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Protocol Title: A Phase 3, randomized, double-blind, placebo-controlled, multicenter, clinical trial to assess the prophylactic efficacy, safety, and immunogenicity of the investigational M72/AS01E-4 Mycobacterium tuberculosis (Mtb) vaccine when administered intramuscularly on a 0,1-month schedule to adolescents and adults

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We use this protocol and it's working

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Abstract

Background: Tuberculosis (TB), caused by *Mycobacterium tuberculosis* (Mtb), remains the leading cause of death from a single infectious agent. The Bacille Calmette-Guérin (BCG) vaccine is currently the only licensed TB vaccine; however, it offers little to no protection against pulmonary TB in adults. The investigational M72/AS01E-4 vaccine, developed by GSK, has shown promising results in Phase 2b clinical trials.
Design: This is a Phase 3, randomized, double-blind, placebo-controlled, multicenter clinical trial to evaluate the prophylactic efficacy, safety, and immunogenicity of the investigational M72/AS01E-4 vaccine. The vaccine will be administered intramuscularly on a 0- and 1-month schedule to adolescents and adults aged 15 to 44 years.
Participants will be randomized into two groups: one receiving M72/AS01E-4 and the other receiving a placebo (0.9% NaCl), with both administered intramuscularly in the deltoid muscle—preferably in the nondominant arm. The trial includes three cohorts: IGRA-positive, IGRA-negative and People living with HIV (PLHIV)
This Phase 3 trial aims to confirm previously observed efficacy in the pahse2b trail of IGRA-positive, HIV-negative individuals and to generate safety and immunogenicity data in both IGRA-positive and IGRA-negative participants, including PLHIV.
ClinicalTrials.gov Identifier: NCT06062238

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Eligibility Criteria

2 **Inclusion criteria:**

- Participant must be 15 to 44 years of age (inclusive), at the time of signing the consent or assent.
- Capable of giving informed consent or informed assent (as appropriate). For participants below the age of consent, the participant's parent, or legally authorized representative (LAR) will be required to sign a statement of informed consent, in addition to the minor's signed statement of assent.
- In the opinion of the investigator, can and will comply with the requirements of the protocol (e.g., completion of diary cards as applicable, and return for follow-up visits).
- Agree to actively stay in contact with the trial site for the duration of the trial for the participants own safety.
- Agree to provide updated contact information as necessary, and have no current plans to relocate from the trial area for the duration of the trial.
- Healthy, or with preexisting stable disease, as established by medical history and physical examination and as determined by the investigator.

- Negative sputum Xpert Ultra or similar assay result at screening.
- Both males and females are included. Females are included with restrictions. Females must either be of non-childbearing potential, defined as pre-menarche, have a history of either current tubal ligation, hysterectomy, or ovariectomy, or post-menopause, or, if she is of childbearing potential, she has practiced abstinence from penile-vaginal intercourse or adequate contraception for 28 days prior to vaccination, has a negative pregnancy test on the day of screening and the day of first vaccination, and agrees to continue abstinence or adequate contraception until 2 months after the second dose of trial intervention.
- HIV-negative test result at screening (IGRA-Positive Cohort and IGRA-Negative Cohort only).
- HIV Cohort only: Participants with documented HIV infection who fulfill all of the following criteria:

1. Have reactive anti-HIV antibody at screening.
2. Have been on antiretroviral therapy (ART) for at least 3 consecutive months at screening and agree to remain on ART throughout the trial.
3. Have documented HIV Ribonucleic acid (RNA) <200 copies per milliliter (/mL) at screening.
4. Have Cluster of differentiation (CD)4+ cell count ≥200 cells/microliter (µL) at screening.
5. Have had Tuberculosis preventive therapy (TPT) in the past and are not receiving TPT at the time of screening, according to the judgment of the investigators.
6. Have an IGRA-positive or negative result at screening.

