Title of the study - Bacille Calmette Guerin (BCG) Revaccination of Healthy Adolescents for the Prevention of Mycobacterium Tuberculosis Sustained Infection

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Statistical Analysis Plan: GatesMRI-TBV01-201

Study Title:	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*
Study Number:	Gates MRI-TBV01-201
Study Phase:	IIb
Sponsor:	Bill and Melinda Gates Medical Research Institute (Gates MRI) One Kendall Square, Building 600, Suite 6-301 Cambridge MA 02139
Version	Final
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Confidentiality Statement

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1 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	adverse event
ADR	adverse drug reactions
AESI	adverse event of special interest
Ag	antigen
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Class
BCG	Bacille Calmette Guerin
BMI	body mass index
BUN	blood urea nitrogen
CAPRISA	Centre for Aids Programme of Research in South Africa
CD4	cluster of differentiation 4
CFB	change from baseline
CI	confidence interval
CoP	correlate of protection
CoR	correlate of risk
COVID-19	Coronavirus Disease 2019
CRO	contract research organization
CSR	Clinical Study Report
CTMS	Clinical Trial Management System
eCRF	electronic case report form
DAIDS	Division of Acquired Immune Deficiency Syndrome
EDC	Electronic Data Capture
HIV	human immunodeficiency virus
HR	hazard ratio
ICS	Intracellular cytokine staining
ID	Intradermal

IDMC	Independent Data Monitoring Committee
IFN-γ	interferon gamma
IL-2	interleukin 2
IL-22	interleukin 22
ITT	intention to treat
IU	international units
IVRS	interactive voice response system
KM	Kaplan-Meier
mITT	modified intention to treat
MedDRA	Medical Dictionary for Regulatory Activities
mL	milliliter
Mtb	*Mycobacterium tuberculosis*
NK cells	natural killer cells
NTM	Non-tuberculosis mycobacteria
PC	post conversion
PD	protocol deviation
PP	Per Protocol
PT	Preferred Term
QFT	QuantiFERON
RHI	Reproductive Health and HIV Institute
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	Severe Acute Respiratory Syndrome-Coronavirus-2
SATVI	South African Tuberculosis Vaccine Initiative
SD	standard deviation
SI	International System of Units
SOC	System Organ Class
TB	tuberculosis
TLF	table, listing, figure

TNF-α	tumor necrosis factor alpha
VE	vaccine efficacy
WHO	World Health Organization

2 INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the framework of the statistical analyses, including the planned tables, listings, and figures to assess the efficacy, safety, and immunogenicity of Bacille Calmette Guerin (BCG) revaccination in healthy adolescents for the prevention of sustained infection with *Mycobacterium tuberculosis* (*Mtb*). The details in this SAP are based on Protocol Version 7, dated 17 Jul 2023.

3 TRIAL OBJECTIVES AND ENDPOINTS

Objectives	**Endpoints**
Primary	
To demonstrate the efficacy of BCG revaccination against sustained *Mtb* infection versus placebo in previously BCG vaccinated QuantiFERON (QFT) negative, healthy adolescents (event-driven analysis).	Sustained QFT conversion (at least 118 events) based on positive QFT test results (initial conversion and QFT-positive at 3- and 6-months post conversion [PC]).
Secondary	
To evaluate the durability of efficacy of BCG revaccination against sustained *Mtb* infection versus placebo in previously BCG vaccinated QFT negative, healthy adolescents.	Sustained QFT conversion based on positive QFT test results (initial conversion and QFT-positive at 3- and 6-months PC) with a follow-up of 36- and 48-months post vaccination.
To evaluate the safety and reactogenicity of BCG revaccination in previously BCG vaccinated, QFT negative healthy adolescents.	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.
Exploratory	
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 QFT conversion at the time of primary endpoint analysis, and after a follow-up of 36- and 48-months post vaccination, using an alternative definition of conversion as a change in IFN-γ concentration from <0.35 IU/mL to ≥4 IU/mL (initial conversion only) [IU = international units]
Exploratory (continued)	

Objectives	**Endpoints**
To evaluate the efficacy and durability of efficacy of BCG revaccination against primary and sustained *Mtb* infection post vaccination versus placebo in previously BCG vaccinated, QFT negative healthy adolescents, based on alternate QFT IFN-γ concentration cut-off values.	Primary and sustained QFT conversion at the time of primary endpoint analysis, and after a follow-up of 36- and 48-months post vaccination, based on a definition of primary and sustained conversions using exploratory IFN-γ concentration threshold values.
To assess the immunogenicity of BCG revaccination	Frequency of *Mtb-, BCG-* and/or non-tuberculous mycobacteria (NTM)-specific cluster of differentiation (CD)4 T cells expressing one or more cytokines, e.g., IFN-γ, tumor necrosis factor (TNF)-α, interleukin (IL)-2 and/or IL-22 by intracellular cytokine staining (ICS).
To describe host attributes and host responses to vaccination To describe host attributes and host responses following QFT conversion To explore and/or develop candidate correlates of risk (CoRs) and correlates of protection (CoPs) To detect and describe incident tuberculosis (TB) disease To characterize *Mtb* isolates	Genetic markers and sequences Transcriptomics and gene expression markers Proteomics Antibody analyses Cellular analyses (e.g., natural killer cells [NK cells], B cells, T cells, myeloid cells) Incidence of laboratory-confirmed TB disease Signs & symptoms of incident TB disease Mtb drug sensitivity and/or Mtb genetic markers
To describe (Coronavirus Disease 2019) COVID-19 among study participants who present with suspected COVID-19 To describe the serostatus of Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2) infection	Signs and symptoms of illness, by treatment group SARS-CoV-2 nucleic acid amplification from nasal or oropharyngeal sample Serological test results for SARS-CoV-2, by treatment group

4 STUDY DESIGN CONSIDERATIONS

4.1 Study Design

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.

Intervention model: Participants will be randomly assigned with equal probability to one of two groups in parallel for the duration of the study.

Intervention groups: BCG group will receive one dose of BCG vaccine (Bacillus Calmette-Guerin SSI, Danish strain 1331, live attenuated 2-8 x 10^5 colony forming units [cfu] in a 0.1 mL volume intradermal [ID] injection). Placebo group will receive one dose of saline control in a 0.1 mL volume ID injection.

Masking: participants, sponsor, investigators, contract research organization (CRO) clinical team, laboratory, and clinical staff will be blinded to intervention (BCG vs placebo) until primary endpoint analyses are completed. Note: BCG vaccine recipients, clinical staff, and any study team members that have access to the Electronic Data Capture (EDC) database or sites may inadvertently become unblinded as soon as a BCG lesion develops. As detailed in a separate unblinding plan, members of the study team (clinical team and sponsor) will be formally unblinded following completion of the analyses to support the primary objective, but laboratory staff will remain blinded until all laboratory studies have been completed to support secondary and exploratory objectives.

