PHARMACOVIGILANCE AND CLINICAL TRIALS DIVISION

CLINICAL TRIAL APPLICATION PUBLIC ASSESSEMENT REPORT

PART 1: ADMINISTRATIVE DETAILS

Title of Study and Protocol Version: A phase 2 randomised, adaptive, dose-ranging, open-label trial of novel regimens for the treatment of pulmonary tuberculosis (RAD-TB) (A5409) version 1.0 dated 2 October 2023.	**Study Ref:** CT274/2024
Date of receipt of the application: 29 February 2024	
Clinical trial Phase: II	
Study Site(s): University of Zimbabwe Clinical Trial Research Centre (UZCTRC) Milton Park CRS, 31 Lawson Avenue, Harare, Zimbabwe	
Applicant/Principal Investigator name and address: Dr Pamela Mukwekwerere, UZCTRC, 15 Phillips Avenue, Belgravia, Harare, Zimbabwe	
Sponsor name and address: National Institute of Allergy and Infectious Diseases, 8757 Georgia Avenue, 12th Floor Silver Spring, MD 20910-3714	
Study duration: 16 months	
Date of Commencement (Expected or Actual):	
Clinical trial authorisation validity period: 6 May 2025 to 31 August 2026	

PART 2: SUMMARY OF EVALUATION

Study design: An adaptive phase 2 randomized, controlled, open-label, dose-ranging, platform protocol to evaluate the safety and efficacy of multidrug regimens for the treatment of adults with drug-susceptible pulmonary tuberculosis (TB).

Population: Participants with Xpert MTB/RIF positive drug-susceptible pulmonary TB, living with and without HIV, aged ≥18 years.

Study Objectives:

1. To compare MGIT liquid culture TTP slope over the first 6 weeks of treatment for each experimental treatment arm to the SOC arm.
2. To compare new Grade 3 or higher adverse events (AEs) (safety) over the first 8 weeks of treatment for each experimental treatment arm to the SOC arm.
3. To compare time to stable culture conversion by MGIT liquid culture by week 8 for each experimental treatment arm to the SOC arm.
4. To compare MGIT liquid culture TTP slope over the first 8 weeks of treatment for each experimental treatment arm to the SOC arm.

5. To compare new Grade 3 or higher AEs (safety) over 26 weeks of treatment for each experimental treatment arm to the SOC arm.
6. To compare discontinuations of anti-TB drugs for any reason prior to 8 and 26 weeks of treatment for each experimental treatment arm to the SOC arm.
7. To determine the dose- and exposure-response relationships between experimental drug estimated pharmacokinetic (PK) parameters with safety and efficacy.
8. To compare a composite of efficacy and safety outcomes using a risk-benefit approach for each experimental treatment arm to the SOC arm.
9. To compare MGIT liquid culture TTP slope over the first 6 weeks of treatment for Arms 3A-3B and Arms 4A-4B compared to Arm 2.
10. To compare durable cure by 52 weeks after treatment initiation in each experimental treatment arm to the SOC arm

Eligibility Criteria:

Inclusion Criteria

1. Pulmonary TB (among individuals either without history of prior TB treatment or with history of TB treatment more than 5 years prior to study entry), identified within 7 days prior to study entry by at least one sputum specimen positive for Mtb by Xpert. Semiquantitative Mtb results of "medium" or "high" are required [Hanrahan 2014].
   NOTE: TB diagnosis for purposes of meeting this inclusion criterion can be from a study testing laboratory or from an outside laboratory, as long as it is from a sputum sample collected within 7 days prior to study entry.
2. Pulmonary TB with documented INH susceptibility (by Line Probe Assay (LPA) or Xpert MTB/XDR or other validated molecular test) and with documented RIF susceptibility (by LPA or Xpert MTB/RIF or Xpert MTB/RIF Ultra or other validated molecular test) within 7 days prior to study entry.
   NOTE: In cases shown to be RIF and INH susceptible by molecular test, but later confirmed to be resistant to either according to phenotypic DST, the participants will be taken off study provided drugs, referred to the national TB program (NTP) or local TB clinic/provider for treatment of their TB according to local SOC, and excluded from the efficacy analyses. The documentation of INH and RIF susceptibility must be from a study testing laboratory.
3. Documentation of HIV-1 infection status, as below:
   Presence or Absence of HIV-1 infection, as documented by:
   - Any licensed rapid HIV test or HIV-1 enzyme or chemiluminescence immunoassay (E/CIA) test kit, any time prior to study entry.