Exclusion criteria:

- Current TB, or history of TB or treatment for TB disease.
- Clinical suspicion of pulmonary TB at screening, defined as a participant presenting with one or more of the following signs or symptoms: unexplained cough, unexplained fever, night sweats, unintentional weight loss, hemoptysis, pleuritic chest pain.
- Any current medical, psychiatric, occupational, or substance abuse problems that, in the opinion of the investigator, will make it unlikely that the participant will comply with the protocol, or that will interfere with the assessments or the safety of the participant.
- Any confirmed or suspected immunosuppressive or immunodeficient condition resulting from disease (e.g., invasive, or malignant cancers), other than HIV infection in the HIV Cohort.
- Known bleeding disorder that is considered a contraindication to intramuscular injection or phlebotomy.
- Any cytotoxic drugs or administration of medications known to have a major impact on the immune system, as determined by the investigator, within 90 days prior to Day 1. These include immune globulin, blood, or blood products, potent immunosuppressants and immunomodulators, and systemic corticosteroids (exceeding 20 mg/day prednisone equivalent). Inhaled, topical, and intra-articular corticosteroids are allowed.

- Planned receipt of blood, or blood products during the trial period.
- Receipt or planned receipt of any vaccine in the period starting 28 days before, and ending 28 days after, each dose of the trial vaccine.
- History of previous administration of an experimental Mtb vaccine including M72/AS01E in a previous trial.
- History of allergy or hypersensitivity to the trial intervention, excipients, or related Substances.
- An indeterminate IGRA test result at screening
- Female participants with any one of the following conditions: currently pregnant or lactating; having positive serum pregnancy test during the screening window, positive urine pregnancy test on Day 1, planning a pregnancy within 2 months after completion of the vaccination series.
- Only in the HIV Cohort: Safety laboratory values at screening that are of concern, based on investigator's judgment. Note that preexisting stable chronic disease will not necessarily lead to exclusion, especially if laboratory values are graded as mild.
- Participation in an interventional clinical trial in which the participant has been or will be exposed to an investigational product (pharmaceutical product or device), within 28 days prior to signing consent or assent, or during the trial period.
- Individuals who are acting as personnel for this trial, or who have immediate family members (brother, sister, child, parent, or the spouse/partner) who are acting as personnel for this trial.
- Child in Care, defined as a child who is under the care (control or protection) of an agency, organization, institution or entity by the courts, the government body, acting in accordance with powers conferred in them by law or regulations. The definition of a child in care can include a child who is cared for by foster parents or living in a care home or institution, provided that the arrangements fall within the definition above. The definition of a child in care does not include a child who is adopted or has an appointed LAR.
- Participants who had a Tuberculin Skin Test (TST) within 6 months prior to Day 1.

Intervention

3 The trial will include 2 groups (M72/AS01E-4 group and placebo group). Participants will receive 2 doses of either M72/AS01E-4 or placebo based on randomization, administered intramuscularly (IM) in the deltoid muscle, preferably in the nondominant arm, given approximately one month apart.
M72/AS01E-4: A 0.5 mL dose of M72/AS01E-4 contains 10µg M72, reconstituted with AS01E-4, a GlaxoSmithKline (GSK) proprietary adjuvant system containing 25 µg MPL (3-Odesacyl-4-monophosphoryl lipid A, produced by GSK), and 25 µg QS-21 (Quillaja Saponaria Molina, fraction 21).
Placebo: A 0.5 mL dose contains 0.5 mL normal saline (0.9% NaCl).

Randomization

4 Participants in each of the cohorts (IGRA-positive, IGRA-negative, and HIV) will be randomized 1:1 to receive M72/AS01E-4 or placebo, stratified by site, age group, and sex.
The participants in the HIV Cohort will also be stratified by IGRA status.

Efficacy Outcomes and Procedure for Sputum Sample Collection

5 **Laboratory-confirmed pulmonary TB** case is defined as a participant with suspected pulmonary TB presenting with one or more of the following signs or symptoms: unexplained cough, unintentional weight loss, hemoptysis, unexplained fever, night sweats, pleuritic chest pain; who has least 2 positive Mtb test results (positive Mtb culture and/or positive test result from Xpert Ultra or similar assay, excluding "trace positive"), from the same or from different sputum samples collected during the 3 suspected TB visits, preferably within a 7-day time frame, before initiation of TB treatment.
Less stringent laboratory-confirmed pulmonary TB case is defined as a participant with suspected pulmonary TB presenting with one or more of the following signs or symptoms: unexplained cough, unintentional weight loss, hemoptysis, unexplained fever, night sweats, pleuritic chest pain; who has at least 1 positive Mtb culture or at least 1 positive result from Xpert Ultra or similar assay (excluding "trace positive"), from the same or from different sputum samples collected during the 3 suspected TB visits, preferably within a 7-day time frame, before initiation of TB treatment.