Project Brief: Gates MRI-TBV02-301 (M72)

Full Title of Study/Programme	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
Technical Focus Area	Research (Adolescents and Adults)
Rationale	Purpose and Rationale: In the previously completed Phase 2b trial, the investigational M72/AS01E-4 Mtb vaccine conferred approximately 50% protection at 36 months (49.7%: 95% confidence interval [CI]: 2.1–74.2) against developing laboratory-confirmed pulmonary tuberculosis disease (TB) when administered to adults who were interferon gamma release assay (IGRA)-positive, and human immunodeficiency virus (HIV)-negative. This Phase 3 trial is designed to confirm the previously observed efficacy in IGRA-positive, HIV-negative people, as well as to generate safety and immunogenicity data in IGRA-positive and negative adolescents and adults, including people living with HIV (PLHIV).
Primary Objectives	To evaluate the vaccine efficacy (VE) of M72/AS01E-4 in the prevention of laboratory-confirmed pulmonary TB among IGR A positive participants without HIV infection (IGRA-Positive Cohort) in the per-protocol (PP) analysis set.
Secondary Objectives	To evaluate the VE of M72/AS01E-4 in the prevention of Mtb infection among the IGRA-Negative Cohort in the PP analysis set.
	To evaluate the VE of M72/AS01E-4 in the prevention of laboratory confirmed pulmonary TB among the IGRA-Negative Cohort in the PP analysis set.
	To evaluate the VE of M72/AS01E-4 in the prevention of laboratory confirmed pulmonary TB among the HIV Cohort in the PP analysis set.
	To evaluate the VE of M72/AS01E-4 in the prevention of less stringently defined laboratory-confirmed pulmonary TB among the IGRA Positive Cohort in the PP analysis set.
Secondary Safety Objective	To evaluate the safety and reactogenicity following administration of M72/AS01E-4 vaccine or placebo.

Secondary Immunogenicity Objective	To assess the humoral immunogenicity of M72/AS01E-4 vaccination.
Primary Endpoint/Outcome	The primary efficacy analysis will be the performed on the PP analysis set. For the primary efficacy objective of vaccine efficacy in the prevention of laboratory-confirmed pulmonary TB, the null hypothesis of this trial is that the VE of M72/AS01 E-4 against laboratory confirmed pulmonary TB in the IGRA-Positive Cohort in the PP analysis set is ≤ 10% (i.e., H0: VE against prevention of TB [VE(D)] ≤ 0.10). VE(D) is defined as (1-hazard ratio)*100% (M72/AS01E-4 vs. placebo) VE(D) will be estimated using a Cox proportional hazard regression model with treatment group as a fixed effect and adjusting for stratification factors, based on IGRA-positive participants without HIV infection (IGRA-positive Cohort) in the PP analysis set, with cases counted over a period starting 1 month post dose 2 and lasting through EoT. The trial will be considered to meet the primary efficacy objective if the corresponding 95% CI of VE(D) rules out 10%, i.e., the lower bound is above 10%.
Secondary Endpoint/Outcome	For the secondary objective of VE for preventing Mtb infection (VE(I)) in participants who have a negative IGRA, without HIV infection, the analysis will be conducted based on accruing the number of disease events required for the primary efficacy analysis. This analysis will be conducted using the PP analysis set. VE(I) will be estimated as (1-hazard ratio)*100% (M72/AS01E-4 vs. placebo), using a Cox proportional hazard regression model with treatment group as a fixed effect and adjusting for stratification factors, with cases counted over a period starting 1 month post dose 2 and lasting up to EoT, where infection/sustained conversion is defined as a negative IGRA test at screening, followed by at least 2 consecutive IGRA-positive results at attended scheduled visits.
	VE(D) will be analyzed in the IGRA-negative participants without HIV infection (IGRA Negative Cohort) and separately, in the virally-suppressed, antiretroviral-treated participants with HIV (HIV Cohort), using the same method as used for the primary analysis. A sensitivity analysis of VE(D) will use the same method as used for the primary analysis, but will be based on a less stringent case definition
Secondary immunogenicity Endpoints	M72/AS01E-4 seropositive rates and GMCs of M72/AS01E-4-specific antibodies at Day 1, Month 1, Month 2, Month 7, Month 13, Month 37, and Month 49 among each of the IGRA-Positive Cohort, IGRA-Negative Cohort, and HIV Cohorts in the PPI analysis set will be calculated by treatment group, Cohort, and time point, with exact 95% CIs. To formally compare GMCs between treatment groups, a linear mixed effect model will be used, including fixed effects for treatment and time, and a random effect for participant. Individual M72-specific IgG antibody titers will be log-transformed. GMCs and 95% CIs will be estimated from the model as the back-transformed

	mean estimate. To formally compare seropositivity rates between treatment groups, a generalized linear mixed effect model will be used, including fixed effects for treatment and time, and generalized estimating equations will be used to account for the dependence in the longitudinal binomial response data. Formal comparisons before and after trial intervention (e.g., geometric mean ratios [GMR], differences in seropositivity rates) will be generated from the model results with 95% CIs. Summaries will include immune responses at pre- and post-trial intervention immunology time points and change from pre-vaccination to post-vaccination time points.
Study Design (R)	This is a Phase 3, randomized, double-blind, placebo-controlled, multicentre, clinical trial to assess the prophylactic efficacy, safety, and immunogenicity of the investigational M72/AS01E-4 Mtb vaccine when administered intramuscularly on a 0,1- month schedule to adolescents and adults (15 to 44 years of age).
Study arms (R)	The trial will include 2 groups (M72/AS01E-4 group and placebo group).
Study population (R)	15-44 Years inclusive.
Study sample size (R)	Approximately 20000 participants will be screened and enrolled.
Follow up/duration	4 and half years plus or when 110 confirmed pulmonary TB cases are accrued.
Study/Programme sites	Wits RHI, Multi Site (Worldwide)
Study/Programme duration	Project started Feb-2024 expected to run 4 and half years plus.
Intervention (R)	(M72/AS01E-4 group and placebo group). Participants will receive 2 doses of either M72/AS01E-4 or placebo based on randomization, administered IM in the deltoid muscle, preferably in the nondominant arm, given approximately 1 month apart.
Operations	Study open to screening and enrollments 5-Mar-2024.
Investigators	**Prof Lee Fairlie, Principal Investigator** **Dr Faeezah Patel, Sub Investigator** **Dr Elizea Horne, Sub Investigator** **Dr Mrinmayee Dhar** **Dr Jeanne Coetzee** **Tiffany Seef**
Other Partners & Collaborators	IQVIA, BARC,
Sponsors/Donors	Bill and Melinda Gates Medical Research Institute (Gates MRI)
Linked Sub Studies and post grad projects	None yet
Publications/key presentations to date	None yet
Progress Update as at Mar-2026	• Screened: 766 • Enrolled: 306 / 61,2% • Screen failed: 459 / 60% • Discontinued: 01 • Withdrawn consent: 10 • LTFU: 07- 485

	• Deceased: 01 • Total Off study: 19 • On follow-up: 287 • Pregnancies :8 Enrolment closed 16-Apr-25.
Frequency of donor narrative report	6 monthly
Overall Study/Project Contact	Dr Hermien Gous ,Prof Lee Fairlie.
Briefing owner and date	Rorisang Komane