.

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SCHEMA

Pharmacokinetics and tolerability of **Adjunctive Linezolid for the Treatment of tubERCulous meningitis (ALTER)**: a Phase II trial, open-label, randomized trial

DESIGN	ALTER is a phase II randomized, open-label trial using a factorial design of high or standard dose rifampicin with or without linezolid for the first 4 weeks of treatment for tuberculous meningitis (TBM). Initial randomization will be to high (35 mg/kg/day) versus standard (10 mg/kg/day) dose oral rifampicin for 4 weeks. After randomization to high versus standard dose rifampicin, participants will undergo a second randomization to linezolid 1200 mg daily versus no linezolid for 4 weeks.
DURATION	24 weeks
SAMPLE SIZE	60 participants
POPULATION	Participants with definite, probable, or possible TBM, aged ≥ 18 years
SETTING	Masaka Regional Referral Hospital, Masaka, Uganda
STRATIFICATION	Participants will be randomized with stratification by HIV status and stage of disease (Grade 1 vs. 2 and 3), as defined by the modified British Medical Research Council criteria.
REGIMEN	<p>Participants will first be randomized 1:1 to:</p> <p>High dose rifampicin 35 mg/kg for 4 weeks vs. standard dose rifampicin 10 mg/kg</p> <p>Participants will then be randomized 1:1 to:</p> <p>Linezolid 1200 mg daily for 4 weeks vs. no linezolid (see Table 1)</p> <p>In addition, all participants will receive standard treatment for TBM with isoniazid 5 mg/kg/day, pyrazinamide 25 mg/kg/day, ethambutol 20 mg/kg/day, corticosteroids (IV dexamethasone 0.4 mg/kg/day for 1 week, 0.3 mg/kg/day for 1 week, followed by a prednisone taper over 6 weeks), and vitamin B₆ 50 mg daily. After the first 4 weeks of therapy, participants in the high dose rifampicin arm (Arm A) will receive standard dose oral rifampicin (10 mg/kg/day) for another 11 months as per national guidelines.</p>

Linezolid	RIF	
	High dose (35 mg/kg)	Standard dose (10 mg/kg)
	Arm A: R ₃₅ HZEL	Arm B: R ₁₀ HZEL
+		
-	Arm C: R ₃₅ HZE	Arm D: R ₁₀ HZE

Table 1: Study regimens

R, rifampicin; H, isoniazid; Z, pyrazinamide; E, ethambutol; L, linezolid

1.0 BACKGROUND AND STUDY RATIONALE

Although TBM is the most devastating form of TB, it has largely been neglected in the global health research agenda. Even with appropriate therapy up to 50% of patients with TBM die, most within the first month after presentation.¹⁻³ Of those who survive, neurologic disability is common.⁴⁻⁶ Despite these bleak outcomes, a paucity of data exists on the optimal approach to TBM treatment, including for people living with HIV (PLWH).

A targeted approach to TBM management must leverage drugs that penetrate the CNS. In the absence of large-scale trials, the same standard drug regimens and dosing used for pulmonary TB—rifampicin (RIF), isoniazid (INH), pyrazinamide (PZA), and ethambutol (EMB) for two months (intensive therapy), followed by RIF and INH in the continuation phase—are empirically employed for TBM, except with a longer continuation phase to complete 9 to 12 months of therapy. This generic approach assumes that the efficacy of TB drugs is equivalent at all sites of infection, disregarding the unique challenges of infection of the CNS.⁷ Effective drugs for TBM must penetrate the blood brain barrier (BBB) and remain in the CNS to achieve bactericidal drug concentrations.⁸

Rifampicin plays an essential role in the treatment of TBM. Of standard TB drugs, INH and PZA have good CNS penetration, while diffusion is poor for RIF, EMB, and streptomycin, particularly in the absence of meningeal inflammation.^{8,9} RIF is essential for the treatment of TBM, as evidenced by the fact that those infected with rifampicin-resistant *Mycobacterium tuberculosis* strains have a near-universal fatal outcome, even with treatment with second-line drugs in resource-rich settings.¹⁰ However, RIF has poor cerebrospinal fluid (CSF) penetration, with reported CSF concentrations often reaching less than 10% of those in plasma. Furthermore, standard oral RIF dosing for TBM rarely exceeds the minimum inhibitory concentration (MIC) against *M. tuberculosis* in the CSF.⁸ Increasing the systemic dose of RIF is one strategy to improve CNS drug concentrations. A Phase II open label randomized trial in Indonesia demonstrated 50% reduction in TBM mortality with high dose IV RIF (600 mg/day).² Higher RIF exposure in the CSF was strongly associated with survival.¹¹ In contrast, a TBM trial in Vietnam found no significant difference in mortality with high dose oral RIF (15 mg/kg), although the lack of efficacy may have been due to inadequate dosing, as oral bioavailability is about 50% of IV RIF.^{12,13} In a dose-finding study in Indonesia, an oral RIF dose of 1350 mg (about 30 mg/kg) was safe and resulted in a large increase in plasma and CSF exposures (Dian et al), with a trend toward lower mortality among those with definite TBM.¹⁴ High dose RIF is a promising strategy to improve outcomes in TBM.

Higher doses of RIF are well tolerated with a favorable safety profile. We will randomize participants to high (35 mg/kg) versus standard dose (10 mg/kg) oral RIF. The most common side effect of RIF is harmless red discoloration of bodily fluid (urine, tears and CSF). Other well-recognized side effects of RIF include gastrointestinal upset, rash, flu-like syndrome and thrombocytopenia. Drug-induced liver injury occurs in 20% HIV-infected patients on TB treatment. The drugs most commonly implicated are INH, PZA, and RIF. However, transaminitis is only seen in 0-2.5% of patients treated with RIF monotherapy, so INH and PZA are the most likely culprits. RIF oral doses as high as 40 mg/kg once daily for 14 days and doses of 35 mg/kg for up to 12 weeks have been safe and well-tolerated in clinical trials^{15,16}. In the ReDEFINE dose-finding study, oral RIF as high as 30 mg/kg daily (1350 mg) for 30 days were well tolerated without any increase in the incidence of adverse effects¹⁴.

Several linezolid characteristics favor its use as adjunctive therapy for TBM. Although RIF is the cornerstone of treatment of TBM, even with higher dosing to overcome poor CSF penetration, adjunctive therapies that enhance the potential benefit of high dose RIF may be needed to improve outcomes of TBM. Of new or repurposed drugs in the development pipeline for TB, many coming into clinical use (e.g., bedaquiline, delamanid) are highly protein bound and thus may not freely penetrate the BBB.^{7,17} Linezolid (LZD), a member of the oxazolidinone family with *in vitro* activity against TB,¹⁸⁻²² combines superb CNS penetration and excellent oral bioavailability.^{9,23-25} LZD has been included as salvage therapy for drug resistant (DR) TB.²⁶ In extensively DR (XDR) pulmonary TB, 89% receiving LZD achieved culture sterility by 6 months.²⁷ Acquired resistance was uncommon and occurred late, suggesting a high barrier to LZD resistance. Of 30 patients receiving 6 months of LZD 1200 mg, bedaquiline, and pretomanid for DR TB in the Nix-TB trial, 75% achieved culture sterility by 8 weeks.²⁸ Although LZD has largely been used for DR TB, it may also be valuable for drug susceptible TB. Few data are available on LZD use in TBM,²⁹ and none from randomized trials. In retrospective studies, LZD 600 mg BID in adults and 10 mg/kg every 8 hours for children was associated with better neurologic outcomes and lower mortality.^{30,31}

Cumulative toxicity is less of a concern when adjunctive LZD is administered for a short duration.³²⁻³⁴ LZD's narrow therapeutic window has tempered the enthusiasm for its therapeutic utility for TB. While most treatment-limiting toxicities, including myelosuppression, gastrointestinal (GI) symptoms and optic neuropathy, are reversible, some, including a painful, sensory-predominant neuropathy, may be permanent.^{35,36} LZD toxicity is driven by both dose and duration.³⁷ In 796 patients with gram-positive bacterial infections on LZD 600 mg BID, hematologic toxicities correlated with treatment duration, occurring in 5% of patients on LZD for 2 to 4 weeks. Peripheral neuropathy occurred in only 3 individuals with a mean treatment duration of 95 days.³⁸ Among 85 patients with DR TB on LZD, the majority of AEs occurred after 2 months.³³ Of 33 patients on LZD 1200 mg for XDR TB, anemia and GI symptoms were common (~50%) but necessitated discontinuation in only 2 patients within the first month.³⁹ No cases of peripheral or optic neuropathy occurred before 2 months. We will use a short course of adjunctive LZD, which has not been studied in a randomized trial for TBM, early in intensive therapy to augment bactericidal activity during the logarithmic growth phase of TB while minimizing cumulative toxicity.

Linezolid and the CSF compartment

CSF to plasma concentration ratios of 0.6 to >0.9 support good to excellent CNS penetration of LZD. However, the distribution of LZD in the CSF, from small studies of mostly neurosurgical patients, varies substantially. After a one-time dose of LZD 600 mg IV, mean CSF maximum concentrations

(C_{\max}) ranged from 5.1 to 6.6 $\mu\text{g/mL}$. At steady state, CSF C_{\max} was 1.3 to 7.1 and up to 10.8 $\mu\text{g/mL}$, and minimum concentrations (C_{\min}) were <0.2 to 3.1 and up to 6.1 $\mu\text{g/mL}$. The ability to achieve adequate CSF concentrations for sufficient duration has been inconsistent. One study found CSF LZD concentrations were >4 $\mu\text{g/mL}$ for the entire dosing interval, while in another few patients reached concentrations >1 $\mu\text{g/mL}$. The minimum inhibitory concentration for 90% of isolates (MIC_{90}) is generally ≤ 0.5 $\mu\text{g/mL}$.

