THE UNITED REPUBLIC OF TANZANIA

MINISTRY OF HEALTH

TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY

PUBLIC ASSESSMENT REPORT FOR A RANDOMIZED CLINICAL TRIAL OF EARLY EMPIRIC ANTI-MYCOBACTERIUM TUBERCULOSIS THERAPY FOR SEPSIS IN SUB-SAHARAN AFRICA

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1. Introduction

In sub-Saharan Africa, sepsis is a leading cause of morbidity and mortality[1.] Approximately 65-85% of all septic patients are living with HIV, and TB is the leading cause of bacteremia in these patients with infection rates of 25-50% and associated mortality as high as 50%[2-10.] Compared to those without HIV, people with HIV are 3-4 times more likely to die from TB sepsis[11]. Factors associated with poor outcomes in people with HIV and TB sepsis include immunosuppression, malnutrition, poor drug absorption, late clinical presentation, and delayed diagnosis and subsequently delayed treatment of TB[6;12]. The protocol manuscript is published in this link Early empiric anti-Mycobacterium tuberculosis therapy for sepsis in sub-Saharan Africa: a protocol of a randomised clinical trial - PubMed (nih.gov))

Treatment of sepsis including TB

In general, the reduction of mortality from sepsis relies upon early detection and prompt initiation of antimicrobial therapy[14]. Sepsis has a similar clinical phenotype regardless of the underlying pathogen and the lack of rapid and effective diagnostic tools for TB can lead to significant delays in the initiation of appropriate therapy and thus poor outcomes[15;16]. Furthermore, TB in the setting of HIV coinfection is often disseminated rather than focal, which is difficult to detect microbiologically[2;5;17].

Culture is the gold standard for the microbiological detection of TB but is expensive, labour-intensive, and has a long turnaround time, making it impractical for clinical decision-making for septic patients. Sputum smear microscopy and PCR-based platforms such as XpertMTB/RIF and XpertMTB/RIF Ultra are faster and increasingly available, but septic patients rarely expectorate sputum and sensitivity is diminished in disseminated or paucibacillary TB[18;19]. Urinary lipoarabinomannan (LAM) testing has a fast turnaround time and can be used at the point of care to guide TB therapy but has limited sensitivity, particularly in HIV-infected patients with CD4+ T cell concentrations above 100 cells/μ[20-23]. For patients who are sputum smear-negative and without confirmed TB, WHO algorithms are available to guide clinicians in the initiation of anti-TB therapy, but these diagnostic algorithms lack sensitivity and specificity[24].

Increased doses of anti-TB therapy

We are not aware of any studies besides our own that have examined PK/PD of anti-TB therapy in patients with sepsis. However, there is growing evidence in related TB populations that PK/PD may be one of the most important drivers of TB outcomes. In patients with pulmonary TB without sepsis from South Africa, serum drug concentration thresholds could be established that predicted outcomes of microbiologic failure, death, or relapse[25]. In a separate study of people living with HIV and being treated for pulmonary

TB in Uganda (N=268) the time to microbiological clearance from the sputum, known as culture conversion, was longer in patients with drug concentrations of isoniazid and rifampin that were below the expected peak concentrations[26]. In a similar high-TB-burden setting at our partner study site in Tanzania, we have also found such PK variability to be common and peak concentrations for key drugs to be well below the expected range for the majority of people studied[27]. In a serum tidal assay that incorporates the patient's serum collected at the time of peak concentrations and their own M. tuberculosis isolate, the degree of cidality correlated with the ratio of the peak concentration of isoniazid and rifampin and the M. tuberculosis minimum inhibitory concentration (MIC) of those drugs, and this methodology has been replicated by other laboratories [28]. We have additionally found that MIC testing reveals M. tuberculosis isolates with elevated MICs still within the conventionally "susceptible" range, but when coupled with suboptimal PK renders those isolates functionally resistant[28;30]. These functionally resistant isolates often do not harbor genetic mutations in resistance-determining regions covered by commercially available molecular diagnostics[37]. Fortunately, these PK/PD dynamics are modifiable and increasing doses of first-line anti-TB drugs increases exposure, and higher exposures can be targeted to improve microbial kill and cure[31]. For instance, in Virginia, among people with pulmonary TB and risk factors for poor treatment outcomes, such as those with HIV or diabetes, we have instituted a program of routine early therapeutic drug monitoring and dose adjustment that has significantly hastened the time to sputum culture conversion to negative[32]. Favourably, several randomized controlled trials have increased rifampin beyond the conventional 10 mg/kg (600 mg maximum daily dose) without significant increases in adverse events[33]. Higher dose isoniazid has now been incorporated into one of the WHO-approved regimens for drug-resistant TB following an acceptable safety profile analysis in various clinical trial[33]. Taken together, there is considerable preliminary evidence that early empiric anti-TB treatment with conventional dosing and/or sepsis-specific higher dose rifampin and isoniazid will be well-tolerated and improve mortality.