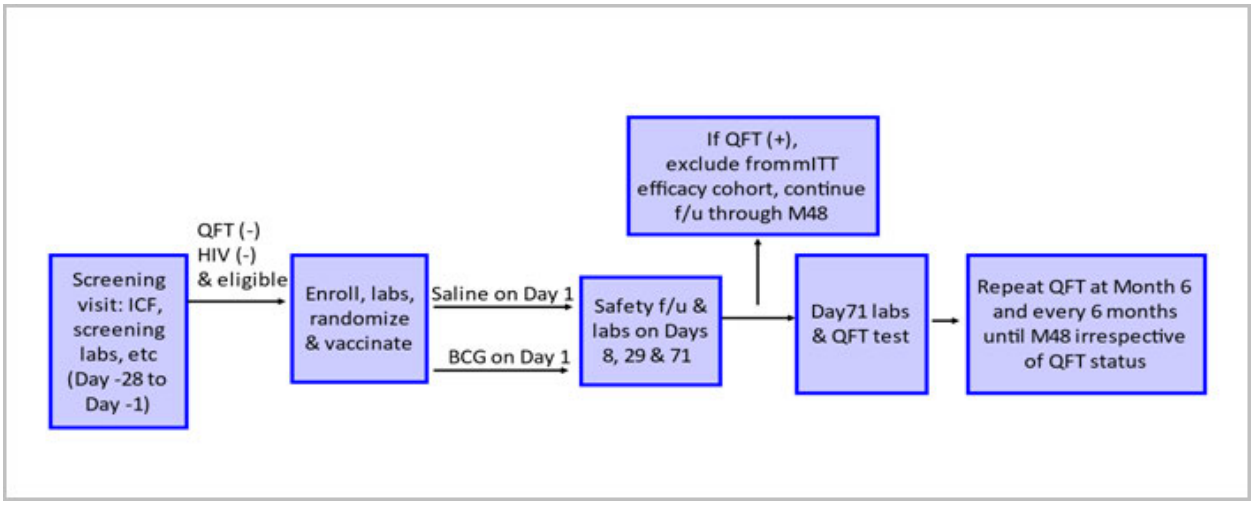
Approximately 1800 healthy participants will be randomized 1:1 to receive either a single dose of BCG vaccine intradermally or a single dose of normal saline placebo intradermally on Day 1. Randomization will be stratified by age group (10-11 years old, 12-14 years old and > 14 years old), sex, study site, and school cluster within the South African Tuberculosis Vaccine Initiative (SATVI) site to account for expected differences in incidence rates. The overall proportion of participants randomized in the youngest strata (10-11 years old) and outside the Western Cape province will be actively monitored and capped at approximately 10% and 20% of the randomized study population, respectively, minimizing risk of study failure by maximizing consistency of study assumptions with available literature data. A subset of 80 participants (the first eighty 10-12-year-old participants who are enrolled at the SATVI site) will be considered for whole blood intracellular cytokine staining (ICS) analysis to assess frequency of *Mtb*-, BCG, or non-tuberculous mycobacteria (NTM)-specific cluster of differentiation 4 (CD4) T cells expressing one or more cytokines, e.g., interferon gamma (IFN)-γ, tumor necrosis factor alpha (TNF-α), interleukin 2 (IL-2) and/or IL-22.

Wash-out period: A 70-day wash-out period will be used to identify participants who become infected with *Mtb* just prior to or soon after enrollment. Participants must have a QFT negative result at Day 71 (or if missed or not feasible, at the next feasible visit). Participants with positive or indeterminate QFT positive results at Day 71 will not be asked to return for Post Conversion (PC) Day 28 and PC Day 84 visits and will be excluded from the Modified Intent-to-Treat (mITT) analysis population (Section 5.1) but will be followed for safety and efficacy to End-of-Study.

Total duration of study participation: Each participant will remain in the study for a minimum of 4 years. Enrollment, originally expected to take place over a 1-year period, was extended due to COVID-19 pandemic-related restrictions. Participants will be asked to consent to extended passive follow-up for TB disease (using the National TB Programme electronic TB register) for up to 10 years post end of study.

Study sites: Five or more sites in South Africa will participate in this study (Appendix 3).

Figure 1: Outline of Study Procedures



A detailed Schedule of Activities is included in Appendix 1 and in Appendix 2.

4.2 Planned Analyses for the Study

4.2.1 Primary Analysis

The primary analysis of the primary efficacy endpoint will occur when at least 118 sustained *Mtb* infection events have accrued in the mITT analysis population (see definition in Section 5.1). *Mtb* infection is defined in this protocol as QFT conversion from a negative to positive test result, as per the manufacturer's QFT-GIT package insert: QIAGEN, QuantiFERON®-TB Gold Plus (QFT®-Plus) Package Insert, July 2018.

The data reviews to confirm the decision to move forward for the primary analysis database freeze will be detailed in a separate document. Agreement on the list of tables, listings, and figures (TLFs) outputs to be provided and the method of distribution will be outlined in a separate document prior to unblinding for analysis.

In addition to the analysis of the primary efficacy endpoint (Section 9.1), exploratory efficacy analyses based on alternative definitions of QFT-conversion (with different IFNγ concentrations), as well as safety analyses generated for IDMC reviews (Section 4.2.3) will also be performed at the same time as the primary efficacy endpoint analysis.

4.2.2 Secondary Analysis

A secondary analysis will be performed to assess the durability of efficacy against (sustained) *Mtb* infection post vaccination. The analysis will be performed subsequently to the initial primary analysis after all participants included in the mITT efficacy population (Section 5.1) have least 36 months of follow-up or have prematurely discontinued the study. Agreement on specific outputs and method of distribution will be outlined in a separate document. However, depending on the timing of the sustained conversion events, the 36-month analysis may be combined with the primary analysis (and only one analysis covering all relevant endpoints will be conducted).

4.2.3 Independent Data Monitoring Committee (IDMC)

An Independent Data Monitoring Committee (IDMC) will be established for the Gates MRI-TBV01-201 study as an independent advisory committee commissioned and charged with the responsibility of evaluating safety data at regular intervals and on an ad hoc basis as necessary, to ensure the rights and safety of the study participants are safeguarded and that potential risks to participants are minimized. The IDMC will also review results from the primary data analysis (after at least 118 sustained *Mtb* infection events occur in the mITT efficacy population) and the secondary analysis (after all participants have 36 months of follow-up).

The independent IDMC will operate according to the IDMC charter. The IDMC structure, participants and other details are provided in the charter.

The IDMC will meet and review blinded and unblinded data as outlined in the IDMC charter. The following outputs will be generated for each IDMC meeting:

- Overall participant status by site, including the number of participants screened, enrolled, completed, and discontinued.
- Critical and major protocol deviations.
- Demographic and key baseline characteristics.
- Study visits entered.
- Overall summary of AEs.
- AEs by System Organ Class (SOC), Preferred Term (PT) and highest grade.
- Summary of respiratory adverse events by PT.
- Serious adverse events (SAEs) by SOC and PT.
- Serious adverse drug reactions (ADRs) by SOC and PT.
- Unsolicited AEs by SOC and PT.
- Adverse events of special interest (AESIs) by SOC and PT.
- Diary card data.
- Injection area and general body symptoms by maximum severity within 7 days after vaccination as solicited on diary card.
- Injection area and general body symptoms on each day after vaccination (solicited on diary card).
- Summary of injection site examination by visit.

- Summary of screening hematology and chemistry laboratory parameters.
- Pregnancy test results and pregnancy outcomes (by participant listings).
- SARS-CoV-2 results by visit and COVID-19 information for participants with suspected COVID-19 (by participant listings)
- QuantiFERON (QFT) Quantitative and Qualitative Results by-participant.
- Overall summary of participants with events contributing to pausing rules.

The pausing rules for the study are included in Protocol Section 7.1.1 and summarized below:

1. Anaphylaxis with or without bronchospasm within 4 hours of injection, indicative of an immediate hypersensitivity reaction to the study injection.
2. 1% of the safety population and at least two participants experience an SAE judged as related to BCG vaccination by the investigator.
3. 20% of participants and at least ten participants experience a Grade 3 or higher event related to BCG vaccination, as judged by the investigator, with the exception of expected local BCG reactions or local injection site reactions that decrease to < Grade 3 within 48 hours.

4.2.4 Final Analysis

A final analysis will be performed after all participants have either 48 months of follow-up or completed/prematurely discontinued the study, all safety clinical assessments and concomitant medication data through to the final study visits have been entered and reviewed and all queries related to the data have been addressed.

Additional exploratory analyses including but not limited to host characteristics, *Mtb* isolate characterization, correlate of protection (CoP) and correlate of risk (CoR) analyses may be conducted separately by Gates MRI. These exploratory analyses are outside the scope of this SAP, hence no details for these analyses are described in this document.

4.3 Efficacy Endpoints

4.3.1 Primary Efficacy Endpoint

Mtb infection is defined in this protocol as QFT conversion from a negative to positive test result, as per the manufacturer's QFT-GIT package insert.

QFT assays will be performed at:

- Screening (used to determine eligibility),
- Day 71 or at the first in-person visit after Day 71 if Day 71 visit was missed or if Day 71 result was not available.
- Every 6 months (counting from Day 1) through Month 48
- Participants who have QFT conversions from a negative to positive test result will have an additional QFT assay three months post initial conversion (Day 84 PC visit).

The primary efficacy outcome measure is sustained QFT conversion in the mITT efficacy population (Section 5.1), defined as primary QFT conversion from QFT-negative to QFT-positive, and sustained

positive QFT tests at both 3- and 6-months after initial (primary) conversion. The initial positive QFT test must be observed after a negative QFT result at Day 71 or at the first in-person visit after Day 71 for which a QFT result is available if the Day 71 visit was missed or if the QFT result at the Day 71 visit was not available.

