SUMMARY EVALUATION REPORT TEMPLATE

Study Title: Six weeks of daily rifapentine vs. a comparator arm of 12-16-week rifamycin-based treatment of latent M. tuberculosis infection: assessment of safety, tolerability and effectiveness
NDA CTA Number: CTA 0262
Protocol No. TBTC Study 37
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Institution /Trial Site: Uganda-Case Western Reserve University Research Collaboration
Sponsor: U.S. Centers for Disease Control and Prevention (CDC)
TBTC Division of TB Elimination US CDC
REC of record: Joint Clinical Research Centre REC
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Study background and Rationale

The global burden of Latent *M. tuberculosis* infection (LTBI) is enormous, with approximately one-quarter to one-third of the world's population infected. Modeling studies have demonstrated that widespread use of effective LTBI treatment would have a profound effect on decreasing the global TB burden. A 9-month course of isoniazid (9H) is highly efficacious in preventing LTBI from progressing to TB disease, but its effectiveness is limited by treatment completion rates of 30-64%. Treatment of LTBI in low and medium TB burden countries is an essential component of the World Health Organization (WHO)'s End TB Strategy. Given the efficacy plus high treatment completion rates of current short-course regimens, they are highlighted in WHO guidelines for treatment of LTBI. To improve TB control worldwide, even shorter treatment for LTBI that is affordable, effective, safe, and well-tolerated is a global priority.
The safety and tolerability of RPT at doses of 600 mg daily and higher (up to 1,200 mg) have been evaluated in a phase II clinical trial. However, in that trial, RPT was administered as part of combination therapy, and the trial was conducted in adults with TB disease. There are no phase II trials that have evaluated the safety and tolerability of rifapentine 600 mg administered daily (alone) for 6 weeks in patients with TB or LTBI.

General objective / Study aims

To compare the safety and effectiveness of a six-week regimen of daily rifapentine (6wP, the experimental arm) with a comparator arm of 12-16 weeks of rifamycin-based treatment of latent M. tuberculosis infection (LTBI)

Primary Objectives and Outcome Measures

1. Compare the safety of daily 6wP to a comparator arm of 12-16 week rifamycin-based treatment (3HP, 3HR, or 4R) for the prevention of TB in persons > 12 years old with LTBI.

2. If safe, compare the effectiveness of daily 6wP to a comparator arm of 12-16 week rifamycin-based treatment (3HP, 3HR, or 4R) for the prevention of TB in persons > 12 years old with LTBI

The primary outcome is as follows;

- Safety: Drug discontinuation due to adverse drug reaction (ADR) associated with 6wP and the rifamycin-based comparator arm (3HP, 3HR, or 4R).
- Effectiveness: Culture-confirmed TB in participants > 18 years old and culture-confirmed or clinical TB in participants < 18 years old.

Secondary Objectives and Outcome Measures

Among those treated with 6wP vs. the comparator arm (3HP, 3HR, or 4R), compare the:

1. Proportion who complete assigned treatment (tolerability)
2. Proportion with drug discontinuation for any reason
3. Proportion with any grade 3, 4, or 5 (i.e., death) adverse event during the time period of 6 months after enrollment
4. Proportion with any grade 3, 4, or 5 (i.e., death) adverse event associated with study drug (ADR)
5. Proportion who have died for any reason
6. Proportion with hepatitis and non-hepatotoxic systemic drug reactions
7. Proportion with culture-confirmed or clinical TB regardless of age
8. Proportion with TB among those who complete assigned therapy (efficacy)
9. Safety, tolerability, and effectiveness among participants with human immunodeficiency virus (HIV) infection.
10. Safety, tolerability, and effectiveness in participants < 18 years old

Among those treated with 6wP, compare the:

11. Safety, tolerability, and effectiveness to each regimen in the comparator arm: 3HP, 3HR, 4R.
12. Proportion with resistance to rifamycins or isoniazid among persons who develop TB to each regimen in the comparator arm: 3HP, 3HR, 4R

Study Design

The study will be an open label, multi-center, phase III randomized controlled non-inferiority clinical trial with 2 arms. Participants will receive daily 6wP (the experimental arm) or a 12-16 week rifamycin-based regimen (3HP, 3HR, or 4R, the comparator arm) for the prevention of TB in persons > 12 years old with LTBI and at increased risk of progression to TB.

Study Population

Persons with LTBI living in low, moderate and high tuberculosis (TB) incidence settings who are at increased risk of progression to TB and require treatment of LTBI

Eligibility Criteria

Inclusion Criteria:

1. Non-pregnant, non-breastfeeding persons > 12 years old. Persons of childbearing potential who are not surgically sterilized must agree to practice an adequate method of contraception (barrier method or non-hormonal intrauterine device) or abstain from heterosexual intercourse during study drug treatment.
2. Persons with LTBI who do not have evidence of TB disease and are at increased risk of progression to TB.
3. Willingness to provide signed informed consent, or parental permission and participant assent.

Exclusion criteria:

1. Failure to document positive IGRA or TST
2. Current confirmed culture-positive or clinical TB.
3. Suspected current TB. Includes cases in which active TB cannot be eliminated as a possibility (by the site investigator)
4. TB resistant to any rifamycin in the source case
5. A history of treatment for > 7 consecutive days with a rifamycin or > 30 consecutive days with INH within 2 years prior to enrollment.
6. A documented history of completing an adequate course of treatment for TB disease or LTBI in a person who is HIV-seronegative.
7. History of allergy or intolerance to rifamycins.

8. Serum alanine aminotransferase (ALT; SGPT) or serum aspartate aminotransferase (AST; SGOT) > 5x upper limit of normal among persons in whom baseline ALT or AST is determined+.
9. HIV-seropositive and on antiretroviral therapy that cannot be given with rifampin or rifapentine due to drug-drug interactions.
10. Receiving concomitant medications that are known to be contraindicated with any study drug.
11. Persons who are currently pregnant, breastfeeding, or intend to become pregnant within 120 days of enrollment.
12. Weight < 25 kg.

Study Duration

The study will last for about 6 years with each enrollee treated and followed up for a total of 2 years.

Investigational Medicinal Product

Rifapentine (RPT) 600 mg daily x 6 weeks (6wP)

Study Arms

Arm I: Daily 6wP (the experimental arm)
Arm II: 12-16-week rifamycin-based regimen (3HP, 3HR or 4R – the comparator arm)

Sample size

250 eligible participants

Evaluator's Risk/Benefit Assessment:

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