1.1. Study details

Clinical Trial Registration number	TZ21CT0025
Title of the study	A randomized clinical trial of early empiric anti-Mycobacterium tuberculosis therapy for sepsis in sub-Saharan Africa
Protocol Identification Number/Code	20-0027
Ethical Clearance Number/ Date of Approval	NIMR/HQ/R.8a/Vol.IX/3664 dated 29.04.2021

TMDA Approval Date	2021-10-18
Name of Investigational Product or Intervention	High dose rifampicin
Dosage Form(s) and Strength(s) (where applicable)	R-150-(B)-100 Rifampicin, 150 mg, Film-coated tablet(s), Blister(s) 100/pack. R-300-(B)-100 Rifampicin, 300 mg, Film-coated tablet(s), Blister(s) 100/pack. H-50-(B)-100 Isoniazid, 50 mg, Uncoated tablet(s), Blister(s) 100. H-100-(B)-100 Isoniazid, 100 mg,Uncoated tablet(s), Blister(s) 100
Route(s) of Administration (where applicable)	Orally
Name (s) of Comparator Product (where applicable)	Standard treatment
Name and address(es) of the Sponsor	The University of Virginia, PO Box 801340 345 Crispell Dr Charlottesville VA 22908
Name and address(es) of the Principal Investigator (PI)	Prof.Dr. Stellah George Mpagama, Kibong'oto Infectious Diseases Hospital P.O Box 12 Mae Street, Lomakaa Road. Siha – Kilimanjaro +255 754 860576
Name and address(es) of Study Site(s)	Kibong'oto Infectious Disease Hospital P.O. Box12 Mae Street, Lomakaa Road, Siha, KilimanjaroTanzania
Name and address of the manufacturer of Investigational medical product (IMP) if applicable	**LUPIN LTD** EPIP, SIDCO Industrial Complex Kartholi, Bari brahmana, Jammu, j & K -181133 INDIA
Name and address of the manufacturer of the comparator product (if applicable	**LUPIN LTD** EPIP, SIDCO Industrial Complex Kartholi, Bari brahmana, Jammu, j & K -181133 INDIA
Phase of Trial	III
Duration of the study	36 Months
The primary purpose of the study (Screening, Diagnosis, Prevention, Treatment)	Treatment
Condition or diseases under study	Tuberculosis
Number of participants intended to be enrolled in the study	436

1.2. Assessment procedure

The application for authorization for a clinical trial of A randomized clinical trial of early empiric anti-Mycobacterium tuberculosis therapy for sepsis in sub-Saharan Africa was submitted on 05-05-2021. The assessment was completed in two rounds of evaluation. The trial was approved on 18-10-2021.

2. Trial information

2.1. STUDY OBJECTIVES

Primary Objective

a) To conduct a randomized 2x2 factorial clinical trial of 1) immediate initiation of empiric anti-TB therapy plus standard care vs diagnosis-dependent anti-TB therapy plus standard care alone and 2) sepsis-specific anti-TB therapy plus standard care vs conventional WHO weight-based anti-TB therapy plus standard care for patients presenting with sepsis to two hospitals in Uganda and Tanzania.
b) To determine if empiric immediate initiation of anti-TB therapy plus standard care improves 28-day mortality compared to diagnosis-dependent anti-TB therapy plus standard care.
c) To determine if sepsis-specific dose anti-TB therapy plus standard care improves 28-day mortality compared to conventional WHO weight-based anti-TB therapy plus standard care.