Due to the required washout period (Section 4.1) and the many Day 71 visits missed due to COVID (lockdown, site closure, etc.), the requirement for a negative QFT test result at Day 71 was extended to include results from the first in-person visit post Day 71. Therefore, throughout this document, Day 71 refers to the Day 71 study visit, or if missing, the first in-person visit post-randomization. Sustained conversion refers to three consecutive positive QFT results following the Day 71 negative QFT result as detailed above. After the initial conversion, a negative or indeterminate result at Post Conversion Day 84 and/or at the biannual visit following the initial conversion would disqualify the conversion event from being a sustained conversion. "Early QFT Reversion" is defined as a reversion from a positive QFT test result to a negative QFT test result at Post Conversion Day 84 or the biannual visit following the initial conversion.

Participants who initially convert to QFT positive at Day 71 will be excluded from the mITT analysis population and the primary endpoint analysis.

Participants who initially convert to QFT positive at the Month 48 visit will be included in the count of primary QFT conversions but will not be included in the count of sustained conversions since the Month 48 visit is the final study visit.

To assess the vaccine efficacy on this primary endpoint, an event driven analysis will be utilized (Section 9.1).

The QFT qualitative classification (negative, indeterminate, or positive) at each visit will be determined by the laboratory as per the manufacturer's QFT-GIT package insert:

Table 1 QFT Algorithm from the QuantiFERON-TB Gold Plus Package Insert

Nil (IU/mL)	TB Ag1 minus Nil (IU/mL)	TB Ag2 minus Nil (IU/mL)	Mitogen minus Nil (IU/mL)	QFT Result
≤8.0	≥0.35 and ≥25% of Nil	Any	Any	Positive
	Any	≥0.35 and ≥25% of Nil		
	<0.35 or ≥0.35 and <25% of Nil	<0.35 or ≥0.35 and <25% of Nil	≥0.50	Negative
	<0.35 or ≥0.35 and <25% of Nil	<0.35 or ≥0.35 and <25% of Nil	<0.50	Indeterminate
>8.0	Any			

Ag= antigen.

4.3.2 Secondary Efficacy Endpoint

For the secondary efficacy objective (durability of efficacy at 36 months and at 48 months), the endpoints are defined as for the primary efficacy endpoint (i.e., sustained QFT conversion [Section 4.3.1]).

Two mITT durability analyses will be performed: the first one after all participants have at least 36 months of follow-up (or have discontinued the study early) and the second one at study completion when all participants have 48 months of follow-up (or have discontinued the study early) (Section 9.3). For the secondary analysis after 36 months of follow-up, all participants will have a data cutoff date corresponding to their Month 36 visit date or their early discontinuation date if it occurred prior to Month 36 visit.

4.3.3 Exploratory Efficacy Endpoints

Exploratory efficacy analyses endpoints will include the following:

- Initial (primary) QFT conversion using an alternative definition of QFT positive/negative derived based on a concentration cut-off value of 4 IU/mL in the QFT assay similarly to the procedure described in Table 1 for the 0.35 IU cut-off (initial conversion only). Primary (initial) QFT conversion corresponds to the first QFT conversion from a negative to positive test result. This endpoint will be evaluated using the mITT analysis population (Section 5.1) at the time of the primary analysis, the secondary analysis, and at the final analysis.

- Initial (primary) and sustained QFT conversion for various thresholds ranging from 0.36 IU/mL to 10 IU/mL. Each threshold cut-off will be used to assess initial conversion similarly to the procedure described in Table 1 for the 0.35 IU cut-off. Sustained conversions for the various thresholds will be a subset of the sustained converters identified for the primary endpoint for which the initial conversion is assessed based on

the various threshold values. Both initial (primary) and sustained QFT conversions based on various thresholds will be evaluated using the mITT analysis population (Section 5.1) at the time of the primary analysis, the secondary analysis, and at the final analysis.

- End of trial sustained conversion defined as QFT conversion from a negative to positive test result (as per the manufacturer's QFT-GIT package insert) any time post Day 71 with all QFT results after the initial conversion also positive. This endpoint will be evaluated using mITT analysis population (Section 5.1) at the time of the final analysis.

- Early QFT Reversion is defined as QFT reversion from a positive to a negative test result at the post conversion Day 84 visit and/or at the biannual visit following initial conversion. This endpoint (rate of Early QFT Reversions) will be evaluated using the mITT analysis population (Section 5.1) at the time of the primary analysis.

A subset of the exploratory efficacy analyses may be performed at the time of the primary analysis (Section 4.2.2) and at the time of the secondary analysis (Section 4.2.3). These will be identified prior to database freeze and/or unblinding for the respective analyses.

All other exploratory objectives (e.g., related to immunogenicity or biomarkers) will be analyzed by Gates MRI. No details of these analyses of these objectives are described within this SAP. Specific objectives and hypotheses related to these analyses will be documented and reported in a separate scientific and statistical analysis plan(s), and results documented outside the clinical study report (CSR).

4.4 Safety Endpoints

Safety outcomes include:

- Solicited AEs through 7 days post vaccination (based on the review of diary card data),
- Unsolicited AEs through 28 days post vaccination,
- SAEs through 6 month post vaccination,
- AEs of special interest through 6 month post vaccination
- Serious adverse drug reactions (ADRs) through the entire study duration
- Laboratory safety tests
- Pregnancy outcomes
- SARS-CoV-2 serostatus

5 STUDY POPULATIONS

5.1 Analysis Populations

Sponsor authorization of the assigned analysis populations is required for the primary analysis, the secondary analysis (after all participants have at least 36 months of follow-up/have discontinued early), and for the final analysis. Agreement and authorization of participants included/excluded from the Per Protocol (PP) population for the primary analysis will be obtained prior to any unblinding activities. Reason(s) for exclusion from the PP population will be applied consistently across all participants with detailed documentation.

	Description
Enrolled population	All participants who provide informed consent.
Randomized population	All participants randomly assigned to study intervention. A participant will be programmatically included in this analysis population if the participant has a randomization number and date of randomization. Participants will be analyzed according to the intervention they were randomized to.
Modified intention to treat (mITT) efficacy population	All participants randomly assigned to study intervention who received the study intervention, and are QFT negative at the Day 71 visit, or at the first study visit post Day 71 for which a QFT result is available if the Day 71 study visit was missed or the Day 71 QFT result was not available [1]. Participants will be analyzed according to the intervention they were randomized to.
Per Protocol (PP) efficacy population	All participants in the mITT population who did not substantially deviate from the protocol procedures and who received the treatment to which they were randomized. Participants who substantially deviated will be identified prior to database lock and unblinding [2]. Participants will be analyzed according to the intervention they were randomized to.
Safety	All participants randomly assigned to study intervention who received the study intervention. Participants will be analyzed according to the intervention they received.

[1] Because of COVID-19, many study participants enrolled less than 70 days prior to the enrollment pause on 19 March 2020, may have missed their Day 71 visit. Participants who missed Day 71 visit are eligible for inclusion in the mITT population if their first QFT result post randomization is negative and are excluded from the mITT population if their first QFT result post randomization is not negative.
[2] Protocol deviations will be evaluated individually by the sponsor to decide whether it has basis to exclude a participant from the PP population.

5.2 Subgroups

The consistency of results with respect to the primary and secondary objectives will be examined within the following subgroups using the mITT analysis population:

- Study site / school quintile (refer to Appendix 3)
- Sex (Male, Female)
- Age Group (10-11 years, 12-14 years, >14 years)
- Method of reporting previous BCG vaccine (scar, self-reporting, or written documentation)

6 CHANGES IN CONDUCT OR PLANNED ANALYSES FROM THE PROTOCOL

ITT efficacy analysis population was mentioned in the Protocol and has been removed from the SAP as no specific analyses are planned based on the ITT population.

7 OVERALL STATISTICAL CONSIDERATIONS

7.1 Research Hypotheses

Primary: Revaccination with BCG reduces the risk of sustained *Mtb* infection (defined for this protocol as sustained QFT conversion) versus placebo in previously BCG vaccinated, QFT negative healthy adolescents.

Secondary (hierarchical):

- Revaccination with BCG reduces the risk of sustained *Mtb* infection versus placebo in previously BCG vaccinated, QFT negative healthy adolescents, with vaccine efficacy (VE) durability that lasts at least 36 months.
- Revaccination with BCG reduces the risk of sustained *Mtb* infection versus placebo in previously BCG vaccinated, QFT negative healthy adolescents, with VE durability that lasts at least 48 months.

7.2 Determination of Sample Size

The primary analysis will be triggered after the number of required events to achieve 90% power with a 1-sided alpha of 2.5% has been accrued. If the true vaccine efficacy is 45%, at least 118 events are required to achieve 90% power or greater.