Although studies have suggested that lower LZD doses may be effective for TB,^{34,40,41} a dose-ranging trial demonstrated doses >600 mg daily are required for optimal effect.⁴² A higher systemic dose will increase the likelihood of achieving adequate concentrations in the CSF, particularly with LZD and RIF drug-drug interactions. We will use LZD 1200 mg daily to maximize peak concentrations while reducing troughs, which correlate with mitochondrial toxicity and AEs.^{42,43} No dose adjustment is needed for renal or hepatic impairment or older age.⁴⁴ We will give LZD for the 1st 4 weeks of intensive therapy to enhance bactericidal activity in the early rapid growth phase when mortality is highest, while minimizing duration-dependent toxicity.

A critical consideration in determining optimal LZD dosing for TBM is LZD RIF drug-drug interactions. As RIF is a potent inducer of hepatic cytochrome P450 (CYP450) enzymes and efflux mechanisms (e.g., P-glycoprotein transport system), RIF can lower drug concentrations with potential loss of efficacy. In addition, with repeated administration, RIF induces enzymes resulting in a decrease in its own concentrations. Although LZD metabolism is independent of CYP450, increased LZD clearance has been observed when given with RIF, with reduced LZD concentrations of up to 30% in healthy volunteers and greater in ill patients. These studies have focused on plasma PK, while the impact of RIF on LZD CSF pharmacokinetics is unknown. We have a unique opportunity to evaluate LZD pharmacokinetics when administered with RIF in TBM patients, in whom various factors (e.g. meningeal inflammation, corticosteroids, critical illness) may influence LZD concentrations. This will be critical to establishing optimal LZD dosing for a Phase III efficacy trial.

STUDY RATIONALE

The current mortality associated with TBM is unacceptably high, particularly among PLWH in low and middle-income countries. The highest proportion of deaths occurs within the first month after TBM treatment initiation, indicating that this time period is critically important when considering improved treatment strategies. RIF, the most important drug in the treatment of TBM, seldom reaches minimal inhibitory concentration for *M.tb* in CSF, which is likely to jeopardize therapy. Furthermore, mortality rates in the aforementioned favorable Indonesian trial still exceeded 33% in the high dose RIF arm, arguing that adjunctive therapies may be needed to further enhance the potential benefit of high dose RIF. Adjunctive linezolid in the first month of TBM treatment, when the highest proportion of deaths occurs, may allow us to augment bactericidal activity during the critical rapid growth phase of TB while minimizing cumulative toxicity. Because of drug-drug interactions (DDI), evaluating LZD pharmacokinetics (PK) when administered with RIF will be critical to establishing optimal LZD dosing for an efficacy trial. In this trial, we will examine CSF and plasma LZD PK in the presence of high or standard dose RIF and will evaluate LZD safety and tolerability in TBM patients living with HIV from an African population, correlating adverse events (AEs) with LZD exposures.

2.0 HYPOTHESIS

CSF and plasma LZD PK exposure parameters will be lower when administered with high dose compared with standard dose RIF.

2.1 PRIMARY OBJECTIVE

To determine the CSF and plasma PK of LZD 1200 mg daily in TBM patients receiving high or standard dose RIF.

2.2 PRIMARY ENDPOINTS

CSF and plasma LZD PK parameters, including CSF to plasma ratio, rate of CSF uptake, and plasma absorption rate constant (k_a), drug clearance (Cl/F), volume of distribution (V_d).

2.3 SECONDARY OBJECTIVE

1. To evaluate the safety and tolerability of 4 weeks of LZD 1200 mg for the treatment of TBM.
2. To determine if LZD exposures in the CSF and plasma predict linezolid AEs.
3. To compare longitudinal neurocognitive and functional outcomes in participants randomized to linezolid versus no LZD for the treatment of TBM.
4. To determine if LZD exposures in CSF and plasma predict neurocognitive and functional outcomes.

2.4 SECONDARY ENDPOINTS

1. Proportion of participants with Grade 3 or higher AEs at 4 weeks
2. Proportion of participants who complete LZD treatment
3. Exposure-response (PK-PD) relationship, with LZD as predictor and Grade 3 or higher AE as outcome variable
4. Modified Rankin Scale (death, severe disability, moderately severe, moderate disability, slight disability, no significant disability, no symptoms) at 12 and 24 weeks
5. Montreal Cognitive Assessment (MoCA) or neurocognitive battery performance at 12 and 24 weeks
6. Exposure-response (PK-PD) relationship, with linezolid as predictor and Modified Rankin Scale as outcome variable

3.0 STUDY POPULATION

A total of 60 adults with definite, probable, or possible TBM, aged 18 years or older from Masaka Regional Referral Hospital.

3.1 Inclusion criteria

1. Age \geq 18 years
2. Written informed consent from participant or proxy
3. Definite, probable, possible, or suspected TBM diagnosis wherein the patient is being committed to a full course of anti-TB treatment for TBM in the setting of routine care.

All participants must have at least one of the following signs/symptoms: headache, irritability, vomiting, fever, neck stiffness, convulsions, focal neurological deficits, altered consciousness, or lethargy. In addition, participants must have CSF glucose to plasma ratio < 0.5 **OR** positive CSF acid-fast bacilli (AFB) smear **OR** positive CSF GeneXpert or Xpert Ultra **OR** clinician intent to initiate TB treatment for suspected TB meningitis.

Definite, probable and possible TBM will be defined as:

Definite TBM is defined by the presence of one or more of the following⁴⁵:

- Acid- fast bacilli (AFB) seen in the CSF, *M tuberculosis* cultured from CSF, or a CSF *M tuberculosis*-positive nucleic acid amplification test (e.g., Gene Xpert Ultra) performed within 14 days of entry
- AFB seen in the context of histological changes consistent with tuberculosis in the brain with suggestive symptoms or signs and CSF changes.

Probable and possible TBM are defined using previously published consensus criteria as shown in Appendix A⁴⁵.

- Probable TBM is defined as a total score of ≥ 12 when neuroimaging is available or total score of ≥ 10 when neuroimaging is unavailable. At least two points should either come from CSF or cerebral imaging criteria.
- Possible TBM is defined as a total score of 6–11 when neuroimaging is available, or total score of 6–9 when neuroimaging is unavailable.

Exclusion of the most likely alternative diagnoses is also required (e.g., negative cryptococcal antigen). Because culture confirmation is rarely available or often delayed in TBM, patients with probable or possible TBM will be recruited based on these predefined criteria, and CSF will be collected for mycobacterial culture and molecular testing. Classification of participants as definite, probable, or possible TBM will be made retrospectively once all necessary data are available.

3.2 Exclusion criteria

1. >5 doses of TB treatment received within previous 5 days
2. Discontinued TB treatment in prior 14 days
3. Known current/previous drug resistant TB infection
4. Known allergy to RIF, INH, PZA, EMB, LZD
5. Previous treatment of TB or TBM with LZD
6. Concomitant or planned use of monoamine oxidase inhibitors, selective serotonin reuptake inhibitors, HIV protease inhibitors, or any other drug with significant interaction with RIF, LZD, or any TB drugs (see **Appendices C and D**)
7. Women who are pregnant or breastfeeding, or women or men of reproductive potential who are unwilling to use at least one reliable form of barrier contraception or to abstain from sexual activity while receiving study drug treatment and for 30 days after stopping study treatment. Acceptable forms of contraception include: condoms (male or female) with or without a spermicidal agent, or diaphragm or cervical cap with spermicide. Hormonal contraception is not recommended as it may be ineffective due to induction of metabolism when receiving rifampicin.
8. Unwillingness to be an inpatient for 2 weeks for initial treatment or to attend follow up clinic visits

9. Lack of informed consent from participant or next of kin/caregiver

10. Serum creatinine >1.8 times upper limit of normal, hemoglobin <7.0 g/dL for men, <6.5 g/dL for women, platelet count <50,000/mm³, absolute neutrophil count <600/mm³, alanine aminotransferase (ALT) >3 times the upper limit of normal, total bilirubin >2 times the upper limit of normal.

11. Severe peripheral neuropathy defined by Grade 3 symptoms AND vibratory loss OR absent ankle jerks for participants able to undergo the Brief Peripheral Neuropathy Screen (see Appendix B).

12. Contraindication to LP, including PLT <50 cells/mm³ or unequal pressures between intracranial compartments (e.g., due to mass lesion, non-communicating hydrocephalus), or unwillingness to undergo or consent to LP

3.3 Late exclusion (exclusion after enrollment)

1. Confirmed drug-resistant MTB infection: Resistance testing will be performed on all *M. tuberculosis* isolates from cerebrospinal fluid or other specimens obtained prior to randomization. If a participant is confirmed to have drug resistant infection, defined as resistance to one or more first-line TB medications or linezolid, they will be excluded from the study. If drug resistance is confirmed through phenotypic susceptibility testing, results may not become available until after a participant is enrolled, at which point they would meet criteria for late exclusion.

2. Identification of an alternative cause of meningitis: If CSF or other laboratory or pathology results return after a participant is enrolled indicating an alternative (or secondary) cause of meningitis, they would meet criteria for late exclusion.

Participants who meet criteria for late exclusion will discontinue study treatment but remain on study. These participants will be replaced in order to maintain a balanced number of participants per arm.

4.0 STUDY DESIGN

This is an open-label, randomized clinical trial with a factorial design. Initial randomization will be to high (35 mg/kg/day) versus standard (10 mg/kg/day) dose oral rifampin for the first 4 weeks of intensive therapy. Participants will then undergo a second randomization to linezolid 1200 mg daily versus no linezolid for the first 4 weeks of therapy. We will use a computer generated permuted block randomization (block size = 2 or 4) stratified by TBM grade (1 vs 2 and 3), given the association between TBM severity and mortality. The trial is open label, although we will endeavor for research staff assessing adverse events, neurocognitive and functional outcomes, and PK data to be blinded.

Initiation of high or standard dose oral rifampicin and linezolid or no linezolid will begin immediately (within 24 hours) after randomization. In addition, all participants will receive a standard backbone of oral TB treatment with INH 5 mg/kg/day, PZA 25 mg/kg/day, EMB 20 mg/kg/day, corticosteroids (IV dexamethasone 0.4 mg/kg/day for week 1, 0.3 mg/kg/day for week 2, followed by a prednisone taper over 6 weeks), and vitamin B₆ 50 mg daily. After the first 4 weeks of therapy, participants will receive standard dose oral RIF (10 mg/kg/day) for another 11 months along with standard treatment for TBM per national guidelines. Patients admitted to Masaka Regional Referral Hospital who meet eligibility criteria will be invited to participate.