Secondary Objective

a) To determine if empiric immediate initiation of anti-TB therapy plus standard care improves in-hospital mortality compared to diagnosis-dependent anti-TB therapy plus standard care
b) To determine if sepsis-specific dose anti-TB therapy plus standard care improves in-hospital mortality compared to conventional WHO weight-based anti-TB therapy plus standard care.
c) To determine if empiric immediate initiation of anti-TB therapy plus standard care improves 6-month mortality compared to diagnosis-dependent anti-TB therapy plus standard care

d) To determine if sepsis-specific dose anti-TB therapy plus standard care improves 6-month mortality compared to conventional WHO weight-based anti-TB therapy plus standard care.
e) To determine the safety of increased dose anti-TB therapy for patients with sepsis
f) To determine if the early achievement of target serum drug concentrations of isoniazid and rifampin, measured on day-2 of TB treatment, is associated with more rapid clinical improvement among patients with confirmed TB.

2.2. OUTCOME MEASURES

2.2.1. Primary Outcome

The primary outcome measure of the study is 28-day mortality

2.2.2. Secondary Outcome measures

The following are the secondary outcome measures of the study: -

a) In-hospital mortality,
b) 6-month mortality,
c) time to death,
d) duration of hospitalization,
e) time to anti-TB therapy,
f) adverse drug events during the 28-day study period,
g) final sepsis aetiology,
h) time to ambulation,
i) time to temperature normalization,
j) Karnofsky score,
k) serum rifampin and isoniazid peak concentrations (Cmax) and total area under the concentration-time curve (AUC)

2.3. INVESTIGATIONAL PLAN

This a phase 3a randomized open-label study aiming aim to enroll a total of 436 participants, to give 80% power, with a two-sided significance level of 5%, for testing each of the main effects of timing and dose on 28-day mortality, assuming 28-day mortality of 45% in the usual timing, conventional dose group, 32% in each of the usual timing, sepsis-specific dosing and immediate dosing, conventional dose groups, and 19% in the immediate, sepsis-specific dose group. Participants will be men or women aged ≥18 years living with HIV in Tanzania or Uganda who are admitted to one of the study hospitals with sepsis, defined by a clinical concern for infection, a modified quick sepsis-related organ failure assessment (qSOFA) score ≥2 (Glasgow Coma Scale score <15, a respiratory rate ≥22, or a systolic blood pressure ≤90 mmHg or a mean arterial pressure of ≤65 mmHg). After enrollment, patients will be randomized to 1) empiric immediate initiation of anti-TB therapy plus standard care vs diagnosis-dependent anti-TB therapy

plus standard care and 2) conventional WHO-recommended weight-based dose anti-TB therapy with rifampin, isoniazid, pyrazinamide, and ethambutol plus pyridoxine, plus standard therapy; or sepsis-specific dose anti-TB therapy with rifampin (~30mg/kg), isoniazid (~7.5mg/kg), pyrazinamide, and ethambutol plus pyridoxine, plus standard care.

2.4. Type and number of the study participants

The study is conducted among HIV individuals. The study plans to enrol about 436 participants.

2.5. SELECTION OF STUDY POPULATION

Inclusion criteria

A subject will be eligible for inclusion in this study only if all of the following criteria apply to meet all (list all inclusion criteria)

a. Provision of signed and dated informed consent form by the subject, their caregiver, or their next of kin.
b. Stated willingness to comply with all study procedures and availability for the duration of the study
c. Male or female aged ≥18 years living with HIV
d. Admitted to hospital with 1) clinical concern for infection; 2) ≥2 qSOFA score criteria (Glasgow Coma Scale score <15, a respiratory rate ≥22, or a systolic blood pressure ≤90 mmHg or a mean arterial pressure of ≤65 mmHg)
e. Resident within a pre-defined geographic area to ensure TB clinic follow-up
f. For females of reproductive potential: use of highly effective contraception through 28 days.