The proposed sample size was determined based on targeting a relatively high probability (~80%) of obtaining the required 118 sustained conversion events within 3.5 years of the study start. The probability of obtaining the required 118 sustained conversion events within 3 and 3.5 years of study start are shown in Table 2 for sample sizes ranging from 600 to 800 in the mITT efficacy population, under the assumptions described herein. Due to COVID-19 related restrictions, it will likely take longer to complete enrollment and to reach the number of events needed for the primary analysis.

After accounting for the expected 7% participants to be ineligible for the mITT efficacy population due to a positive QFT assay result at Day 71, the table shows that randomizing approximately 800 participants to each treatment group is sufficient to detect a true VE of at least 45% under the specified assumptions, resulting in ~80% probability to accrue the required number of events (118) within 3.5 years of study initiation when the attack rate is as low as 8%. Since it is expected that approximately 12% of the population enrolled will be 10- or 11-year-old adolescents, where there is limited information on the attack rate and potential VE, a further inflation of the required 800 participants per group by 12% resulted in a final proposed sample size of 900 participants per group, or a total of 1800 participants.

Approximately 6720 participants will be screened to enroll and randomize up to 2150 participants.

Table 2: Sample Size Requirements to Ensure 75%-80% Probability of Performing the Primary Analysis within 3.5 years

N/group mITT Efficacy Population	Attack rate = 10%		Attack rate = 8%		N/group Randomized*	N/group (+12%)**	Final N (Total)
	Prob (analysis in ≤ 3 yrs)	Prob (analysis in ≤3.5 yrs)	Prob (analysis in ≤ 3 yrs)	Prob (analysis in ≤3.5 yrs)			
600	4.3	75.4	<0.1	5.4	646	723	1446
650	21.9	94.0	0.2	20.8	699	783	1566
700	50.4	99.4	0.8	52.7	753	844	1688
750	**77.0**	**>99.9**	**5.3**	**80.2**	**807**	**904**	**1808**
800	93.0	>99.9	20.5	94.5	861	964	1928

Assumes equal randomization (randomization ratio 1:1)
Probability analysis occurs within 3 and 3.5 years (yrs) based on 2000 simulations, assuming 1 yr accrual, 70% of primary infection remain sustained, 5% annual drop-out rate

- *Assumes 7% removed from those randomized due to QFT + result at Day 71
- ** Assume additional 12% of participants will be 10 or 11 year olds, where we have limited information on attack rate and potential VE

7.3 General Conventions

Frequency (n) and percentages (%) will be used to summarize categorical variables; mean, standard deviation (SD), median, minimum, and maximum will be used to summarize continuous variables.

Decimal precision for summary statistics of continuous variables will be based on the mean value. Typically, the mean will contain one more decimal place than actual values but the decimal precision may vary in order to obtain an organized and understandable table or listing. The median will contain the same number of decimal places as the mean; the standard deviation will contain one more decimal place than the mean; and the minimum and maximum will contain one less decimal place than the mean.

Unless otherwise specified, the denominators for percentages will be the number of participants in each treatment group with non-missing data for the variable of interest.

The day of receiving study intervention is defined as Study Day 1 or Day 1. All other study days will be computed relative to Day 1.

- For events on or after Day 1, study day for a particular event or visit will be calculated as $Date_{event} - Date_{Day\ 1} + 1$.
- For events before Day 1, study day for a particular event will be calculated as $Date_{event} - Date_{Day\ 1.}$ Day 0 will not be used.

All data will be presented by treatment group.

For a given parameter (e.g. y) change from baseline (CFB) will be calculated as $y_t - y_b$ where y_t is a given participant's value t days post-baseline and y_b is a given participant's value at baseline. CFB will be computed for participants with both a baseline value and a post-baseline value. If a participant is missing a post-baseline value, there will be no imputation of the missing value. Only observed case data will be used for post-baseline analyses. For parameters which are not fully numeric, CFB will not be computed and values will be summarized in a listing.

7.4 Baseline Definition

Unless otherwise specified, baseline is defined as the last non-missing assessment (scheduled or unscheduled) prior to the study vaccination. In the case where the last non-missing assessment and the reference start date coincide, that assessment will be considered pre-vaccination (baseline). For example, if laboratory assessments fall on the date of study vaccination and the time of the assessment is missing, the applicable assessment will be considered as baseline. However, adverse events starting on the reference start date (date of study vaccination) will be considered as treatment-emergent, therefore post-baseline.

7.5 Handling of Missing Data

Missing data will not be imputed. Handling rules of indeterminate or missing QFT results are included in Section 9.1.

7.6 Pooling Strategy for Study Sites

This study is being conducted at multiple sites in various regions within South Africa. One site, Site 103, will enroll participants from various schools in the region.

Generally, all schools/regions will be pooled by intervention for analysis purposes. Because it is expected that enrollment at some sites or schools by socio-economic status quintiles might be low, the analysis of the primary efficacy will not include study site or school in the model. Efficacy analyses will be presented by subgroup = site/school quintile. Details are provided in the relevant SAP sections.

7.7 Visit Windows/Unscheduled Visits

Visit windows will not be applied for the purposes of identifying sustained conversion.

Primary and secondary efficacy endpoints analysis based on the mITT and PP efficacy populations will use the visits designation (e.g., Day 84 post conversion) as the visit date in the study database, regardless of when the actual visit took place within the protocol-specified window (i.e., including out-of-window visits).

Missed visits due to COVID-19 related restriction with telephone contact performed will be documented as protocol deviations.

For participants who converted (QFT negative to QFT positive), the 1-month post initial QFT conversion visit (labeled as Post QFT Conversion Day 28 on the eCRF) will be relabeled to Month (x + 1 month),

where x is the visit where the participant originally converted to QFT positive, for display purposes of the relevant assessments (i.e., focused physical examination, TB symptom screen). For example, if the participant converted to QFT positive at Month 3, then the Post QFT Conversion Day 28 visit will be relabeled to Month (3 + 1), therefore Month 4.

Similarly, the 3-month post initial QFT conversion visit (labeled as Post QFT Conversion Day 84 on the eCRF) will be relabeled to Month (x + 3 months) for display purposes of the relevant assessments (i.e., focused physical examination, TB symptom screen, and QFT assay).

Unscheduled visits will not be included in by-visit summaries or analyses but may contribute to the baseline value and worst post-baseline assessments. In the case of a retest (i.e., when the same visit number is assigned), the latest available test result as provided in the data transfer for that visit/time point will be used for by-visit summaries. Unscheduled QFT assessments may contribute to the determination of initial and sustained conversions.

7.8 Multiplicity

The primary analysis will be triggered when at least N=118 sustained *Mtb* infection events (defined as QFT conversion from a negative to positive test result, as per QuantiFERON-TB Gold Plus Package Insert) in the mITT efficacy population have accrued.

The primary efficacy endpoint (Section 4.3.1) will be analyzed using a log-rank test, stratified by sex and age group (10-11 years old, 12-14 years old, and >14 years old) to evaluate differences in the distributions of event times between the BCG vaccination and placebo groups. The two durability analyses will be performed: the first one after all participants in the mITT efficacy population have either prematurely discontinued the study or have at least 36 months of follow-up (secondary analysis; a data cutoff date will be established at the date of each participants Month 36 visit) and the second one after all participants in the mITT efficacy population have either prematurely discontinued or have completed 48 months of follow-up at the end of study (final analysis).

Therefore, the following null hypotheses: $H_{01} \rightarrow H_{02} \rightarrow H_{03}$ will be assumed:

- H_{01} corresponding to the primary analysis (at least N=118 sustained QFT conversion events in the mITT efficacy population have accrued): $S_{s,BCG}(t) = S_{s,Pbo}(t)$
- H_{02} corresponding to the secondary analysis (when all participants have prematurely discontinued the study or have at least 36 months of follow-up): $S_{s,BCG}(t) = S_{s,Pbo}(t)$
- H_{03} corresponding to the final analysis (when all participants have prematurely discontinued the study or have completed the study with 48 months of follow-up): $S_{s,BCG}(t) = S_{s,Pbo}(t)$

for strata s=1, 2, …, 6 (6 strata = sex and age group [10-11 years old, 12-14 years old, and >14 years old]), where S(t) is the survival probability (probability that a participant's time to sustained *Mtb* infection > t).