   AND
   Confirmed by one of the following:
   - A second antibody test from different manufacturers or based on different principles and epitopes (combination antigen-antibody-based rapid tests may be used), or
   - HIV-1 antigen, or
   - Plasma HIV-1 RNA viral load, or
   - A licensed Western blot

   NOTE A: The term "licensed" refers to a U.S. FDA-approved kit.
   NOTE B: WHO and U.S. Centers for Disease Control and Prevention (CDC) guidelines mandate that confirmation of the initial test result must use a test that is different from the one used for the initial assessment. A reactive initial rapid test should be confirmed by either another type of rapid assay or an E/CIA that is based on a different antigen preparation and/or different test principle (e.g., indirect versus competitive), or a Western blot or a plasma HIV-1 RNA viral load.
4. For individuals with HIV: CD4+ cell count ≥100 cells/mm3 based on testing performed within 30 days prior to study entry.
   NOTE: CD4+ cell count must be obtained from a laboratory certified for protocol testing by the DAIDS Immunology Quality Assurance (IQA) Program.
5. For individuals with HIV: Currently being treated with dolutegravir-based antiretroviral therapy (ART), or plan to initiate dolutegravir-based ART at or before study week 8.

NOTE: See section 5.4.2 and Appendices I-V for a list of excluded ARV medications. Dosing of ART should be reflective of local SOC based on WHO or national guidelines, and adjusted, as needed, when given in combination with RIF-containing TB therapy.

6. Individuals age ≥18 years.
7. The following laboratory values obtained within 7 days prior to study entry at any network-approved non-US laboratory that operates in accordance with Good Clinical Laboratory Practices (GCLP) and participates in appropriate external quality assurance programs:
    - Serum or plasma alanine aminotransferase (ALT) ≤3 times the upper limit of normal (ULN)
    - Serum or plasma total bilirubin ≤2 times ULN
    - Serum or plasma creatinine ≤2 times ULN • Serum or plasma potassium ≥3.5 mEq/L
    - Serum or plasma magnesium ≥1.0 mEq/L (≥0.500 mmol/L)
    - Absolute neutrophil count (ANC) ≥1500/mm3
    - Haemoglobin ≥9.5 g/dL for individuals assigned to female sex at birth and ≥10.0 g/dL for individuals assigned to male sex at birth
    - Platelet count ≥100,000/mm3
    - Negative for hepatitis B core antibody (HBcAb) total, hepatitis B surface antigen (HBsAg)
    - Negative for hepatitis C virus (HCV) antibody (or if HCV antibody positive, must have a negative HCV PCR)

      NOTE: For hypokalaemia or hypomagnesemia, potassium and magnesium may be repleted and electrolytes rechecked once before study entry.
8. For individuals assigned to female sex at birth and who are of reproductive potential, negative pregnancy test (urine HCG or serum β-HCG) within 3 days (72 hours) prior to entry by any network-approved non-US laboratory or clinic that operates in accordance with GCLP and participates in appropriate external quality assurance programs.

   Individuals assigned to female sex at birth, who are of reproductive potential, and who participate in sexual activity that could lead to pregnancy must agree to use at least two of the following forms of birth control while receiving TB study medications and for 12 months after stopping study medications:
    - Male or female condoms
    - Diaphragm or cervical cap (with spermicide, if available)
    - Intrauterine device (IUD) or intrauterine system (IUS)
    - Hormone-based birth control (e.g., oral contraceptives, Depo-Provera, NuvaRing, implants)

   NOTE: Individuals assigned to female sex at birth who are not of reproductive potential are eligible without requiring the use of contraceptives. Self-reported history is acceptable documentation of menopause (i.e., at least 1-year amenorrhoeic), hysterectomy, bilateral oophorectomy, or bilateral tubal ligation; these candidates are all considered not of reproductive potential.
9. For individuals who are assigned male sex at birth who engage in sexual activity that may lead to pregnancy in their partner must agree to either remain abstinent or use male contraceptives. They are also strongly advised to inform their non-pregnant sexual partners of reproductive potential to use effective contraceptives while the individual is on study and for 90 days after experimental treatment discontinuation.

   NOTE: Individuals assigned to male sex at birth who have undergone successful vasectomy with documented azoospermia or have documented azoospermia for any other reason, are eligible without requiring the use of contraceptive
10. For individuals assigned male sex at birth with pregnant partners, willingness to use condoms during vaginal intercourse while on study and for 90 days after experimental treatment discontinuation.
11. For individuals assigned male sex at birth, willingness to refrain from sperm donation while on study and for 90 days after experimental treatment discontinuation.