Exclusion criteria

A subject is not eligible for inclusion in this study if any of these criteria apply (list all exclusion criteria)

a. Known active TB or receiving anti-TB therapy
b. Pregnancy or lactation. Women will undergo urine pregnancy screening. Pregnant women will be excluded due to the possible toxicity and teratogenicity of high-dose rifampin and isoniazid included in anti-TB therapy as well as possible teratogenicity of dolutegravir which is recommended as first-line antiretroviral therapy in this study.
c. Known allergic reactions to the components of the anti-TB therapy
d. Treatment with another investigational drug or other intervention within one month

e. Known liver disease
f. Alcohol use > 14 standardized drinks per week and/or > 4 drinks per day for men and >7 standardized drinks per week and/or >3 drinks per day for women, defined as 14 grams of ethanol, as found in example 5 ounces of wine, 12 ounces of beer, or 1.5 ounces of 80 proof spirits
g. Positive serum cryptococcal antigen test
h. Current treatment with a drug known to have significant interaction with anti-TB therapy
i. If after enrollment a study participant is found to have a grade 4 or 5 renal (serum creatinine >3.5x upper limit of normal or creatinine clearance < 30 ml/min) or hepatic (alanine transaminase [ALT] or aspartate transaminase [AST] >10x upper limit of normal) dysfunction, then they will be terminated from the trial.

2.6. DRUG FORMULATION OR DEVICE DESCRIPTION IN CASE OF DEVICES

The following is the formulation of the IMPs which will be used in the trial

Single Medicines (Global Drug Facility)

R-150-(B)-100 Rifampicin, 150 mg, Film coated tablet(s), Blister(s) 100/pack
R-300-(B)-100 Rifampicin, 300 mg, Film coated tablet(s), Blister(s) 100/pack
H-50-(B)-100 Isoniazid, 50 mg, Uncoated tablet(s), Blister(s) 100
H-100-(B)-100 Isoniazid, 100 mg, Uncoated tablet(s), Blister(s) 100

Fixed-Dose Combinations (Global Drug Facility)

4-FDC/RHZE150/75/400/ 275-(B)-672 Rifampicin/Isoniazid/ Pyrazinamide/ Ethambutol, 150 mg/75 mg/400 mg/ 275 mg, Film-coated tablet(s), Blister(s) 672/pack

Ceftriaxone (Baxter Healthcare Corporation)

Ceftriaxone for injection is supplied as a sterile crystalline powder in glass vials.

Instructions for safe handling:

In general drugs under study should be administered consistent with the package inserts and /or instructions provided by the non-study sources who prescribe or supply the drugs to participants

State the accountability procedures for the investigational product(s), placebos and comparator(s) and disposal:

The study follows the normal procedures used in the hospital setting since the trial used the medicines used for the standard of care

2.7. TREATMENTS

Treatments administered in case of biologicals or medicines.

2.7.1. The name(s) of all the product(s): rifampin (~10 mg/kg), isoniazid (~5 mg/kg), pyrazinamide, and ethambutol in fixed-dose combination (FDC) tablets, plus pyridoxine

2.7.2. Dose(s): rifampin (~30 mg/kg), isoniazid (~7.5mg/kg) utilizing a combination of the single tablet (isoniazid and rifampin) and FDC containing the WHO recommended doses of pyrazinamide and ethambutol, plus pyridoxine.

2.7.3. The dosing schedule(s): Participants randomized to receive empiric immediate initiation of anti-TB therapy will receive anti-TB therapy per protocol until 28 days to coincide with the evaluation of the primary endpoint of 28-day mortality.

2.7.4. The route/mode(s) of administration: Orally

2.7.5. The treatment period(s): Participants randomized to receive 1) empiric immediate initiation of anti-TB therapy plus standard care or diagnosis-dependent anti-TB therapy plus standard care, and 2) conventional WHO recommended weight-based dose anti-TB therapy plus standard care or sepsis-specific dose anti-TB therapy plus standard care. The anti-TB therapy will include rifampin, isoniazid, pyrazinamide, and ethambutol plus pyridoxine per protocol until 28 days to coincide with the evaluation of the primary endpoint of 28-day mortality.