To account for multiple testing, a step-down approach will be used to preserve the overall Type I error at a one-sided 2.5%. Specifically, if the one-sided p-value associated with the primary hypothesis H_{01} of BCG vaccine efficacy relative to placebo (p_1) is less than or equal to 0.025, the durability of the vaccine efficacy after all participants have 36 months of follow-up (H_{02}) will be formally assessed. If both H_{01} and H_{02} are rejected at one-sided 2.5% then the H_{03} will be formally assessed at one-sided 2.5%.

Once a hypothesis is not rejected, no further testing is formally permitted.

Any inferential statistics calculated for the exploratory objectives/endpoints are for exploratory/descriptive purposes only.

8 STATISTICAL ANALYSIS METHODS

A database freeze and unblinding is planned for the primary analysis (Section 4.2.2) after at least 118 sustained *Mtb* infections (defined as QFT conversion from a negative to positive test result, as per QuantiFERON-TB Gold Plus Package Insert) occur in the mITT efficacy population. An additional follow-up database freeze is planned for the secondary analysis (Section 4.2.3) after all participants have completed 36-months of follow-up or prematurely discontinued the study. A full database lock and final analysis (Section 4.2.4) is planned after all participants have completed 48 months of follow-up or prematurely discontinued the study.

Planned analyses for reporting disposition, protocol deviations, demographics, baseline characteristics, and treatment exposure are included in this section (Section 8).

Planned analyses for efficacy parameters are included in Section 9. Analysis of safety and tolerability can be found in Section 10. Other relevant data analyses/summaries are described in Section 11.

8.1 Disposition

All participants who provide informed consent will be accounted for in this study.

The number of participants screened, re-screened, number of screening failures, screening failure participants who were QFT positive at Screening, and the number of participants randomized will be summarized for all screened participants per site and overall.

Participant disposition and withdrawals (including reasons for discontinuation as provided on the electronic case report form [eCRF]) will be summarized and listed for the randomized analysis population.

A summary table containing the number of participants in each analysis population and reasons for exclusion from each analysis population will be provided.

8.2 Protocol Deviations

Protocol deviations (PDs) for this study will be documented in IBM-CD (the online study database). Although IQVIA's clinical trial management system (CTMS) was used until July 2020, IBM-CD was updated during July 2020 to include unique identifiers and to accommodate participant and site level protocol deviations. Following the data migration, the IQVIA team moved PDs documented in IQVIA CTMS to IBM-CD.

Protocol deviations will be summarized for the randomized analysis population by major deviation categories and will be included in a by-participant data listing.

Sites and all relevant parties involved were instructed to track all protocol deviations related to COVID-19 proactively. Protocol deviations due to the COVID-19 pandemic will be described in the clinical study report based on study records.

A separate by participant listing will be generated for protocol deviations related to COVID-19.

8.3 Demographics and Baseline Characteristics

Demographic data and other baseline characteristics will be summarized using descriptive statistics for the Safety population, mITT efficacy population, and the PP efficacy population.

The denominators for percentages will be the number of participants in each treatment group with non-missing data available for the variable of interest.

The following characteristics will be summarized:

- Age (years) and Age group (10-11 years, 12-14 years, >14 years)
- Sex (Male, female)
- Race (Asian, Asian Indian, Black, South African Coloured, White, Other, Mixed Race)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Reported, Unknown)
- Weight (kg)
- Height (cm)
- Body mass index (BMI) (kg/m^2)

BMI (kg/m^2) will be calculated using the following formula:

$$BMI = \frac{weight\ (kg)}{height\ (m) \times height\ (m)}$$

- Method of reporting previous BCG vaccine (scar, self-reporting, or written documentation)

Additionally, a by-participant listing will report the above listed characteristics, as well as study site / school quintile (refer to Appendix 3).

8.4 Treatment Exposure and Compliance

Participants will be administered a single dose of BCG vaccine or placebo.

The date and time of the vaccine administration will be listed for each participant. Treatment compliance is not relevant and will not be calculated. Diary completion/compliance will be calculated as described in the respective Section 10.4.

9 EFFICACY ANALYSES

9.1 Primary Analysis

The primary efficacy endpoint will be analyzed when at least N=118 sustained *Mtb* infection events (defined as QFT conversion from a negative to positive test result, as per QuantiFERON-TB Gold Plus Package Insert) in the mITT population have accrued.

The primary efficacy endpoint (sustained QFT conversion as defined in Section 4.3.1) will be analyzed using a log-rank test, stratified by sex and age group (10-11 years old, 12-14 years old, and >14 years old) to evaluate differences in the distributions of event times between the BCG vaccination and placebo groups.

Censoring and event times will be defined as follows:

- For participants with sustained QFT conversion (censor = 0), time to event will be derived in days as (date of initial conversion – date of Day 71 +1) and converted to months. Note that Day 71 here refers to either Day 71 or, if missed, the first in-person visit after Day 71. Date of initial conversion = date of a positive QFT test observed after a negative result at Day 71 or after a negative test at the first in-person visit after Day 71 if the Day 71 visit was missed.

- For participants without sustained QFT conversion (censor = 1), censoring time will be derived in days as (censoring date – date of Day 71 + 1) and converted to months. Again, Day 71 refers to either Day 71 or, if missed, the first in-person visit after Day 71.

The censoring date for participants without sustained QFT conversion is the last date at which a non-missing QFT result is available prior to the date of data cut-off. There are several scenarios in which participants may have an initial QFT conversion but fail to meet the requirements for sustained QFT conversion due to subsequent negative, missing, or indeterminate QFT results. Appendix 6 provides details on derivation of event and censoring times for all the expected possible scenarios.

Conventions for additional scenarios not covered in Appendix 6, but based on actual data may need to be considered and detailed in the ADaM specifications prior to all planned analyses. An indeterminate test result will be interpreted as negative for the derivation of a participant's time to event.

For the sustained conversion analysis based on the PP efficacy population, which is a subset of the mITT efficacy population, sustained QFT conversion including events and censoring and event times will be defined the same way as for the analysis based on the mITT efficacy population. The sustained conversion analysis based on the PP efficacy population will be performed both with and without stratification factors.

The null and alternative hypothesis in terms of the survival functions S(t) and the 6 strata: sex and age group (10-11 years old, 12-14 years old, and > 14 years old) are (Klein & Moeschberger [1997]):

H_0: $S_{s,BCG}(t) = S_{s,Pbo}(t)$, for all strata s=1, 2, …, 6 versus

H_1: $S_{s,BCG}(t) > S_{s,Pbo}(t)$, in some stratum s=1, 2, …, 6.

The primary null hypothesis will be rejected if the 1-sided p-value associated with evaluating whether the event-free distribution is longer in the BCG vaccination group relative to the placebo group is less than or equal to 0.025. SAS PROC LIFETEST will be used for this analysis (Appendix 7).

Summaries of the number and percentage of participants experiencing a sustained QFT conversion and participants censored (overall and by reason for censoring including participants who discontinue and are censored at date of discontinuation) will be provided along with median (and 95% confidence interval [CI]) time of sustained QFT conversion (displayed in months) for each treatment group.

The hazard ratio (HR) and 95% CIs will be estimated from a stratified Cox Proportional Hazards model with sex and age group (10-11 years old, 12-14 years old, and > 14 years old) as stratification variables. The primary results will be based on stratification as per interactive voice response system (IVRS).

To assess the robustness of the primary results due to the change in randomized strata, a sensitivity analysis may be performed according to their derived actual strata instead of the randomized strata, i.e. any participants mis-stratified in IVRS will be included in the stratified log-rank test using the strata based on baseline data collected in the eCRF. This analysis will be performed if >10% of participants are mis-stratified in IVRS.

The Cox-model estimate of the log-hazard ratio and its standard error will be used to construct a model-based estimate of the confidence limits on the HR. The confidence limits are first constructed for the log HR and then exponentiated to provide the corresponding confidence limits on the HR scale. In case of ties in reporting event times, the Efron option in the SAS procedure PHREG will be used.

The log HR estimate obtained from the Cox proportional hazard model is a consistent (asymptotically unbiased) estimate. However, the Cox-model based estimate of the standard error is biased when the proportional HR model assumption does not apply. Thus, if the test for the statistical significance of the coefficient associated with the interaction of survival time and treatment group is nominally significant at the 0.10 level, then the robust sandwich estimate (Li and Wei [1989]; Lachin [2000]) will be employed to provide a consistent estimate of the variance of the log HR estimated from the proportional HR model. The resulting robust confidence limits on the HR will then have the desired coverage probability even though the proportional HR assumption may not apply for the treatment effect.