4.1 Study enrollment procedures

Prior to implementation of this protocol, and any subsequent amendments, sites must have the protocol and the protocol consent form approved by their local institutional review board (IRB)/ethics committee and any other applicable regulatory entity. Site-specific informed consent forms must also be reviewed and approved by the local IRB/ethics committee. Once a candidate for study entry has

been identified, details will be carefully discussed with the participant. The participant (or, when necessary, the next of kin/caregiver if the participant lacks capacity to provide consent) will be asked to read and sign the approved protocol consent form. Participants from whom a signed informed consent has been obtained may be screened and enrolled, if they otherwise qualify. Participants who are enrolled through a next of kin/caregiver will provide consent once they regain capacity to consent.

4.1.1. Identification of participants and screening

Patients presenting to Masaka Regional Referral Hospital with suspected TBM will be identified by ward doctors. As part of routine clinical care they will undergo HIV test and lumbar puncture (LP), which can be done by the ward medical team or by the study team.

- In most cases, the ward medical team will perform the initial LP as part of routine care. However, study personnel can also perform the LP, if needed. If the participant has undergone a diagnostic LP as part of routine care, a repeat LP for screening is not necessarily required.
- If the LP has already been performed as part of routine care, after consent has been obtained, study personnel will facilitate the necessary diagnostic testing of the previously collected CSF.
- If persons are referred from outside health care facilities with appropriate documentation of TBM per study inclusion criteria, they will be eligible; however these persons must have a LP with a full diagnostic CSF analysis performed at the site approved laboratory after study consent is obtained to exclude alternative diagnoses.
- Screening evaluations, which can be performed as part of routine care, are outlined in the Schedule of Evaluations (Table 5)

Additional consent will be sought for long-term storage of samples, including blood and CSF. In this case, samples will be stored indefinitely, unless the participant asks for them to be destroyed. Participants may also give limited consent to the collection and testing of samples for the purposes of this research only, after which the samples will be destroyed.

4.1.2 Enrollment visit

The enrollment visit will be Day 1 of the study, which will correspond to the first day of study drug. During the enrollment visit, clinical history, examination findings and available laboratory results or radiology will be reviewed to ensure inclusion criteria are met and no exclusion criteria are present. The enrollment CRF will be completed. If participants meet entry criteria, they will be invited to participate in the clinical trial. After informed consent has been obtained, the participant will be allocated a study participant number and randomized to treatment allocation.

4.1.3 Informed consent

TBM is a medical emergency requiring prompt treatment so it is not necessary to wait for complete screening LP results before initiating TBM treatment and enrolling into the trial. The proximity to the screening visit will depend on the time required to make a provisional diagnosis of TBM. In most cases, there will be clear supporting evidence of TBM by clinical and/or CSF findings, whereas in other cases further investigation (e.g. to find evidence of extra-meningeal TB or perform brain imaging) may be required. Participants will not have their emergent diagnostic or medical care delayed.

All informed consent forms will be read in full to potential study participants. The consent forms will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. The potential participant or their surrogate must be given sufficient time to review and ask questions. After sufficient time for consideration, study participants will sign all applicable consent forms prior to performance of any study-related procedures or administration of study-related medications. Study personnel obtaining consent must also sign the consent form. A copy of the consent form will be given to the participant or surrogate but if she/he does not want to keep a copy, it will be kept at the study site on behalf of the participant.

4.1.4 Assessment of capacity to provide informed consent

Potential participants will be evaluated by study personnel (medical officer or nurse) to determine if they have the capacity to provide consent. The Glasgow Coma Scale (GCS) will be used to assess level of consciousness and neurological status. Only participants with a GCS of 15 will be able to provide consent. In addition to having a GCS of 15, participants must also demonstrate understanding of the purpose and risks and benefits of the study and participate in a detailed review of the consent form with a trained study team member. If the study team member deems the participant's comprehension of the study to be appropriate, the participant will be able to provide consent. Otherwise, surrogate consent from the participant's next of kin/caregiver will be sought.

4.1.5 Surrogate Consent by a Next of Kin/Caregiver

A potential participant who lacks the capacity to provide informed consent due to altered mental status (e.g., confusion, somnolence, unconsciousness), which may be present in more than 50% of TBM patients, may be considered if they have a designated surrogate caregiver/next of kin who can consent on their behalf. The designated surrogate is a next of kin or caregiver who has the ability to provide consent for the participant's participation in this research protocol.

If participants regain the capacity to give consent, information will be provided to them and written informed consent will be sought for continuation in the trial. If a participant declines to give consent for continuation in the trial, they will be withdrawn. For participants enrolled by surrogate consent, capacity will be assessed regularly prior to hospital discharge and at clinic follow up visits.

4.1.6 Illiterate/Unable to Provide Signature

A participant who speaks and understands the language of the informed consent document, but does not read and write, can be enrolled in the study by "making their mark" or via a thumbprint on the informed consent document. In this event, an impartial, literate third party, which excludes study team members, must witness the entire consent process and sign the informed consent document. The witness's name, signature, and relationship must be recorded on the informed consent document.

4.1.7 Randomization

At study entry and prior to the 4th dose of TB treatment, participants will first be randomized by a computer-generated permuted block randomization (block size of 2 or 4) with a 1:1 randomization to high (35 mg/kg) versus standard dose (10 mg/kg) rifampicin. A second 1:1 randomization will then be performed to linezolid 1200 mg daily or no linezolid. Randomization will be stratified by British Medical Research Council (BMRC) TBM disease grade (Table 2), determined at the time of consent, given the association between worse disease severity and higher mortality¹.

Table 2. British Medical Research Council (BMRC) TBM disease grade

GRADE I	Glasgow coma score 15, no focal neurological signs
GRADE II	Glasgow coma score 11–14 with or without focal neurological sign or Glasgow coma score 15 with focal neurological signs
GRADE III	Glasgow coma score \leq 10 with or without focal neurological signs

The randomization schedules will be provided to the site pharmacy in a listed sequence. The sequential, unique randomization code will be recorded on the study entry CRF to assure there is no

skipping of the randomization order. All randomized participants will initiate their allocated study TB treatment within 24 hours of randomization and ideally the same day. For participants from whom informed consent has been obtained, but who are deemed ineligible or who do not enroll into the protocol, a Screening Failure form must be completed and entered into the database.

4.1.8 Co-enrollment Guidelines

Participants may be co-enrolled in observational studies but not in other interventional trials.

5.0 STUDY TREATMENT

Participants will be randomized in a factorial design to receive one of the following regimens shown in Table 3.

Table 3: Study treatment regimens

Arm	Weeks 1-4	Weeks 5-8*	Weeks 9-24*
A	R ₃₅ HZEL	R ₁₀ HZE	R ₁₀ H
B	R ₁₀ HZEL		
C	R ₃₅ HZE		
D	R ₁₀ HZE		

Abbreviations: R, RIF; H, INH; Z, PZA; E, EMB; L, LZD;

*After the first 4 weeks of therapy, participants will receive treatment for TBM as per national guidelines.

Corticosteroid dosing: All participants will receive adjunctive corticosteroids, in addition to pyridoxine 50 mg daily.

Week 1: Dexamethasone IV 0.4 mg/kg/day
 Week 2: Dexamethasone IV 0.3 mg/kg/day
 Week 3: Prednisone PO 60 mg/day
 Week 4: Prednisone PO 50 mg/day
 Week 5: Prednisone PO 40 mg/day
 Week 6: Prednisone PO 30 mg/day
 Week 7: Prednisone PO 20 mg/day
 Week 8: Prednisone PO 10 mg/day

5.1 Administration

The intervention period will be for the first 4 weeks of TB therapy, after which all participants will receive the same standard therapy for TBM as per national guidelines.

Table 4: Treatment administration by weight bands through study period

	Intervention period				Standard intensive phase	Standard continuation phase				
	Week									
	1	2	3	4	5 to 8	10	12	16	20	24

Arm A	Standard co-formulated TB treatment with additional 300mg rifampicin tablets				Standard intensive phase in all participants, as per national guidelines	Standard continuation phase in all participants, as per national guidelines		
	Weight	Number of RHZE tabs (150/75/400/275 mg)	Additional R 300mg tablets	Total R dose (mg)				
	30-37 kg	2 tabs	3 tabs	1200				
	38-54 kg	3 tabs	4 tabs	1650				
	55-70 kg	4 tabs	5 tabs	2100				
	≥ 71 kg	5 tabs	6 tabs	2550				
	PLUS Linezolid (600 mg) 2 tablets							
Arm B	Standard co-formulated TB treatment							
	Weight		Number of RHZE tablets: (150 / 75 / 400 / 275 mg)					
	30-37 kg		2 tabs					
	38-54 kg		3 tabs					
	55-70 kg		4 tabs					
	≥ 71 kg		5 tabs					
	PLUS Linezolid (600 mg) 2 tablets							
Arm C	Standard co-formulated TB treatment with additional 300mg rifampicin tablets							
	Weight	Number of RHZE tabs (150/75/400/275 mg)	Additional R 300mg tablets	Total R dose (mg)				
	30-37 kg	2 tabs	3 tabs	1200				
	38-54 kg	3 tabs	4 tabs	1650				
	55-70 kg	4 tabs	5 tabs	2100				
	≥ 71 kg	5 tabs	6 tabs	2550				
Arm D	Standard co-formulated TB treatment							
	Weight		Number of RHZE tablets: (150 / 75 / 400 / 275 mg)					
	30-37 kg		2 tabs					
	38-54 kg		3 tabs					
	55-70 kg		4 tabs					
	≥ 71 kg		5 tabs					

The study pharmacist will dispense medication according to study arm and weight and will log all medication dispensed, the date, participant identification number and participant initials.