2.7.6. Follow-up period(s) for participants for each investigational product treatment/trial treatment group/arm of the trial: All participants will be evaluated at the 28-day visit in person. If the participant remains in the hospital for 28 days, the evaluation will occur in the hospital. If the participant is unable to return for the 28-day visit, then the evaluation will occur by telephone, after sufficient attempts at an in-person visit, either at the research facility or at the participant's home, as per the relevant SOPs.

2.7.7. Concomitant Medication(s)/treatment(s) permitted (including rescue medication) and not permitted before and/or during the trial: Ceftriaxone is the first-line recommended agent, as it has repeatedly been shown to cover the most common non-TB bacterial pathogens.

2.7.8. Procedures for monitoring participant's compliance: All participants will be evaluated during the 28-day visit in person. If the participant remains in the hospital for 28 days, the evaluation will occur in the hospital. If the participant is unable to return for the 28-day visit, then the evaluation will occur by telephone, after sufficient attempts at an in-person visit, either at the research facility or at the participant's home, as per the relevant SOPs.

2.7.9. Wash-out period (Description for pre-, during- and post-trial, as applicable)

2.7.10. N/A

2.8. PRE-STUDY SCREENING AND BASELINE EVALUATION

The recruitment of study participants is from the emergency and medical wards of the study hospitals. It involves the review of all admissions to the study hospital emergency wards on a twice-daily basis to identify and recruit study participants. To assist with recruitment, we discuss the study with hospital staff at educational conferences; post study flyers in the emergency and medical wards; and ensure study staff are stationed in the emergency department. To assist with retention, we collect telephone numbers from study participants and the caregiver or next of kin that accompany them to the hospital. Using this strategy, we have been able to reach >90% of participants in prior studies 32. Additionally, study participants that receive anti-TB therapy will follow up in local TB clinics per routine care. We expect the study population to be comprised of approximately half women and half men from the local Tanzanian and Ugandan populations. We will not include pregnant women or prisoners in our study. Because we are studying patients with critical illness, some will be cognitively impaired due to infection and shock. In these cases, we will obtain surrogate consent from the subject's caregiver or next of kin. We will not provide compensation or incentives to study participants.

Patients admitted to the emergency ward of the study hospitals will be screened by study staff for inclusion in the study within 24 hours of admission. After enrollment, study participants will undergo baseline laboratory testing as outlined below, including chest x-ray, urinary lipoarabinomannan (LAM-Alere) and bacterial culture, and sputum Expert MTB/RIF Ultra and mycobacterial culture, and bacterial/mycobacterial culture of blood. Study participants will be assessed by the study team daily while they are hospitalized. The results of these tests will be forwarded to the clinical team responsible for the hospital care of the participant. Participants who are not randomized to empiric immediate initiation of anti-TB therapy but who later receive anti-TB therapy based on a new TB diagnosis or clinical suspicion will receive either conventional WHO-recommended weight-based dose anti-TB therapy plus standard care or sepsis-specific dose anti-TB therapy plus standard care according to their randomization.

2.9. EFFICACY AND SAFETY MEASUREMENTS TO BE ASSESSED

Efficacy assessment

Patients admitted to the emergency ward of the study hospitals will be screened by study staff for inclusion in the study within 24 hours of admission. After enrollment, study participants will undergo baseline laboratory testing as outlined below, including chest x-ray, urinary lipoarabinomannan (LAM-Alere) and bacterial culture, and sputum Xpert MTB/RIF Ultra and mycobacterial culture, and bacterial/mycobacterial culture of blood. Study participants will be assessed by the study team daily while they are hospitalized. The results of these tests will be forwarded to the clinical team responsible for the hospital care of the participant. Participants who are not randomized to empiric immediate initiation of anti-TB therapy but who later receive anti-TB therapy based on a new TB diagnosis or clinical suspicion will receive either conventional WHO-recommended weight-based dose anti-TB therapy plus standard care or sepsis-specific dose anti-TB therapy plus standard care according to their randomization.

The detailed complete physical exam will include HEENT (head, eyes, ears, nose, and throat), neck, chest, cardiovascular, abdomen, extremities, skin, and neurologic exam, as well as GU exam as culturally appropriate.

The focused physical exam will be directed at current symptoms and complaints with a targeted physical exam by study physicians at a minimum.