Vaccine efficacy will be calculated as $VE = 1 - Hazard\ Ratio\ (\frac{BCG}{Placebo})$

The 95% CI for vaccine efficacy will be derived using the HR CI as follows:

- $VE_{\text{lower limit}} = 1 - \text{Hazard ratio}_{\text{upper limit}}$
- $VE_{\text{upper limit}} = 1 - \text{Hazard ratio}_{\text{lower limit}}$

The following information will also be summarized in tables for the mITT efficacy population and repeated for the PP efficacy population:

- Initial QFT conversions by calendar month (mITT efficacy population only).
- Sustained conversion rates with 95% confidence intervals for each treatment group. 95% CIs will be constructed based on the Miettinen and Nurminen method without stratification (Miettinen O, Nurminen [1985]).
- Overall sustained conversion incidence rates along with 95% CIs will be determined based on the total event/censoring time used as denominator. The sequence of sustained conversions will be modelled to follow approximately a Poisson process with constant intensity θ. The rate parameter θ will be estimated as λ = D/T, where $T = \sum_{j=1}^{n} t_j$ and D is the number of participants with a sustained conversion and time t_i (i=1,…n) is the time to sustained conversion if observed, or if not observed, the censored time. Conditional on T, an exact 100*(1-α)% confidence interval for a Poisson variable with parameter θT and observed value D can be obtained using an exact 100*(1-α)% confidence interval for D/T will be derived as follows:

  Lower confidence limit $L = \frac{0.5c_{\alpha/2,2D}}{T}$ for D>0, 0 otherwise,

  Upper confidence limit $U = \frac{0.5c_{1-\alpha/2,2D+2}}{T}$

  where $c_{\alpha,k}$ is the α^{th} quantile of the Chi-square distribution with k degrees of freedom.

The following figures will be presented for the mITT efficacy population and repeated for the PP efficacy population:

- Kaplan-Meier plots for time to initial conversion and time to sustained conversion, with tick marks to identify censored observations by treatment group.

Sustained conversion rates and incidence rates will be repeated by site, age, sex, and method of reporting previous BCG vaccine subgroups for the mITT efficacy population only.

Additional listings will be produced, including whether the participant had the event or not (for initial conversion, early QFT reversion, sustained conversion, and end of trial conversion), date of event/censored date, the start date, and the time to event.

9.2 Primary Endpoint: Sensitivity Analysis

QFT conversion is detected at fixed timepoints when samples are collected at in-person visits at the study sites. However, conversion may actually occur any time in the interval between planned visits. Interval censoring will be used as sensitivity analysis (based on sustained conversion) using the PROC ICPHREG procedure in SAS (Appendix 7) and data from the mITT efficacy population.

Left censoring duration in days or months is derived from the date of initial conversion. Right censoring duration in months is derived from the date of initial conversion. Left and right censoring values are dependent on the visit at which the event is identified.

Table 3. Interval Censoring Information

Visit at Which Primary Event Identified	Visit Associated with Left Censoring Value	Visit Associated with Right Censoring Value
M6	Day 71*	M6
M12	M6	M12
M18	M12	M18
M24	M18	M24
M30	M24	M30
M36	M30	M36
M42	M36	M42
M48	M42	M48

* Note: If Day 71 was missed, the first in-person visit post Day 71.

For participants who did not experience a conversion, the left censoring value will be equal to the duration from the Day 71 visit (or, if missed, the first in-person visit post Day 71) and the right censoring value will be missing.

A hazard ratio estimate, 95% CI, and p-value will be obtained from this interval censoring procedure and summarized in tables. Vaccine efficacy and associated 95% CI's will also be estimated based on these results.

To assess the rate of early infections, a summary of the number of participants who had positive QFT results at Day 71 (and were therefore excluded from the primary mITT analyses) will also be generated by the treatment group.

9.3 Secondary Analyses

To address the secondary objectives (sustained QFT conversion based on positive QFT test results in participants with a follow-up of 36- and 48-months post vaccination), two analyses will be performed to assess the durability of efficacy against sustained *Mtb* infection post vaccination.

The first secondary analysis will be performed subsequent to or at the same time with the primary analysis after all participants have had at least 36 months of follow-up (or prematurely discontinued), and the second secondary (i.e., final) analysis will be performed subsequent to the initial and the 36-month analysis after all participants have 48 months of follow-up (or prematurely). Both analyses will be based on the mITT efficacy population.

Log-rank tests, stratified by sex and age group (10-11 years old, 12-14 years old, and > 14 years old), will be used to evaluate differences in the distributions of event times between the BCG vaccination and placebo groups. Hazard ratios and 95% confidence intervals will be estimated using stratified Cox proportional hazards regression models.

If the one-sided p-value after all participants have 36 months of follow-up is less than or equal to 0.025, durability after all participants have 48 months of follow-up will be assessed. As such, durability after all participants have reached 36- and 48-months of follow-up will only be concluded if statistically significant differences in event times between the BCG vaccination and placebo arms were met at all prior time points evaluated. Failure to meet the primary or 36- month durability hypothesis will not result in a formal early stopping of the study.

9.4 Exploratory Analyses

The exploratory QFT endpoints (Section 4.3.3) will be analyzed in a manner similar to the primary endpoint.

The following summary results will be presented:

- Analyses based on the 4.0 IU/mL threshold for the initial QFT conversion where initial QFT conversion corresponds to the first QFT conversion after a negative (at or after Day 71) test result. These will be performed for both mITT and PP efficacy populations.
    - Overall initial QFT conversion rates and incidence rates, with 95% CIs for each treatment group.
    - A Kaplan-Meier plot by treatment group displaying the time to initial conversion based on 4.0 IU/mL threshold, displayed in months, measured from the vaccination date. Participants with no conversion will be censored at the date of data cut-off.
- Analyses based on a range of thresholds for the initial conversion from 0.36 IU/mL to 10 IU/mL using mITT population only.
    - Overall initial conversion rates with 95% CIs for each treatment group will be calculated for threshold values at each 0.01 increment from 0.36 IU/mL to 10

IU/mL. These pointwise estimates and 95% CIs will be plotted for the entire range of threshold values examined. A tabular presentation of the estimated conversion rates and 95% CIs will be displayed for threshold values of 0.36 IU/mL, 0.40 IU/mL, 1.0 IU/mL, 2.0 IU/mL, 3.0 IU/mL, 4.0 IU/mL, 5.0 IU/mL, 6.0 IU/mL, 7.0 IU/mL, and 10.0 IU/mL.

- Overall sustained conversion rates with 95% CIs for each treatment group will be calculated based on the subset of sustained conversion events identified in the primary analysis for which the initial conversion would have been "positive" using each alternative threshold value ranging from 0.36 IU/mL to 10 IU/mL. A tabular presentation of the estimated rates and 95% CIs will be displayed for the same threshold values as noted above for initial conversions.

- End of trial conversion rates with 95% confidence intervals for each treatment group, where end of trial conversion is defined as QFT conversion from a negative to positive (as per QuantiFERON-TB Gold Plus Package Insert) test result any time post-Day 71 with all QFT results after the initial conversion also positive.

- Kaplan-Meier plots for time to time to end of trial conversion, with tick marks to identify censored observations by treatment group

- Early QFT Reversion rates with 95% confidence intervals for each treatment group will be presented.

9.5 Other Exploratory Analyses

The SARS-CoV-2 serostatus will be summarized by time point (calendar month/year) and by treatment group.

Among participants who present with suspected COVID-19, the proportion of participants with positive nucleic acid amplification will be summarized overall, by site, and by treatment group.

10 SAFETY AND TOLERABILITY ANALYSES

Safety outcomes include:

- Solicited AEs (including solicited local injection site pain, redness, and swelling and solicited general body symptoms such as headache, fatigue /tiredness, stomach problems, and fever).

- Unsolicited AEs

- All SAEs

- Vaccination-related SAEs (serious adverse drug reactions [ADRs]).

- AEs of special interest through 6 month post vaccination
- Laboratory safety tests
- Pregnancy outcomes

10.1 Adverse Events

AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 22.0 or higher.

AE severity will be graded using the Division of Acquired Immune Deficiency Syndrome (DAIDS) Table for Grading for Intensity (Severity) of Adult and Pediatric Adverse Events Version 2.1, July 2017 as Grade 1 (Mild), Grade 2 (Moderate), Grade 3 (Severe) or Grade 4 (Potentially Life-threatening) on the eCRF.

