Project Brief: BCG Revax Gates MRI

Full Title of Study/Programme	A Randomized, Placebo Controlled, Observer-Blind, Phase IIb Study to Evaluate the Efficacy, Safety, and Immunogenicity of BCG revaccination in Healthy Adolescents for the Prevention of Sustained Infection with *Mycobacterium tuberculosis*
Technical Focus Area	Research (Adolescents)
Rationale	Recently published results from a Phase 2 study evaluating Bacillus Calmette-Guerin (BCG) revaccination in healthy adolescents in South Africa suggest that BCG revaccination of adolescents 12 to 17 years of age may lead to prevention of sustained *Mycobacterium tuberculosis* (*Mtb*) infection (POSI) over a 24 month period following vaccination, as assessed by sustained QuantiFERON-TB Gold® in-Tube (QFT GIT) conversion (ie, initial QFT conversion and remaining QFT positive at three and six months post conversion) (Nemes, 2018). This current study intends to *i)* confirm that BCG revaccination protects against sustained *Mtb* infection in a larger independent study, *ii)* assess the duration of protection through at least 48 months post revaccination, *iii)* evaluate BCG revaccination in children ten years of age and above and *iv)* identify/validate biomarkers that correlate with risk for or protection against transient and/or sustained *Mtb* infection, as assessed by QuantiFERON plus (QFT) assay, which is the newer version of the QFT GIT assay.
Primary Objectives	To demonstrate the efficacy of BCG revaccination against sustained *Mtb* infection versus placebo in previously BCG vaccinated QFT negative, healthy adolescents (event-driven analysis)
Secondary Objectives	To evaluate the durability of efficacy of BCG revaccination against sustained *Mtb* infection versus placebo in previously BCG vaccinated, QFT negative, healthy adolescents To evaluate the safety and reactogenicity of BCG revaccination in previously BCG vaccinated, QFT negative healthy adolescents To evaluate the efficacy and durability of efficacy of BCG revaccination against primary *Mtb* infection post vaccination versus placebo in previously BCG vaccinated, QFT negative healthy adolescents
Primary Endpoint/Outcome	Sustained QFT conversion based on an IFN-γ concentration cut-off value of 0.35 IU/mL (initial conversion and QFT-positive at 3- and 6-months post conversion)

Secondary Endpoint/Outcome	Sustained QFT conversion based on an IFN-γ concentration cut-off value of 0.35 IU/mL (initial conversion and QFT-positive at 3- and 6-months post conversion) with a minimum follow-up of 36- and 48-months post vaccination Solicited adverse events (AEs) through 7 days post vaccination Unsolicited AEs through 28 days post vaccination All serious adverse events (SAEs) and adverse events of special interest (AESIs) through Month 6 Serious adverse drug reactions (Serious ADRs) through the end of the study Primary QFT conversion based on a QFT IFN-γ concentration cut-off value of 4 IU/mL at the time of primary endpoint analysis, and after a minimum follow-up of 36- and 48-months post vaccination, based on IFN-γ concentration cut-off value of 4 IU/mL (initial conversion only)
Study Design (R)	This is a randomized, placebo controlled, observer-blind, phase IIb study with two arms (BCG vaccine and saline placebo). An independent data monitoring committee (IDMC) will be established to oversee the safety of this study.
Study arms (R)	Intervention Groups: 2 study groups (BCG group and placebo group) will each receive a single intradermal (ID) injection:
Study population (R)	Adolescents 10-18 Years of age
Study sample size (R)	Approximately 5625 participants will be screened to enrol and randomize 1800 healthy participants across all sites.
Follow up/duration	Each participant will remain in the study for a minimum of 4 years (or 4.5 years for participants converting to QFT positive at Month 48). Enrolment is expected to take place over a 1-year period. However this has been extended to Sep 2021 to compensate time lost due to COVID lockdown.
Study/Programme sites	B Part, Emavundleni, WRHI, CAPRISA, SATVI
Study/Programme duration	Project started Dec-2019 to end mid 2024
Intervention (R)	BCG vaccine SSI / Normal saline
Operations	
Investigators	Dr Lee Fairlie, Principal Investigator Dr Masebole Masenya, Sub Investigator Dr Faeezah Patel, Sub Investigator Dr Elizea Horne, Sub Investigator
Other Partners & Collaborators	AQVIA, BARC,
Sponsors/Donors	Bill and Melinda Gates Medical Research Institute (Gates MRI)
Linked Sub Studies and post grad projects	
Publications/key presentations to date	
Progress Update as at Jul 2020	Enrolled: 165 On study: 162 Withdrawal 03
Frequency of donor narrative report	
Overall Study/Project Contact	Dr Hermien Gous (hgous@wrhi.ac.za)
Briefing owner and date	Prof Lee Fairlie Oct-2020 reviewed Dr Hermien Gous Mar 2021