For each study participant, chest x will be obtained

All routine clinical tests as specified on the schedule of events will be performed at the local site laboratory: Kilimanjaro Christian Medical Center, Tanzania

Haematology

CBC monitoring will consist of haemoglobin, hematocrit, red blood cells (RBC), mean corpuscular volume (MCV), white blood cell count (WBC), differential WBC, absolute neutrophil count (ANC), absolute lymphocyte count, absolute monocyte count, absolute eosinophils, and platelets.

HIV confirmatory testing and viral load measurements will be performed at baseline

Chemistry

Serum creatinine, sodium, potassium, HCO3, and LFTs (AST, ALT, total bilirubin, albumin) will be monitored at the site laboratory. Serum aliquots of 0.5-1mL will be frozen at-80ºC. Estimated creatinine clearance can be obtained using the Modification of Diet in Renal Disease (MDRD) Study equation (57):

GFR (mL/min/1.73 m^2) = 186 x $(S_{cr})^{-1.154}$ x $(Age)^{-0.203}$ x (0.742 if female) x (1.212 for African)

The calculator at: http://www.nkdep.nih.gov/professionals/gfr_calculators

T cell Profiles

CD4 profiles (CD4 absolute, CD4%, CD8 absolute, CD8%, and CD4:CD8) will be performed at the local DAIDS-approved site laboratory.

Microbiology

Blood for standard bacterial and mycobacterial culture (10mL)

Urine for urinary lipoarabinomannan (~5 mL) and bacterial culture

Sputum (2mL) for Xpert Ultra, AFB staining and mycobacterial culture

Taqman Array Card PCR for Febrile Illness Pathogens testing

Investigators will collect 5 mL of whole blood to be stored at -80^{o}C for this research laboratory assay which will be done at Kilimanjaro Clinical Research Institute affiliated with Kibong'oto Infectious Diseases Hospital and the Kilimanjaro Christian Medical Center Hospital in Tanzania.

For participants randomized to the immediate empiric anti-TB groups (conventional dose and sepsis-specific dose), blood will also be collected on day 2 for PK measurement. A 6 ml red-top tube of venous blood will be drawn at 1, 2, 4 and 6 hours after anti-TB medication administration. The serum will be separated and stored at -80^{o}C for testing in those ultimately confirmed to have TB. Testing will be done in batches after shipment to the University of Virginia and subcontracting laboratory, the Infectious Diseases Pharmacokinetics Laboratory (University of Florida).

Currently, the best practice for the management of sepsis in sub-Saharan Africa is not known. Accordingly, supportive care including intravenous fluids and diagnostic evaluation and therapeutics beyond those provided by the study will be determined by the attending non-study affiliated clinical team. The study team will perform a daily chart review for each study participant while they are hospitalized and record the findings of any additional diagnostic procedures that are performed by the clinical team responsible for the patient, (e.g., ultrasound results).

Safety assessment

Daily while admitted, the participant is visited by the research nurse who will dispense the interventional therapies as directed. These encounters will also serve as an opportunity for the participant to report any concerns. Regular visits with the study doctors will occur

as stated in the Schedule of Activities. All follow-up visits will include a review of systems and medications and a physical examination with measurement of vital signs. Blood-based laboratory assessments for toxicity monitoring will be conducted weekly while the participant is admitted, or sooner if needed based on concerns reported by the participant or noted by the medical team. Once discharged, the participant will have another blood draw at 28 days for toxicity monitoring. If symptoms are reported by the participant, a detailed investigation will be conducted; AEs will be assessed as detailed in the study protocol and manual of procedures (MOP)

3. ETHICAL CONSIDERATIONS

3.1. Ethical Clearance

The study is approved by the National Health Research Ethics Committee on 29-04-2021 with ethical clearance. No NIMR/HQ/R.8a/Vol.IX/3664 dated 29th April 2021

3.2. Insurance

The study participants are insured through the National Insurance Corporation OF Tanzania (NIC) via the study titled A randomized clinical trial of early empiric anti-Mycobacterium tuberculosis therapy for sepsis in sub-Saharan Africa, protocol No. 20-0027 The cover is valid until 14-12-2023 with policy no. CDT 34/12/2020 and the amount of insurance is TSH 23,000,000.