12. Documentation of Karnofsky performance score ≥60 obtained within 14 days prior to study entry.
13. Chest x-ray obtained within 14 days prior to study entry.
14. A verifiable address or residence readily accessible for visiting, and willingness to inform the study team of any change of address during study treatment and follow-up period.
15. Ability and willingness of individual to provide informed consent

Exclusion Criteria

1. More than cumulative 7 days of treatment directed against active TB for the current TB episode in the 60 days preceding study entry.
2. Current extrapulmonary TB, in the opinion of the investigator.
3. QTcF interval >450 ms within 7 days prior to study entry. NOTE: In case of hypokalaemia or hypomagnesemia, ECG can be repeated once before study entry following electrolyte supplementation.
4. History of or ongoing heart failure.
5. Personal or family history of congenital QT prolongation.
6. History of known, untreated, ongoing hypothyroidism.
7. History of or ongoing bradyarrhythmia.
8. History of torsade's de pointes.
9. Current Grade 2 or higher peripheral neuropathy. NOTE: Peripheral neuropathy assessment must be obtained within 7 days prior to study entry.
10. Other medical conditions (e.g., diabetes, liver or kidney disease, blood disorders, chronic diarrhoea), in the opinion of the site investigator, in which the current clinical condition of the participant is likely to prejudice the response to, or assessment of, treatment.
11. Pregnant or breastfeeding or planning to become pregnant within the next 12 months.
12. Weight <35kg
13. Unable to take oral medications.
14. Taking any of the prohibited medications as described in section 5.4.2 and the appendices for the investigational agents.
15. Known allergy/sensitivity or any hypersensitivity to components of investigational agents or their formulation.
16. Active drug or alcohol use or dependence; or mental illness (e.g., major depression) that, in the opinion of the site investigator, would interfere with adherence to study requirements.
17. Taking an investigational drug or vaccine within 30 or more days prior to study entry.

Vulnerable/High Risk Groups

None

Informed Consent, Decision-making & Confidentiality

Shona and English Informed Consent Forms were provided which were satisfactory.

Scientific and Technical Issues

The study design was found to be scientifically sound. The justification for the study was acceptable and follow up procedures were satisfactory. All scientific and technical aspects were satisfactory.

Other materials, documents and study instruments (Patient recruitment materials, Questionnaires)

Recruitment materials, and participants open ended interview questionnaires were satisfactory.

Clinical Trials/Study Medicines

Study medicines

1. Isoniazid manufactured by Oxalis and acquired from Macleods Pharmaceuticals
2. Pyrazinamide manufactured by Oxalis and acquired from Macleods Pharmaceuticals

3. Ethambutol manufactured and acquired from Macleods Pharmaceuticals
4. Linezolid manufactured and acquired from Macleods Pharmaceuticals
5. Rifampicin manufactured and acquired from Macleods Pharmaceuticals
6. Pretomanid manufactured by Viatris (Mylan) and donated by the Global Alliance for Tuberculosis Drug Development ("TB Alliance")
7. Sutezolid manufactured by Piramal Pharma Limited and provided by the Global Alliance for Tuberculosis Drug Development ("TB Alliance")
8. TBI-223 manufactured by Piramal Pharma Limited and provided by the Global Alliance for Tuberculosis Drug Development ("TB Alliance")
9. Bedaquiline manufactured by Johnson and Johnson and provided by the Global Alliance for Tuberculosis Drug Development ("TB Alliance")

The justification for the study products was acceptable.

Summary of review of:

1. Quality
2. Safety
3. Efficacy

Quality, safety, efficacy and benefit risk analysis data were assessed and were satisfactory.

Application Review Process

The application was reviewed under the normal pathway.

Status after review:

The clinical trial was authorised on the 6th of May 2025.

PART 3: OVERALL COMMENTS AND CONCLUSION:

The Principal Investigator (PI) was required to address queries raised by the MCAZ Pharmacovigilance and Clinical Trials Committee after review of the application. The PI addressed all the queries and was authorised, with approval of the Secretary for Health and Child Care, to conduct the trial subject to the contents of the application and the following conditions:

1. Reporting of all serious adverse events to MCAZ;
2. Submission of all amendments to the protocol for approval by MCAZ;
3. Submission of a progress report of the clinical trial by the 31st of January annually;
4. Submission of the final report and copy of any publication of the clinical trial prior to publication of results;
5. In compliance with the current Good Clinical Practices (cGCP) and all other relevant MCAZ guidelines;
6. Submission of the completed indemnity form for conducting clinical trials to the Director-General prior to commencement of the clinical trial;
7. Expiry date of this authorisation is 31 August 2026.

Name of 1st Evaluator: R. Manyevere Signature:  Date: 03/09/2025

Name of 2nd Evaluator: L. Chirinda Signature:  Date: 03/09/2025