Intervention period: Weeks 1-4

Arm A: Fixed-dose combination tablets according to weight bands (Table 4) will be dispensed with additional 300 mg oral RIF tablets to equal a RIF dose of ~35mg/kg/day, along with standard dose INH ~5 mg/kg, PZA ~25 mg/kg, and EMB ~20 mg/kg. LZD 1200 mg daily will be dispensed as two 600 mg tablets. Participants will receive intact tablets or via nasogastric tube. If participants are discharged before the 4-week intervention period, they will be discharged with an adequate supply of study drug to last until the week 4 visit. Participants will be weighed at each visit and TB drug dose will be adjusted as necessary. Fixed dose combination antituberculous therapy will be prescribed through routine care pathways initially via the hospital and subsequently via linked TB clinics according to national guidelines.

Arm B: Fixed-dose combination tablets according to weight bands (Table 4) will be dispensed

to equal standard dosing for TBM treatment: oral RIF ~10 mg/kg, INH ~5 mg/kg, PZA ~25 mg/kg, EMB ~20 mg/kg. LZD 1200 mg daily will be dispensed as two 600 mg tablets.

Participants will receive intact tablets or via nasogastric tube. If participants are discharged before the 4-week intervention period, they will be discharged with an adequate supply of study drug to last until the week 4 visit. Participants will be weighed at each visit and TB drug dose will be adjusted as necessary. Fixed dose combination antituberculous therapy will be prescribed through routine care pathways initially via the hospital and subsequently via at TB clinics according to national guidelines.

Arm C: Fixed-dose combination tablets according to weight bands (Table 4) will be dispensed with additional 300 mg oral RIF tablets to equal a RIF dose of ~35mg/kg/day, along with standard dose INH ~5 mg/kg, PZA ~25 mg/kg, and EMB ~20 mg/kg. Participants will receive intact tablets or via nasogastric tube. If participants are discharged before the 4-week intervention period, they will be discharged with an adequate supply of study drug to last until the week 4 visit. Participants will be weighed at each visit and TB drug dose will be adjusted as necessary. Fixed dose combination antituberculous therapy will be prescribed through routine care pathways initially via the hospital and subsequently via linked TB clinics according to national guidelines.

Arm D: Fixed-dose combination tablets according to weight bands (Table 4) will be dispensed to equal standard dosing for TBM treatment: oral RIF ~10 mg/kg, INH ~5 mg/kg, PZA ~25 mg/kg, EMB ~20 mg/kg. Participants will receive intact tablets or via nasogastric tube. If participants are discharged before the 4-week intervention period, they will be discharged with an adequate supply of study drug to last until the week 4 visit. Participants will be weighed at each visit and TB drug dose will be adjusted as necessary. Fixed dose combination antituberculous therapy will be prescribed through routine care pathways initially via the hospital and subsequently via TB clinics according to national guidelines.

Standard intensive phase: Weeks 5-8

For the remainder of the standard intensive phase of treatment, all participants in all arms will receive standard treatment as per Ugandan national guidelines (**Table 4**), which recommend a total of 8 weeks of 4-drug therapy with RIF, INH, PZA, and EMB. Where isoniazid monoresistance or another clinical indication exists for alternative regimen this should be discussed with the treating clinician and PI.

Standard continuation phase: Weeks 9-24

For the continuation phase of treatment during the study period, all participants in all arms will receive standard treatment as per Ugandan national guidelines (**Table 4**), which recommend an additional 10 months of RIF and INH. After the study period ends at 24 weeks, participants will continue to receive routine care through TB clinic. Where isoniazid monoresistance or another clinical indications exist for alternative regimen this should be discussed with the treating clinician and PI.

5.2 Acquisition

The study will provide all TB medications for the first 4 weeks that are **not** part of current standard of care. This includes single drug formulation of rifampicin 300 mg tablets (Brand Name Rifacos, Cosmos Ltd), along with linezolid 600 mg tablets (Brand Name Lizolid, Star Pharmaceuticals Ltd), both of which will be purchased locally. Fixed-dose combination tablets will be supplied by the clinical site as part of routine care from a licensed nationally approved source.

5.3. Product Storage and Stability

The study medication will be stored at the site's secure pharmacy. All drugs will be protected from light and stored at room temperature (at or below 25°C in adherence with manufacturers' instructions and documented on a temperature log in the pharmacy). If study medication has expired, it will be destroyed according to the local regulations. At the conclusion of the trial study medication will be

destroyed.

5.4 Study Product Accountability

The site pharmacist is required to maintain complete records of all dispensed study medications. Clinical personnel involved in the dispensation and administration of study drugs will adhere to Good Clinical Practice guidelines. Compliance with the protocol will be assessed via on-going quality assurance monitoring. A record of study medication final accountability and destruction will be kept and filed throughout.

5.5 Concomitant Medications

All concomitant prescription medications will be recorded on medication CRFs. Concomitant medications that are prohibited for the duration of the study due to known interactions with rifampicin include protease inhibitors (ritonavir, atazanavir, lopinavir), as rifampicin substantially reduces concentrations, which may result in loss of antiviral efficacy and development of HIV resistance. Due to a substantial reduction in the concentration of atovaquone, clarithromycin, digoxin, posaconazole, quinine, and voriconazole, rifampicin should also not be used concurrently with any of these drugs. There is not a danger in taking these medications; however, clinical investigators are advised to use alternatives for these medications. Monoamine oxidase inhibitors and selective serotonin reuptake inhibitors are also prohibited due to interactions with linezolid, in addition to tricyclic and other anti-depressant, lithium, carbamazepine, diphenhydramine, atypical antipsychotics, and anti-Parkinsonian medications (see **Appendices C and D**). Patients using systemic hormonal contraceptives should change to a non-hormonal method during rifampicin therapy. Barrier contraception is required for sexually active women of childbearing potential.

5.6 Adjunctive Corticosteroids

Adjunctive corticosteroid treatment has been shown to improve survival in TBM and is recommended for all patients with CNS TB according to WHO guidelines. Persons in *Strongyloides stercoralis* endemic regions are recommended to receive albendazole 400 mg orally twice daily for three days to reduce the risk of *Strongyloides* hyperinfection.

5.7 Antiretroviral Therapy

In a randomized trial of TBM participants in Vietnam, immediate ART did not improve survival and was associated with significantly more grade 4 adverse events compared with delayed ART initiation at 8 weeks.⁴⁶ As there is no available evidence that earlier ART confers a survival advantage, the international standard for ART initiation in persons living with HIV with TBM is currently at about 8 weeks.⁴⁶ HIV-infected participants not already receiving ART will be recommended to initiate ART at about 8 weeks after TB treatment initiation according to international guidelines. For persons on ART presenting with virologic failure, they would switch regimens at about 8 weeks after initiation of TB treatment. Appropriate counselling will be undertaken in HIV clinics. ART regimens will be prescribed and provided per National HIV Treatment Guidelines. HIV-infected participants will receive cotrimoxazole prophylaxis, unless allergic. We expect that the majority of our HIV-infected participants will not be receiving ART at TBM presentation; according to WHO guidelines they will be offered ART 8 weeks after starting TB treatment. Earlier initiation of ART is associated with an increase in adverse events and does not reduce mortality.³⁶ Early ART is associated with immune reconstitution inflammatory syndrome (IRIS), which can be fatal in TBM. Patients who are culture positive for *M. tuberculosis* from CSF at TBM diagnosis are also at increased risk of TBM-IRIS.³⁷

6.0 CLINICAL AND LABORATORY EVALUATIONS

6.1 Schedule of evaluations (Table 5)

Table 5: Schedule of evaluations													
Evaluation	Screen ^a	Entry (Day 1)	Day 2	Wk 1	Wk 2	Wk 3	Wk 4	Wk 8	Wk 12	Wk 18	Wk 24	Sick visit, Rx fail, relapse	Early withdrawal
Visit window (days)			+/- 1	+/-1	+/-2	+/-2	+/-2	+/- 7	+/- 7	+/-14	+/-14		
Complete medical history	•												
Symptom assessment		•	•	•	•	•	•	•	•	•	•	•	•
Medication review	•	•	•	•	•	•	•	•	•	•	•	•	•
Adherence assessment				•	•	•	•	•	•	•	•	•	•
Complete physical exam	•												
Targeted exam		•	•	•	•	•	•	•	•	•	•	•	•
Neurologic exam with Glasgow Coma Scale	•	•	•	•	•	•	•	•	•	•	•	•	•
MRC TBM disease grade	•	•	•	•	•	•	•	•	•	•	•	•	•
Brief peripheral neuropathy screen	•			•	•		•	•					•
Vision testing	•			•	•		•	•					•
Neurocognitive testing									•		•		•
Patient Health Questionnaire-9									•		•		•
Modified Rankin Scale							•		•		•		•
Hematology ^b	•	•		•	•		•					• if indicated	• if indicated
Chemistries ^b	•	•		•	•		•					• if indicated	• if indicated
Liver function tests ^{b,c}	•	•		•	•		•					• if indicated	• if indicated
Pregnancy test	•	As clinically indicated											
Documentation of HIV	•												
CD4 count		•										• if indicated	• if indicated
Lumbar puncture for CSF cell count, glucose, protein, AFB smear and culture ^d	•		•		•		• optional if out-patient					• if indicated	• if indicated
CSF Xpert Ultra	•						• if LP done						
Chest x-ray ^d	•												
Head CT scan	• if indicated											• if indicated	• if indicated
Plasma PK ^e			•		•		•						
CSF PK ^e			•		•		•						
Stored TB isolate	•												
Stored plasma	•	•	•		•		•					•	•
Stored CSF	•		•		•		•					•	•

^aScreening evaluations can occur as part of routine care

^bCan defer at entry if screening labs obtained within 72 hours prior to entry

^cInclude hepatitis B surface antigen, hepatitis C antibody, and INR if ALT abnormal.

^dCan use chest x-ray and lumbar puncture performed as part of routine clinical care **within 14 days prior to screening**. Repeat lumbar puncture must be performed if AFB smear, culture, or Xpert Ultra were not performed prior to screening.