The following reporting windows are applicable for AEs:

AE Category	Reporting Window
Solicited	Through 7 days post vaccination
Unsolicited	Through 28 days post vaccination
SAEs and AESI	Through 6 months post vaccination
Serious related AEs [ADRs]	Through the end of the study

Only AEs within the reporting window will be included within the relevant category in summary tables. All AEs will be listed, regardless of if it was reported within the applicable reporting window.

Adverse events of special interest (AESIs) are AEs that the sponsor wants to monitor carefully. The following AEs will be collected and reported and summarized as AESIs:

System Organ Class	Preferred Term
Immune system disorders	Anaphylactic reaction
General disorders	Disseminated BCG disease
Infections and Infestations	Osteomyelitis Suppurative lymphadenitis Injection site abscess
Skin and subcutaneous tissue disorders	Injection site lupus vulgaris

	Injection site keloid formation
Bone disorders	Osteitis

An AE overview table will be generated containing the frequency and percent of participants with at least 1 event as well as total number of reported events in each of the following categories (summarized by treatment group) and also the 95% CI (calculated for a single proportion using mid-p binomial option [refer to Appendix 7]):

- Any AE.
- Unsolicited AEs.
- Related AEs.
- Grade 1 AEs.
- Grade 2 AEs.
- Grade 3 or higher AEs.
- Related, Grade 3 or higher AEs.
- AEs leading to premature study discontinuation.
- AEs of special interest (AESI).
- SAEs.
- SAEs with outcome of death.
- Serious adverse drug reactions (ADRs).

Additionally, the following will be summarized by System Organ Class (SOC) and by preferred term (PT), for each treatment group:

- Incidence of AEs.
- Incidence of AEs by highest grade.
- Incidence of SAEs.
- Incidence of serious ADRs.
- Incidence of unsolicited non-serious AEs.

- AESIs

Summaries of AEs by SOC and PT will be sorted alphabetically by SOC and by decreasing frequency of PT in the BCG treatment group. If a participant has more than one AE at a given level (e.g. SOC and PT), the participant will only be counted once within that level. Missing severity grade and relationship will not be regarded as 'worst case' and will be reported as missing values in the summary tables.

10.2 Reactogenicity Data

Reactogenicity data is used synonymously with solicited AEs. The reactogenicity data collected from the paper diary will include: injection area symptoms (pain at injection site, redness and swelling), general body symptoms (headache, tiredness, stomach problems, temperature), and use of medication.

The paper diary will record reactogenicity data from Day 1 to Day 7 following vaccination. The analysis interval for reactogenicity data will be 'Any Day 1 to 7' which includes data from Day 1 to Day 7. The day of vaccination is considered as Day 1.

The diary card is used to record duration and intensity/severity (Grade 1 to 4) and largest diameter in mm of the red and swollen area of solicited injection area symptoms and general body symptoms AEs for 7 days following vaccination.

Reactogenicity data will be presented for the Safety population. The number of participants who returned the diary card, including the reason for not returning the diary card will be summarized. Participants reporting any symptoms (for both injection area symptoms and general body symptoms) on each day after vaccination will be summarized.

A listing for the diary card data will be displayed for the Safety population. Participants reporting any symptoms (for both injection area symptoms and general body symptoms) on each day after vaccination will be summarized.

The following additional summaries will be presented for the Safety population:

10.2.1 Injection Area Symptoms

The proportion of participants reporting each injection area symptom will be presented by treatment group for the safety population. For each injection area symptom, the determination of whether or not the specific symptom occurred on each day and 'Any Day 1 to 7' will be made.

For the 'Any Day 1 to 7' summary tables, the derivation of the proportion is calculated as n1/(n1+n2) where

- n1: Any Day 1 to 7 participant reports the symptom as 'mild', 'moderate' or 'severe' on any Day 1 to 7.
- n2: Participant reports the symptom as 'none' on all 7 days or as a combination of 'none' and missing on all 7 days.

Participants that report the symptom as missing on all 7 days are not included in the proportion calculations.

For redness and swelling, 'mild', 'moderate', and 'severe' categories are based on the largest diameter of the redness or swelling reported in mm and they are age-group specific:

- for participants >15 years: Mild 25 to <50mm; Moderate >=50 to <100 mm; Severe >=100 mm;
- for participants <=15 years: Mild 0 to <=25mm; Moderate >25 to <50 mm; Severe >=50 mm

(refer to the 'Site Reactions to Injections and Infusions' table in Appendix 5 of the study protocol which is based on the Division of AIDS Table for Grading the Intensity [severity] of Adult and Pediatric Adverse Events Version 2.1, July 2017). For participants > 15 years old, 'none' = largest diameter reported on the diary card<25 mm.

95% CI based on the conditional binomial Clopper-Pearson method with mid-p correction (refer to Appendix 7) will be provided.

The maximum severity (highest grading) of each local reaction within 7 days of vaccination will be derived as follows:

- =., if values are missing for all Days 1 to 7.
- =0, if the participant reports all reactions as 'None' or a combination of missing and none for all Day 1 to 7.
- =highest grade (maximum reported severity) within 7 days of vaccination if the answer is not 'None' for at least 1 day.

Results will be summarized for each local reaction reporting n (%) participants by maximum severity within each age group (>15 years and <=15 years).

Duration and Onset Day of Injection Area Symptom:

For participants experiencing any injection area symptom, the onset day (first day of the injection area symptom reported via diary relative to the vaccination) and the maximum duration (last day of symptom – first day of symptom + 1) will be derived. Resolution of the event is the last day in which the event is recorded in the diary or the date the event ends if it is unresolved during the participant diary-recording period.

The following summary results will be generated for injection area symptoms within 7 days after vaccination:

- number and percentage of participants with injection area symptom (any severity) and by severity grade

- number and percentage of participants with any injection area symptom within 7 days after vaccination
- number and percentage of participants by injection area symptom onset day
- number and percentage of participants by injection area symptom duration (number of days)
- for each injection area symptom: mean, median, Q1-Q3, and min-max for symptom duration.

10.2.2 General Body Symptoms

For each general body symptom event recorded on the diary, the following summaries and analyses will be presented similarly to injection area symptoms:

- Each general body symptom on each day (up to Day 7) after vaccination
- Each general body symptom event on 'Any Day 1 to 7' after vaccination
- Maximum severity of each general body symptom event on 'Any Day 1 to 7' after vaccination
- Maximum duration of each general body symptom after vaccination
- Any general body symptom event (including fever) on 'Any Day 1 to 7' after vaccination

Grading for fever is as follows: Mild=38.0 to <38.6°; Moderate>=38.6 to <39.3°C; Severe>=39.3 to <40.0°C; Life-threatening>=40°C. The derivation of these variables is similar to the derivation of the variables for injection area symptoms.

10.3 Use of Medication

The use of medication will be recorded on the Diary Card for 7 days after vaccination.

The following variable will be derived:

- Use of medication on 'Any Day 1 to 7' after vaccination

10.4 Diary Card Completion

The number of participants who returned the diary card, including the reason for not returning the diary card will also be summarized. For any given day, the diary will be considered as complete if all expected data (the 3 injection area symptoms, the 4 general body symptom events, and the use of medication for the 7 days) are available (i.e. a non-missing response is available). If any of the items in the diary is missing on a specific day, the diary is considered as incomplete.

The following diary compliance variables will be derived as follows and presented by treatment group:

- Compliance per day: the numerator is the number of participants who completed the diary on a given day (Day 1 to Day 7) and the denominator is the total number of participants who receive the vaccination.

- Compliance at least x days for x = 1, 2, ….7: the numerator is the number of participants who completed the diary on any x days, and the denominator is the total number of participants who received the vaccination.

10.5 Injection Site Examination

Injection site reaction assessments are recorded at Day 8, Day 29, Day 71, and Month 6 (refer to Protocol Section 8.2.6) and will be summarized for the Safety population. A corresponding listing will be presented for the Safety population.

In addition to the scheduled time points, an 'Any Time Point' will be derived. This will be defined as the worst case result per assessment and participant. Worst case assessment is defined as the largest measurement (mm) for assessments with measurements or the presence of the reaction if 0 measurements are available.

The presence and maximum diameter of injection site reactions will be recorded as follows:

- redness, swelling, or induration <=20 mm is considered as anticipated

- redness, swelling, or induration >20 mm is reported as an AE

- papule, vesicle, pustule, ulcer, or scar <=5 mm is considered as anticipated

- papule, vesicle, pustule, ulcer, or scar >5 mm is reported as an AE.