3.3. Informed Consent

Informed consent version 1.0 was approved by the ethics committee on 29-04-2021.

3.4. Patient Information Leaflet

Patient information leaflet version No. 1.0 was provided as approved by the ethics committee on 29-04-2021.

3.5. Payment

The study participants are receiving the token amounting to TZS 15,000 as remuneration for their time and inconveniences.

4. WHAT ARE THE BENEFITS OF BEING IN THE STUDY?

The study participants will benefit from the study in either of the following: -

a. Getting additional test results such as blood counts and urine results.
b. Additional medical attention that you receive from the research team (nurse/doctor), including additional education about the nature of sepsis, HIV and/or TB disease and how it impacts you and your family.

c. Participants who receive TB medicine may have improved health outcomes at the 28 days and 6-month marks. All participants are likely to have urine- and sputum-based TB tests performed more quickly than people who do not participate in the study.

5. ARE THERE ANY POTENTIAL BENEFITS TO OTHERS THAT MIGHT RESULT FROM THE STUDY?

The study could help doctors in other areas of the country (and around the world) where HIV and TB are widespread, to learn how to better treat patients who have sepsis and improve their chances of surviving the disease.

6. WHAT ARE THE RISKS OF THE STUDY

Medications given in this study may cause side effects. Participants who are randomly assigned to receive standard or sepsis-specific TB medicine may experience the following common symptoms including, but not limited to nausea, vomiting, abdominal pain, and nerve damage that causes a loss of sensation or movement in part of the body. A less likely, yet more serious side effect includes liver damage. Doctors will monitor all patients' liver health regularly and will provide treatment for any symptoms as needed, including taking away the study drug, if necessary.

Pain or discomfort from the needle stick used for blood draws. Sometimes this can lead to bruising. Very rarely, an infection can develop when the blood is taken. This is no different than routine medical care. To minimize the chances of these risks, only experienced nurses and/or doctors will be asked to do this procedure.

Loss of confidentiality: We will take great care to protect your information by using it only for our research purposes. Only a part of the research team will have access to information such as your name; this information will be kept in a locked and secure location and will not be released to others outside the team.

Details on treatment and/or management of participants and their disease condition(s) after completion of the trial (Post-trial medicine access) if provided

The patients are insured twelve months of treatment from the day they are discharged from the hospital (after 28-days of treatment)

7. PRE-CLINICAL STUDIES (IF APPLICABLE)

N/A

8. HUMAN EXPERIENCE (CLINICAL STUDIES) IF APPLICABLE

N/A

9. PHYSICAL, CHEMICAL, AND PHARMACEUTICAL PROPERTIES AND FORMULATION OF THE INVESTIGATIONAL MEDICINAL PRODUCT OF DRUG SUBSTANCE (VACCINES AND DRUGS ONLY)

N/A

9.1. Drug Substance(s)

9.1.1. Description

N/A

9.1.2. Name(s)

N/A

9.1.3. Structural Formula and Molecular Formula

N/A

9.1.4. Physical-Chemical Properties

N/A

9.1.5. Drug Substance Stability

N/A

9.2. Drug Product

9.2.1. Drug Product Formulation

N/A

9.2.2. Placebo Formulation (In case applicable)

N/A

9.2.3. Drug Product Stability

N/A

9.2.4. Drug Product Storage

N/A

10. BENEFIT-RISK ASSESSMENT AND CONCLUSION

Based on the data provided, the current state of knowledge regarding an investigational product, including the non-clinical and clinical information that is currently available, is sufficient to support the proposed clinical trial and compliance with Good Clinical Practice (GCP), and the anticipated benefits of conducting the trial justify the risks associated with its use when done by the approved protocol and ethical principles that have their origin in the Declaration of Helsinki

11. POST-APPROVAL UPDATES

11.1. Amendment applications

Reference number	Date submitted	Change Requested	Recommendation	Granting date

PART 5: CHANGE HISTORY

Version number	**Date**	**Description of update**	**Section(s) Modified**	**Approval date**

12. REFERENCES:

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