^eIntensive PK sampling at Day 2, sparse sampling at Week 2; CSF PK at Week 4 if LP performed

6.2 Timing of evaluations

6.2.1 Screening Evaluations

Screening evaluations must occur prior to the participant starting any study medications, treatments, or interventions. Screening evaluations to determine eligibility must be completed within 14 days prior to study entry unless otherwise specified. For participants from whom informed consent has been obtained but who are deemed ineligible or who do not enroll into the study, they will be logged as a screening failure. Participants who meet the enrollment criteria will be randomized to the study.

6.2.2 Entry Evaluations

Entry evaluations must occur within 14 days of the first screening evaluation unless otherwise specified. Participants should begin treatment ideally on the day of but at most *24 hours* after randomization.

6.2.3 Discontinuation Evaluations

Evaluations for Randomized Participants Who Do Not Start Study Treatment

All CRFs must be completed and keyed for the period up to and including the entry visit. Participants who do not start study treatment will be taken off study with no further evaluations required.

Premature Treatment Discontinuation Evaluations

Participants who prematurely discontinue study treatment permanently will have premature discontinuation evaluations performed as noted in Section 6.1 as soon as possible after stopping study treatment, but no later than 14 days after stopping treatment. If the participant discontinues treatment prematurely, the participant will be encouraged to continue on study and receive all evaluations per 6.1 Schedule of Events.

Premature Study Discontinuation Evaluations

Participants who prematurely discontinue participation in the study should have the premature study discontinuation evaluations noted in Section 6.1 performed as soon as possible.

Evaluations for Participants Who Die

All CRFs must be completed and keyed for the period up to the week of death.

6.2.4 Sick visit

After discharge from the hospital, participants will be encouraged to attend the clinic for unscheduled visits if they experience symptomatic deterioration where they will be assessed by the study doctor. If the suspected reason for deterioration is a drug reaction, AE CRF and reporting will be completed. Other clinical problems will be managed as appropriate. If patients are sick enough to require hospital admission for investigation and management, the study team will closely monitor their clinical condition while they are managed by the medical staff on the inpatient service.

Procedures to be performed during unscheduled sick visit include:

- Symptom assessment history
- Medication review
- Targeted physical examination and neurologic examination
- Laboratory evaluation as clinically appropriate
- Lumbar puncture as clinically appropriate

- Head CT scan and other radiology testing as clinically appropriate

6.3 Instructions for evaluations

6.3.1 Complete medical history

A complete medical history, including history of tuberculosis, AIDS-defining conditions, diabetes mellitus, cardiovascular disease, cancer, hepatitis, or any neurologic disease (e.g., ischemic stroke, intraparenchymal hemorrhage, subarachnoid hemorrhage, traumatic brain injury, epilepsy/seizures, CNS infections) must be recorded. Any allergies to medications and their formulations must also be documented.

6.3.2 Symptom assessment

At entry, record on the CRFs all signs/symptoms occurring within 30 days prior to entry. After entry, all Grade ≥ 2 signs/symptoms, any signs/symptoms regardless of grade that lead to a change in treatment, that meet expedited or serious adverse event guidelines, or are defined by the protocol as reportable events that require detailed event reporting.

6.3.3 Medication history and review

A medication history, including alternative therapies and/or dietary supplements, must be present, including start and stop dates. After entry, all concomitant medications, including alternative therapies and/or dietary supplements, must be recorded on the CRFs.

Record all TB medication modifications, including initial doses, participant-initiated and/or protocol-mandated modifications, and inadvertent and deliberate interruptions of ≥ 7 days since the last visit. Record any permanent discontinuation of treatment.

All modifications to antiretroviral medications will be recorded on the CRF, including actual start dates and stop dates, initial doses, and inadvertent and deliberate interruptions of ≥ 7 days since the last visit. Record any permanent discontinuation of antiretroviral treatment.

6.3.4 Assessment of adherence

Participants will be hospitalized for the first 2 weeks of therapy, during which directly observed therapy will occur. After 2 weeks, participants can be discharged at the discretion of the inpatient physician. Once discharged, adherence will be assessed at in-person follow up visits by self-report (or by proxy report) and pill counts. Study staff will also endeavor to contact participants weekly by phone for remotely observed therapy.

6.3.5 Complete physical exam

A complete physical examination will be performed at screening and is to include, at a minimum, an examination of the skin, head, mouth, and neck; auscultation of the chest; cardiac exam; abdominal exam; examination of the lower extremities for edema. The complete physical exam will also include height, weight and vital signs (temperature, pulse, respiration rate, and blood pressure).

6.3.6 Targeted physical exam

A targeted physical examination performed as scheduled in section 6.1 is to include weight and vital signs (temperature, pulse, respiration rate, and blood pressure), and is to be driven by any previously

identified or new adverse event/targeted condition that the participant has experienced since the previous study visit.

6.3.7 Neurologic exam and Glasgow Coma Scale

Neurologic exam to include, at a minimum, examination of mental status, cranial nerves, tone, power, reflexes, sensation, and coordination, and assessment of the Glasgow Coma Scale (GCS), will be performed as per section 6.1.

6.3.8 MRC TBM disease grade

Tuberculous meningitis stage will be defined using a modified British Medical Research Council system:

- Grade 1 - GCS 15, no focal neurological signs
- Grade 2 - GCS 11-14, or GCS 15 with focal neurological signs
- Grade 3 - GCS ≤ 10

6.3.9 Brief Peripheral Neuropathy Screen

Study staff will administer the Brief Peripheral Neuropathy Screen, a validated neuropathy screening tool for HIV,⁴⁷ to participants who are able to provide subjective information regarding symptoms and participate in sensory testing.

6.3.10 Vision testing

Visual acuity (Snellen chart), color vision (Ishihara plates), and contrast sensitivity (Pelli-Robson chart) testing will be performed in participants who are able to participate.

6.3.11 Neurocognitive testing

Neurocognitive testing will be performed as scheduled in 6.1 on individuals who are able to participate. The battery will take approximately 45 minutes to an hour to complete:

Neurocognitive Test Battery

- Wechsler Adult Intelligence Scale-III Digit Symbol (Speed of Information Processing)
- Color Trails 1 (Attention/Working Memory)
- Color Trails 2 (Executive Function)
- Category Fluency (Executive Function)
- Hopkins Verbal Learning Test-Revised or WHO-UCLA Auditory Verbal Learning Test (Verbal Learning and Memory)
- Grooved Pegboard Bilateral, Finger-tapping Bilateral (Fine Motor)

For participants unable to undergo the full test battery, we will attempt to perform the Montreal Cognitive Assessment (MOCA). We will endeavor to have staff assessing neurocognitive and functional outcomes to be blinded to treatment arm.

6.3.12 Functional outcomes

Participants will also be assigned to a **Modified Rankin Scale** level using the structured interviewer questionnaire. In addition we will collect data on disability and depression using the **WHO Disability Assessment 2.0** and the **Patient Health Questionnaire (PHQ-9)**.

6.3.13 Laboratory assessments

At screening and entry all laboratory values must be recorded on the CRF. For post-entry assessments, record on the CRF all laboratory values regardless of grade. Blood samples will be collected via venous blood draw.

Hematology

A complete blood count, including hemoglobin, white blood cell count (WBC), differential WBC (to include only neutrophils, lymphocytes, and monocytes), absolute neutrophil count (ANC), and platelet count will be performed.

Liver Function Tests

AST and/or ALT; total and direct bilirubin; and alkaline phosphatase will be performed.

Blood Chemistry

Sodium, potassium, bicarbonate, and creatinine will be performed.

Pregnancy Test

For women of reproductive potential: Serum or urine β -HCG may be used (urine test must have a sensitivity of <25 mIU/mL).

Documentation of HIV infection

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.

CD4+ for participants living with HIV

Obtain absolute CD4+ count and percentages at entry unless the results are available within 14 days prior to entry.

Other laboratory testing

Additional laboratory tests can be undertaken at the discretion of the physician with agreement of the site PI.

6.3.14 Lumbar Puncture

Lumbar puncture (LP) will be performed as per section 6.1. Prior to LP, participants must have platelets $\geq 50,000$ cells/mm³ measured within 72 hours prior to the LP and no contraindication to LP per the treating clinician. Opening pressure in the lateral decubitus position will be measured by manometry, when possible, and recorded. CSF cell count, glucose, protein, and AFB smear and culture will be performed. Repeat lumbar puncture must be performed if AFB culture and/or Xpert Ultra are not performed on the CSF obtained during routine care used for screening.

6.3.15 TB Laboratory Diagnostics and Microbiology

AFB smear and culture

CSF will be used for cell count, glucose, protein, direct smear examination by Ziehl-Neelsen (ZN) stain, and culture (in conventional solid medium and/or Becton Dickinson Mycobacterial Growth

Indicator Tube (MGIT) liquid culture).

CSF Xpert Ultra

Xpert Ultra will be performed on collected CSF. If the Xpert Ultra machine is unavailable, we will store the CSF until Xpert Ultra becomes available.

Resistance testing

Molecular and phenotypic resistance testing for participants with positive CSF culture will be performed on CSF samples. Participants with RIF resistance on molecular testing will be excluded. If participants are determined to have resistant infection based on phenotypic testing after enrollment, they will be taken off study treatment but will continue to be followed. Participants in whom resistance is identified after the 4 weeks of LZD will be referred to clinic for management of resistant TB infection. Their CSF and plasma samples and collected data will be analyzed, unless the participant chooses to withdraw from the study.

To assess response to treatment, development of complications and other outcome measures participants will be reviewed daily by the clinical research team while hospitalized. GCS and focal neurological signs will be recorded daily on the CRFs during the inpatient stay. Participants may be discharged at the discretion of the attending physician.

6.3.16 Chest X-Ray

A chest x-ray should be performed at screening unless one performed as part of routine clinical care within the previous 14 days is available for review.

6.3.17 Computed Tomography Imaging

CT brain and other radiological tests can be undertaken at the discretion of the physician with agreement of the site PI.

6.3.18 Pharmacokinetic studies

CSF sampling via lumbar puncture (LP) will occur at Day 2 (with intensive plasma sampling 0, 2, 4, 8 hours after dosing) and Day 14 (with sparse plasma sampling at one time point), with an LP at Day 28 (Week 4) +/- 2 days for RIF and LZD PK that may be optional for participants who are no longer hospitalized. Participants will be randomized to CSF sampling at an early (0-2 hours), medium (2-6 hours), or late (6-8 hours) interval after drug administration. After centrifugation, specimens will be stored at -80C for batched analysis.

6.3.19 Storage of *M. tuberculosis* bacterial isolates

Any *M. tuberculosis* bacterial isolates from screening, as well as isolates cultured from specimens obtained after screening will be stored. Isolates should be labeled with study identification number and collection date, and not with participant name.

6.3.20 Storage of biospecimens

Blood and CSF specimens will be stored from consenting participants. Specimens collected for storage will be labeled with study identification number and collection date, and will not be labeled with participant name. Specimens will be stored at the site and shipped in batches to the US-based team for testing. Additionally, samples should be collected a) if failure or relapse is suspected and the participant is evaluated at an unscheduled or sick visit or b) if a participant voluntarily withdraws from the study. Participant consent for collection and storage of specimens will be part of the study consent

form which will be administered during the entry visit, with an independent signature line.

7.0 ADVERSE EVENTS AND STUDY MONITORING

7.1 Definition of Adverse Events

An adverse event (AE) is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or diagnosis that occurs in a study participant during the conduct of the study REGARDLESS of the attribution (i.e., relationship of event to medical treatment/study product/device or procedure/intervention). This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition.

7.2 Adverse Event Collection Requirements for this Study

All AEs must be recorded on the CRFs if any of the following criteria have been met.

- All Grade 3 to 5 AEs
- All AEs that led to a change in study treatment/intervention regardless of grade
- All AEs meeting serious adverse event definition or expedited adverse event reporting requirement

All AEs that are reported must have their severity graded. AEs will be graded according to the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), Corrected Version 2.1, July 2017, which can be found on the DAIDS RSC website at <https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables>

Serious Adverse Events (SAEs)

A SAE is defined as any untoward medical occurrence that:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is an important medical event that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above.

All pre-existing conditions present at study entry **must be clearly documented on the CRF at entry**. If the frequency, intensity, or the character of the condition worsens to Grade 3 to 5 level during the reporting period, the event should be defined as an AE.

7.3. Reporting Requirements for this Study

- Requirements, definitions and methods for expedited reporting of AEs are outlined in Version 2.0 of the DAIDS EAE Manual, which is available on the RSC website at <https://rsc.niaid.nih.gov/clinical-research-sites/manual-expedited-reporting-adverse-events-daids>.
- The SAE Reporting Category, as defined in Version 2.0 of the DAIDS EAE Manual, will be used for this study from the time of enrollment through week 8 for all participants. For the remainder of the trial, only SAEs which are judged by the site as having a reasonable possibility of being related to study drug (SARs) should be reported.
- The study agents for which expedited reporting is required are: rifampicin and linezolid
- The expedited AE reporting period for this study is the entire study duration of 24 weeks for an individual participant (from study enrollment until study completion or discontinuation of the participant from study participation for any reason).

7.4 Expected disease-related events

This study population, with TB and advanced HIV, are both critically ill and profoundly immunosuppressed will have a complicated clinical course. Opportunistic and nosocomial infections are expected. Disease-related events will be frequent and include:

- Death due to TBM (~40% enrolled participants). **Will always be reported as an SAE.**
- Disability due to TBM. **Will not be reported as an AE.**
- TBM-IRIS events and symptoms. **Will not be reported as an AE.**
- Neurological complications of TBM, including tuberculoma, infarct, seizures, headache due to raised ICP. **Will not be reported as an AE.**
- Other opportunistic infections. **Will not be reported as an AE.**
- Nosocomial infections, including hospital acquired pneumonias or aspiration pneumonias. **Will not be reported as an AE.**

Expected disease-related events do not require reporting unless the severity of the event was considered to be unexpected.

7.5 Evaluation of events

The PI and site PI will monitor the conduct and safety of the study via regular summaries of accrual rates, deaths, SAEs, AEs, and study discontinuation, as appropriate.

The PI and/or site PI will evaluate all SAEs received for seriousness, expectedness and causality. Investigator reports of suspected unexpected serious adverse reactions (SUSAR) will be reviewed and those that are SUSARs identified and reported to the regulatory authorities.

7.5.1 Assessment of Seriousness

When an AE occurs the investigator must first assess whether the AE is serious or not using the definition in Section 7.2. If the event is serious and not only related to disease progression it must be reported within 24 hours of the investigator becoming aware of the event. The regulatory authorities

must then be notified within 7 days.

7.5.2 Assessment of Severity

The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), Corrected Version 2.1, July 2017, must be used to determine severity of events and is available on the DAIDS RSC website at <https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables>.

7.5.3 Assessment of Causality

The investigator must determine causality in relation to rifampicin and linezolid, based on temporal relationship and clinical judgment. The degree of certainty about causality will be assigned using the definitions in Table 6. If causality is assessed as unrelated or unlikely to be related it is classed as an SAE. If the event is possibly, probably or definitely related, then the event is classed a serious adverse reaction (SAR).

7.5.4 Assessment of Expectedness

If there is at least a possible involvement of the trial treatment, the investigator must assess the expectedness of the event. An unexpected adverse reaction (UAR) is one not previously reported in summary of product characteristics or more severe than previously reported. If an SAR is assessed as unexpected, it becomes a SUSAR, Expected disease-related events will not be reportable as SUSARs.

Side-effects of rifampicin and linezolid should be checked in the latest version of the summary of product characteristics at: <http://www.medicines.org.uk/emc>

Table 6: Assigning type of SAE through causality

Relationship	Description	SAE Type
Unrelated	The AE is completely independent of study drug administration, and/or evidence exists that the event is definitely related to another aetiology. There must be an alternative, definitive aetiology documented.	Unrelated SAE
Unlikely	A clinical event, including an abnormal laboratory test result, whose temporal relationship to drug administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the trial medication) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the subject's clinical condition, other concomitant treatments).	Unrelated SAE
Possible	There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g., the subject's clinical condition, other concomitant events). Although an adverse drug event may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate – for example should a re-challenge occur with the same effect.	SAR
Probable	There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time sequence to administration of the drug, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (de-challenge).	SAR
Definite	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to drug administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (de-challenge) should be clinically plausible. The event must be pharmacologically definitive, with use of a satisfactory re-challenge procedure, if necessary or appropriate	SAR

7.6 Recording of AEs

The objective of the AE endpoint is to assess linezolid drug toxicity when administered with high and standard dose rifampicin among this critically ill population with high mortality. AEs grade 3-5 will be recorded via the AE recording CRF. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment is not the cause. All unresolved AEs at study termination should be followed until the events are resolved, otherwise explained.

Asymptomatic laboratory abnormalities are not reportable AEs. However, abnormal laboratory results constitute an AE if the abnormality:

- is associated with a serious adverse event (e.g. death, hospitalization)
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests, (other than repeat lab check), or
- is considered by the investigator to be of clinical significance

7.7 Reporting of SAEs

The PI and site PI should be notified of all SAEs within 24 hours of the investigator becoming aware of the event. The AE CRF must be completed. Investigators should notify the PI and site PI of all SAEs occurring from the time of randomization until 28 days after the last protocol treatment administration (through Week 8). SARs and SUSARs must be reported until trial closure.

The study site is responsible for the reporting of SAEs, SUSARs, and other SARs to the regulatory authorities and the research ethics committees, as appropriate. The PI and/or site PI will review all SAE reports. SAEs and SUSARs must be then reported to the competent authorities within 7 days.

Reporting will be submitted to the local IRB as per their specified reporting requirements. Copies of each report and documentation of IRB notification and receipt will be kept in the regulatory binder. At the time of the initial report, the study identifier, participant identification number, date of event, description of event, relationship to linezolid or rifampicin, intervention if any, working diagnosis, and current vital status will be provided.

Within the 7 days of the initial report (or concurrently), the investigator will provide further information on the AE Reporting CRF in the form of a written narrative. This will be documented along with any other diagnostic information that will assist understanding of the event. Significant new information on on-going SAEs will be provided promptly to the study sponsor and local IRB. Serious AEs that are still on-going at the end of the reporting period must be followed up to determine the final outcome. Grade 3-4 AEs that are not serious and unrelated to the investigational medicinal product will be reported in aggregate in a safety report.

7.8 Independent Data Safety Committee

The study will undergo interim review by the appointed Data Safety and Monitoring Board, which will include expertise in statistics, clinical trials, and HIV/TB co-infection, after 30 participants have completed the Week 8 visit, or no more than nine months after the enrollment of the first study participant. An interim review may also be convened if a concern is identified by the PI, site PI, other study team member in consultation with the team, IRB, or regulatory authorities. The DSMB will be separate from the investigators and will have full access to all accumulating data on safety and efficacy. The DSMB can also modify the frequency of interim analysis.

8.0 CLINICAL MANAGEMENT ISSUES

Criteria for participant management, dose interruptions, modifications, and discontinuation of treatment are mandated only for toxicities attributable to study-provided drugs. The PI and site PI must be notified within 24 hours regarding toxicities that result in a change in study treatment (including transient or permanent discontinuation) during the study-defined treatment period (first 4 weeks).

8.1 Toxicity Management

Only toxicities Grade 3 or higher related to study medications provided through the study (linezolid, rifampicin) will be considered in the toxicity management section. For toxicities potentially attributed to one or more of the study medications, one or more of the study medications may be held or permanently discontinued.

8.1.1 Liver toxicity

A liver toxicity management plan will be implemented if either of the criteria outlined below are met:

- ALT > 5x the upper limit of normal (ULN)
- ALT > 3x ULN with signs or symptoms suggestive of clinical hepatitis including one or more of the following: nausea, vomiting, abdominal pain, dark or clay colored stools, unexplained fever, jaundice, liver tenderness, or hepatomegaly

Management plan:

1. Discontinue pyrazinamide
2. Assess for use of other hepatotoxic drugs and discontinue potentially hepatotoxic, non-essential medications (e.g., co-trimoxazole, fluconazole)
3. Repeat ALT, bilirubin, and INR every 2 (+/-1) days
4. If the transaminases fall to <5x ULN and symptoms resolve, continue treatment without pyrazinamide.
5. If the transaminases do not fall to <5x ULN or bilirubin is >2.0 mg/dL or INR >1.5, or symptoms worsen, stop rifampicin and isoniazid, and start alternative regimen for TB meningitis (e.g., streptomycin and fluoroquinolone).
6. Continue to follow ALT every 2 (+/-1) days until stable. If the ALT return to <2x ULN and symptoms resolve, rifampicin will be restarted. If ALT remain stable after a minimum of 7 days, isoniazid will be restarted, and streptomycin and fluoroquinolone stopped.
7. Continue to follow ALT every 2 (+/-1) days until stable. If ALT begin to rise again to >5x ULN after reintroduction of either rifampicin or isoniazid, stop the offending medication. Depending on which medication has to be stopped (or potentially both), treat with 1) streptomycin, fluoroquinolone, and ethambutol OR 2) rifampicin, fluoroquinolone, and ethambutol OR 3) isoniazid, fluoroquinolone, and ethambutol.

8.1.2 Hematological toxicity

A hematological toxicity management plan will be implemented if any of the following criteria are met:

- Hemoglobin < 7.0 g/dL for men, <6.5 g/dL for women
- Platelets <50,000/mm³
- Absolute neutrophil count <600/mm³

Management plan:

1. Discontinue linezolid

2. Assess for use of other myelosuppressive medications and discontinue non-essential medications (e.g., co-trimoxazole)
3. Repeat blood count will be performed every 2 (+/-1) days until stable. If the abnormal hematological parameter(s) returns to Grade ≤ 2 and any associated symptoms resolve, linezolid 1200 mg can be restarted.
4. Continue to follow blood count every 2 (+/-1) days until stable. If after restarting linezolid, the abnormal hematological parameter returns to the above criteria, linezolid should again be discontinued.
5. Continue to follow blood count every 2 (+/-1) days until stable. If the abnormal hematological parameter(s) returns to Grade ≤ 2 and any associated symptoms resolve, linezolid can be restarted at 600 mg daily.
6. Continue to follow blood count every 2 (+/-1) days until stable. If after restarting linezolid, the abnormal hematological parameter returns to the above criteria, linezolid should be discontinued permanently.

8.1.3 Gastrointestinal toxicity

Study treatment will be stopped for any Grade 3 or higher gastrointestinal adverse events, including nausea, vomiting, diarrhea, or loss of appetite with weight loss. If a participant develops Grade 3 or 4 GI symptoms, rifampicin will be discontinued first until symptoms have resolved to Grade ≤ 2 , at which point it can be reintroduced. If GI symptoms do not improve after discontinuing rifampicin, linezolid will be discontinued until symptoms have resolved to Grade ≤ 2 , at which point it can be reintroduced.

8.1.4 Neurotoxicity

Mild to moderate headache is an expected adverse reaction linezolid, whereas peripheral neuropathy and optic neuropathy are expected to be relatively uncommon over a 4-week treatment period. Study treatment will be stopped for any Grade 3 or higher neurologic adverse events, including neuropathy or visual changes. If participants develop signs/symptoms of optic neuropathy, we will endeavor to have them evaluated by an ophthalmologist in Masaka if safe and logistically feasible. If a participant develops Grade 3 or higher symptoms, linezolid will be discontinued for up to 14 days until symptoms have resolved to Grade ≤ 2 , at which point linezolid 1200 mg can be reintroduced.

8.1.5 Rash

Mild to moderate rash is a potential adverse reaction to rifampicin or linezolid. Participants with a Grade 1 or 2 rash may continue study medications at the site investigator's discretion. The participant should be advised to contact the site investigator immediately if there is any worsening of the rash, if any systemic signs or symptoms worsen, or if mucosal involvement develops. Study treatment should be discontinued in participants who develop Grade 3 or higher rash. Participants will be followed off study treatment, on study. Participants should be treated as clinically appropriate and followed until resolution of the AE. If the etiology of the rash can be definitely diagnosed as being unrelated to study medications and due to a specific medical event or a concomitant non-study medication, routine management should be performed and documentation of the diagnosis provided.

8.1.6 Other toxicities

Grade 2 toxicities: For grade 2 toxicities, the participant will be followed more carefully, with additional laboratory and/or clinic visits as necessary, and the study drugs temporarily held at the investigator's discretion.

Grade 3 toxicities: For any grade 3 toxicity that, in the investigator's judgment is due to rifampicin or linezolid, the causative drug should be held. The clinician should rule out other possible causes of the symptoms before discontinuing study medication. When possible, concomitant medications should be held first at the discretion of the investigator if he/she suspects they are contributing to the toxicity. Depending on the nature and severity of the toxicity, the degree to which it resolves, and/or the emergence of alternative explanations for the toxicity or the subject's deterioration, the study drugs(s) may be restarted at the discretion of the investigator.

Grade 4 toxicities: Any participant with grade 4 renal, hepatic, cardiac, hematological, or neurologic toxicity will be immediately discontinued from study therapy. The laboratory test or clinical finding in question will be reassessed as soon as possible. The repeat test will guide management of the event as follows:

1. If the repeat assessment shows toxicity of grade 3 or lower, and if the participant has continued to receive study drugs between the two testing dates, then the participant will be managed according to the appropriate toxicity level of the repeat test.
2. If the repeat test shows toxicity of grade 3 or lower, and if the participant has not received study drugs between the two testing dates, then the participant will be managed at the discretion of the investigator with regard to the re-administration of study drugs, and otherwise according to the toxicity level of the repeat test.
3. If the repeat test shows grade 4 toxicity, then the participant will be permanently discontinued from study medications unless a clear alternative cause for the toxicity has been identified, in which case, re-administration of study drugs may be considered but only with prior approval from the PI and site PI. Further treatment of TB will be directed by the investigator and treating clinician on an individualized basis. The participant will continue to be followed for study monitoring purposes (as are other participants who make a permanent departure).

For other grade 4 toxicities, the study drugs will be temporarily held and may be restarted or permanently stopped at the discretion of the investigator. For all toxicities that are treatment-emergent and that require the study therapy to be temporarily or permanently discontinued, relevant clinical and laboratory tests will be obtained as clinically indicated and repeated as needed until final resolution or stabilization of the toxicity.

Temporary or permanent discontinuation of study drugs: Certain events or conditions may necessitate temporary or permanent discontinuation of the study medication. Participants who experience such events or conditions, however, will still be "on study" and will be followed until study completion. Any participant for whom the study medication is temporarily discontinued will be restarted on study medication as soon as possible. Study regimens will be discontinued and non-study regimens will be used with continued study follow-up for participants who fail to respond to study therapy either clinically and/or bacteriologically, for participants in whom treatment-emergent drug toxicity warrants discontinuation of study therapy. If study drugs are permanently discontinued, further TB therapy will be administered at the investigator and treating clinicians' discretion.

8.1.7 Criteria for temporary discontinuation of study therapy

- Development of a toxicity that, depending on its nature and severity, requires temporary discontinuation of the study medication until the toxicity resolves as indicated in the preceding toxicity management section.
- Development of another medical condition that makes the administration of the study drug inadvisable. The decision to discontinue temporarily the study medication in this situation will be at the investigator's discretion. The period during which the participant is off study medication will be as short as clinically possible.

8.2 Management of CNS tuberculomas

Participants with radiologic evidence of a CNS tuberculoma or other mass lesion on initial head CT or MRI are eligible for the study. Participants who develop a CT or MRI-confirmed CNS tuberculoma or other mass lesion after enrollment can remain on study treatment. In both circumstances, the duration of therapy and corticosteroids can be modified at the discretion of the investigator and treating clinician.

8.3 Management of Resistant TBM

Participants with known current or previous drug resistant TB infection will be excluded from the trial. If participants are determined to have resistant infection based on phenotypic testing after enrollment, they may discontinue study treatment at the discretion of the investigators and treating clinicians but will remain “on study” for follow up evaluations as per the schedule of events, including:

- Symptom assessment since last study visit.
- Targeted physical exam, including neurologic exam with GCS
- Medication review
- Adherence questionnaire, including documentation of all doses received
- Neuropathy and vision testing
- Neurocognitive and functional outcome assessment

8.4 Management of Participants with Suspicion of Relapse Post-treatment or New Neurological Event

All efforts should be made to complete the assessments listed below as soon as possible:

- Symptom assessment
- Targeted physical exam, including neurologic exam with GCS
- Medication review
- Adherence questionnaire, including documentation of all doses received
- Blood draw for a complete blood count and chemistries including LFTs if indicated
- Brain imaging if indicated
- CSF specimen for protein, cell count, differential, glucose, gram stain, bacterial culture, AFB smear and culture, and Xpert Ultra. Positive culture isolates will be sent for drug susceptibility testing for *M. tuberculosis*
- Whole blood and plasma collected for storage

8.5 Management of Pregnancy

If a participant becomes pregnant during the study, she will be discontinued from study medications and will continue treatment of her TB according to local standards of care, to a prenatal care program for management of her pregnancy according to local standards of care, and to their local HIV clinic. Participants who become pregnant during the study will be followed through the end of the study period. At the end of the pregnancy, the outcome and AEs for the participant and the infant will be recorded. If a participant has completed the study or chooses to discontinue from the study before the end of the pregnancy, then the study team should request permission to contact her regarding pregnancy outcomes at the end of pregnancy. If the information is obtained, pregnancy outcomes will be recorded at the end of the pregnancy.

All four first line antituberculous drugs have an excellent safety record in pregnancy and are not associated with human fetal malformations. The effects of higher dose rifampicin and linezolid on the developing human fetus are unknown. For this reason, women of childbearing potential must agree to use adequate barrier contraception or abstinence for the duration of study participation. Women of childbearing-potential will have a pregnancy test prior to enrollment. Should a woman become pregnant while participating in this study, she should inform study staff immediately. Female participants of “childbearing potential” are defined as women who have reached menarche or who have not been post-menopausal for at least 24 consecutive months or have not undergone surgical sterilization. Hormonal contraception is not recommended because it will not be effective due to induction of metabolism when receiving rifampicin. This information will be discussed with female participants when their mental status normalizes at the time they are re-consented.

8.6 Management of ART

During the trial HIV therapy will be provided in partnership with local HIV services through Masaka Regional Referral Hospital. For those participants already on effective first-line ART at presentation, it will be continued. In participants on a failing first-line ART-regimen, it will be switched after the intensive phase of TB treatment in accordance with local guidelines. Patients on a protease-inhibitor based regimen at presentation are not eligible to be enrolled into the trial due to the drug interactions.

9.0 CRITERIA FOR DISCONTINUATION

9.1 Permanent and Premature Treatment Discontinuation

- Drug toxicity that is possibly, probably or definitely related to high-dose rifampicin or linezolid, and that requires permanent discontinuation of any of these drugs
- Confirmed drug-resistant MTB infection
- Another infection cause found that is not MTB
- Sustained non-adherence that, in the opinion of the investigator, warrants early discontinuation.
- Requirement for prohibited concomitant medications.
- Pregnancy or breastfeeding.
- Request by participant or next of kin/caregiver to terminate treatment.
- Clinical reasons believed life threatening by the physician, even if not addressed in the toxicity section of the protocol

Participation is entirely voluntary so participants may choose to discontinue the trial treatment at any point without penalty. Participants should be encouraged to remain in the trial for the purpose of follow-up and data analysis. Where study drug is discontinued or the dose is modified it should be recorded in the follow-up CRF.

9.2 Premature Study Discontinuation

- Request of a medical provider or investigator if they think the study is no longer in the best interest of the participant.
- The participant or next of kin/caregiver refuses further follow-up evaluations (i.e., withdraws continued consent to participate).
- At the discretion of the IRB and other regulatory authorities as part of their duties to ensure that research participants are protected, or the industry supporter or its designee.

10.0 STATISTICAL CONSIDERATIONS

10.1 Sample size estimation

Sample size calculations for the PK analyses are based on different study designs (varying number of participants and time points) using clinical trial simulations. We used the stochastic simulation-estimate “sse” methodology for clinical trial simulation and re-estimation to determine sample sizes required to evaluate key PK parameters with precision adequate to determine optimal dosing for a future efficacy trial of LZD. This methodology simulates the data from a planned trial with a proposed design (e.g., number of participants) followed by the estimation of the parameters under the true and alternative models. This is repeated a minimum of 1000 times to estimate PK parameters, standard errors and inter-individual variability. With 30 participants receiving LZD, we will be able to estimate PK parameters with required precision of relative standard errors <10% for typical values and <25% for random effects (inter-individual variability). For the evaluation of LZD adverse events, if we assume 40% of participants in the LZD arm and 10% in the no LZD arm will experience myelosuppression,^{78,84} the planned sample size of 60 participants (n=30 per arm) will provide at least 80% power to detect a similar or greater difference in the frequency of myelosuppression between arms at a significance level of 0.05. Given the modest sample size, we recognize that we may not have adequate power to compare the frequency of myelosuppression in participants on LZD and standard versus high dose RIF; however, if the frequency of myelosuppression in participants on LZD and high dose RIF (n=20) is anticipated as ~25%, the 90% confidence interval of this estimate is 10% to 46% with a precision of 18%.

10.2 Planned analyses

The primary outcomes will be CSF and plasma LZD PK parameters, including CSF to plasma ratio, rate of CSF uptake, and plasma absorption rate constant (k_a), drug clearance (Cl/F), volume of distribution (V_d). We will employ a model-based approach using non-linear mixed effects modeling in NONMEM to estimate plasma and CSF PK parameters based on simultaneous analysis of all plasma and CSF drug concentration data.⁷⁴ We will perform post-hoc Bayesian predictions of secondary LZD PK parameters, including C_{max} , time to C_{max} , AUC_{0-24} , and elimination half-life in plasma and in CSF. Based on this approach, we will characterize the dynamic uptake of LZD in the CSF when administered with high and standard dose RIF over 4 weeks and derive a dosing algorithm for LZD to achieve target exposures through simulations. Pharmacodynamic breakpoints for LZD against TB are not established, but we will use target AUC_{0-24} , AUC/MIC , $T>MIC$ for LZD of 160 $\mu g \cdot hr/mL$, 100, and 85%, respectively.^{23,75,76} We will use sparse sampling to estimate the AUC curve based on CSF sampling early, at steady state, and before LZD discontinuation.⁷⁷

For the LZD adverse event evaluation, the primary outcome will be a dichotomous measure of Grade 3 or higher (yes/no) myelosuppression (e.g., anemia, thrombocytopenia, leukopenia) during the 4 weeks of therapy. A secondary outcome will be LZD discontinuation or dose reduction (yes/no) for any AE. We will compare the frequency of myelosuppression between the LZD and no LZD arms across RIF dosing with the Cochran-Mantel-Haenszel test, which accounts for stratified randomization. Within

the LZD arm, we will explore differences in the frequency of myelosuppression between the standard and two high dose RIF arms combined by a chi-square test. We will use an exposure-response model using logistic regression to test if the probability of myelosuppression and LZD discontinuation is related to PK measurements, including C_{min} , C_{max} and AUC_{0-24} .

11.0 DATA COLLECTION AND MONITORING

11.1 Records to be Kept

Case report forms (eCRFs) will be provided for each participant. Participants must not be identified by name on any CRFs. Participants will be identified by a participant identification number (PID).

11.2 Clinical Site Monitoring and Record Availability

The PI and site PI will visit the site to review individual participant records, including consent forms, CRFs, supporting data, laboratory specimen records, and medical records (physicians' progress notes, nurses' notes, participants' hospital charts), to ensure protection of study participants, compliance with the protocol, and accuracy and completeness of records. The monitors also will inspect sites' regulatory files to ensure that regulatory requirements are being followed and sites' pharmacies to review product storage and management.

The site investigator will also make study documents (e.g., consent forms, drug distribution forms, CRFs) and pertinent hospital or clinic records readily available for inspection by the local IRB, study sponsors, or other designated local, US, and international regulatory authorities for confirmation of the study data.

Study data forms will be digitally scanned for permanent record keeping and to enable rapid resolution of any discrepancies. The DSMB and regulatory inspectors will have full access to source documents.

The following data will be verifiable from source documents:

- Signed consent forms
- Dates of assessments including dates specimens were processed in the laboratory
- Eligibility and baseline values for all participants
- Clinical endpoints
- Adverse events
- Participant clinical and laboratory data
- Study drug compliance
- Pharmacy logs for dispensing / returns of study drugs
- Concomitant medication

11.3 Role of Data Management

The study paper-based CRF is the primary data collection instrument for the study. All data requested on the CRF will be recorded. Entering study data on CRFs will be performed in a timely fashion by the site.

11.4 Data collection, Entry and Retention

Data collection is the responsibility of the study staff under the supervision of the PI and site PI. The investigator is responsible for ensuring accuracy, completeness, legibility and timeliness of data

collection and entry. The investigator will retain study essential source documents for 20-years after the completion of the study, as per Ugandan guidelines. Digital images of the source documents will be retained for an indefinite period.

11.5 Protocol violations

A protocol deviation is any noncompliance with the clinical trial protocol or GCP requirements with an impact on patient safety or scientific integrity. The noncompliance may be either on the part of the participant, the investigator or study site staff. Corrective actions are to be developed by the PI and implemented promptly. It is the responsibility of the site to be vigilant, to identify and report deviations within 5 working days on the deviation. All deviations must be addressed in source documents and sent to local IRB as per their guidelines.

As this trial duration is 24 weeks, reportable deviations include:

- 1) Participant Eligibility Criteria
- 2) Informed Consent
- 3) Randomization Procedures
- 4) Administration of Study Investigational medicine

11.6 Laboratory Quality Control

All laboratory work will be undertaken in accredited laboratories with internal and external validation procedures.

12.0 ETHICS AND PROTECTION OF HUMAN SUBJECTS

This study is to be conducted according to the international standards of Good Clinical Practice (International Conference on Harmonization guidelines), Declaration of Helsinki, and International Ethical Guidelines for Biomedical Research Involving Human Subjects, applicable national government regulations, and Institutional research policies and procedures. All investigators must have received human subject protection and GCP training prior to human subject involvement.

12.1 Institutional Review Board (IRB) Review and Informed Consent

This protocol, the informed consent documents, and any subsequent modifications will be reviewed and approved by the appropriate IRB/ethics committees. A signed consent form will be obtained from the participant (or proxy for participants who cannot consent for themselves). The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy of the consent form will be given to the participant or proxy and if they are unwilling to keep a copy, it will be kept at the study site on their behalf.

12.2 Participant Confidentiality

All participant-related information, including laboratory specimens, CRFs, and other records will be kept confidential and identified by participant ID only to maintain confidentiality. All records will be kept in a secure, locked location and only research staff will have access to the records. All computerized databases will identify participants by numeric codes only, and will be password-protected. Clinical information will not be released without written permission of the participant, except as necessary for monitoring by local, US, or international regulatory authorities as part of their duties, or the study sponsor.

12.3 Study Discontinuation

The study may be discontinued at any time by the IRB, study sponsor, independent DSMB, or other regulatory agencies as part of their duties to ensure that research participants are protected.

12.4 Future Use of Stored Specimens

If *additional* storage consent has been given residual participant specimens will be stored for future research. Specimens to be stored include CSF and blood.

12.5 Conflict of Interest

No conflict of interest exists by any investigator. Any investigator who develops a new conflict of interest will disclose this to their relevant institutional oversight board and to the study sponsor.

13.0 PUBLICATION OF RESEARCH FINDINGS

All publications and presentations relating to the study will be authorized by the trial investigators. Named authors will include at least the trial's PI, site PI, co-investigators, and statistician. Members of the DSMB will be listed as contributors if published in a journal where this does not conflict with the journal's policy.

14.0 REFERENCES

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