10.6 Clinical Laboratory Assessments

Clinical laboratory assessments including hematology, serum chemistry, urinalysis, a human immunodeficiency virus (HIV) test and a serum pregnancy test (females only) will be measured at Screening. HIV testing is repeated yearly.

Hematology	Complete blood count (hematocrit, hemoglobin, platelets, and white blood cells) and absolute counts for neutrophils, lymphocytes, basophils, eosinophils, and monocytes
Serum chemistry	Alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, total bilirubin, creatinine, blood urea nitrogen (BUN), potassium, sodium.
Urinalysis	Specific gravity, pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick

Descriptive statistics (based on Systeme Internationale [SI] units) for laboratory parameters will be presented at Screening by treatment group.

HIV testing results will be presented by yearly visits, as per time and event schedule.

The laboratory values will be graded programmatically by using the grading criteria in the Protocol Appendix 5: Toxicity table. The number and proportion of participants will be summarized by grading category and treatment group.

Detailed participant listings of all laboratory data collected during the study will be provided. Laboratory values outside normal limits will be identified in a participant data listing. A column will display any applicable toxicity grading of the laboratory value.

10.7 Vital Signs and Weight

Vital signs, including blood pressure, pulse rate, respiratory rate, and body temperature, will be collected at Screening and Day 1 (pre vaccination). These will be presented in a listing for the Safety population.

Height and weight will be measured at Screening, Day 1, and every 6 months thereafter. The results (including change from baseline for height, weight, and BMI) will be included in a by-participant listing and summarized at each visit by treatment group for Safety population.

10.8 Physical Examination

Findings from physical examinations will be presented in listings for the Safety population. Focused physical examination will be collected throughout the study and will be summarized descriptively by treatment group and by visit. Summary results will include the number and percentage of participants with clinically and non-clinically significant results at each visit.

10.9 Signs and Symptoms of TB

Tuberculosis symptom screen results at each visit and overall clinical TB diagnosis will be included in a by-participant listing for Safety population.

The following will be reported overall during the study by treatment arm for Safety and mITT for efficacy populations:

- Number of suspected TB diagnoses (events) by treatment group (across all participants withing each treatment group).
- Rate of reported TB symptoms (events) reported for all suspected TB diagnoses (events) by treatment group (across all participants withing each treatment group). The analysis will be based on the number of events and a participant may have more than one event throughout the study.
- Rate of referral to the National TB Programme for treatment (based on a ‘yes’ response from the following question on the eCRF: ‘Was the participant referred to the National TB program for treatment?’) events based on suspected TB diagnoses (events).

- The incidence rate of confirmed TB cases defined as bacteriologically-confirmed TB (Positive culture result [Mycobacterium tuberculosis positive] or positive GeneXpert result [MTB detected]) cases. The incidence rate will be calculated using the number of bacteriologically confirmed TB cases across all visits as the numerator and the duration of follow-up (in months) as the denominator. For participants with bacteriologically confirmed TB, the duration of follow-up will be from the randomization date up to the visit date when case is confirmed. For all other participants, the duration for follow-up will be calculated from the randomization date up to the study completion or early discontinuation date.

The following will be reported by calendar month (as reflected in study visit date) and by treatment group for Safety and mITT for efficacy populations:

- Number and percentage of participants who were diagnosed with suspected TB (yes/no) with percentages calculated based on number of participants still in the study in the respective calendar month.

- Number and percentage of participants with bacteriologically-confirmed TB (Positive culture result [Mycobacterium tuberculosis positive] or positive GeneXpert result [MTB detected]).

10.10 Pregnancy Outcome Data

Pregnancy outcome data collected during the study including number of previous pregnancies (and their outcome), any reported problems during pregnancy, estimated due date, pregnancy outcome, delivery type, and infant information will be listed for Safety population.

11 OTHER RELEVANT DATA ANALYSES/SUMMARIES

11.1 Medical History

Medical history will be coded using MedDRA version 22.0 or higher. Medical history will be summarized by SOC and PT by treatment group for the Safety population and listed for the Safety population. Summaries of SOC and PT will be sorted alphabetically by SOC and by descending frequency of PT in the BCG group. If a participant has more than one medical history even at a given level (e.g., SOC and PT), the participant will only be counted once within that level. A listing of medical history will also be presented.

Number and percentage of participants reporting an acute respiratory or febrile illness or lost sense of smell (ie, COVID-like symptoms) in the past 6 Months will be summarized by treatment group and listed for the Safety population.

No imputation of partial or missing dates will be performed for medical history and study days will not be presented for these cases.

11.2 Concomitant Medications

Concomitant medications will be coded using the World Health Organization (WHO) Drug Global Mar2019 or later version. A concomitant medication is defined as a medication with a stop date on or after the first dose date, thus a medication that is ongoing at the time of a participant's vaccination is considered concomitant. Partial and missing dates for concomitant medications will be imputed using the guidance in Appendix 5. The recorded partial/missing dates will be displayed in the listings and study days will not be presented for these cases.

Medications will be summarized by Anatomical Therapeutic Chemical (ATC) level 3 and preferred name by treatment group for the Safety population. Summaries of ATC level 3 and preferred name will be sorted alphabetically by ATC level 3 and by decreasing frequency of preferred name in the BCG group. If a participant has more than one medication at a given level (e.g., ATC level 3 and preferred name), the participant will only be counted once at that level.

Medications will be listed for the Safety population.

For participants in the mITT for efficacy population who have sustained conversion events, if preventive treatment can be identified in the database, the number of participants who had preventive treatment initiated following the sustained conversion event will be tabulated by site and overall and a corresponding by participant listing will be generated. The list of concomitant medications associated with preventive treatment will be provided by clinical team and will be included as source for planned analyses.

12 REFERENCES

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13 APPENDICES

Appendix 1 Schedule of Assessments

Study Visit Day (D) or Month (M)	Screen D -28 to D -1	D1	D8[a]	D29[b]	D71[b,c]	M6,12,18, 24,30, 36, 42, 48	Suspected TB Visit	Discon Visit[d]	Notes
Eligibility criteria verification	X	X							Confirm eligibility prior to randomization on D1
Obtain informed consent & assent	X								Re-consent of participants enrolled before study pause
Medical history	X								
Physical examination	X								
Focused physical examination		X	X	X	X	X			Exam if indicated by interval history
Body weight and height measurement	X	X				X			
Body temperature	X	X							
Interval history		X	X	X	X	X			
Vital signs	X	X							
Distribute/review diary cards		X							
Collect diary cards			X						
Distribute memory aid			X						
Collect memory aid				X					
Solicited AEs		X	X						
Unsolicited AEs	X	X	X	X					AEs will be collected from the time informed consent is obtained.
All serious adverse events (SAEs) and AESI	X	X	X	X	X	X (M6 only)			
Serious ADRs		X	X	X	X	X		X	Collected through the last study visit

Study Visit Day (D) or Month (M)	Screen D -28 to D -1	D1	D8[a]	D29[b]	D71[b,c]	M6,12,18, 24,30, 36, 42, 48	Suspected TB Visit	Discon Visit[d]	Notes
Concomitant prescription medications & antipyretic/anti-inflammatory drugs		X	X	X	X				
Immunosuppressive and/or TB medication (curative & preventive)		X	X	X	X	X		X	
Ask about pregnancy		X	X	X	X	X		X	
Injection site examination			X	X	X	X (M6 only)			
TB symptom screen	X			X	X	X		X	
βHCG test <u>all</u> females (mL)	5	X							Serum test at screening Urine test on Day 1, and if pregnancy suspected on subsequent visits
BCG or placebo administration		X							
Urinalysis	X								May be repeated as described in Protocol Section 8.
QFT assay (mL)	4				4	4			[e] regarding unevaluable sample
HIV test (mL) with pre- and post-test counselling	3					3	3		At screening, and M12, 24, 36, 48 only, and if TB disease is suspected. [f] regarding unevaluable screening sample
Serum chemistry (mL)	5								Refer to Protocol Section 8.2.5
CBC, differential (mL)	2.5								[f] regarding unevaluable screening sample.
Absolute blood cell count (mL)		0.5	0.5	0.5	0.5	0.5			
PAXgene tube for RNA (mL)		2.5	2.5	2.5	2.5	2.5			

Study Visit Day (D) or Month (M)	Screen D -28 to D -1	D1	D8[a]	D29[b]	D71[b,c]	M6,12,18, 24,30, 36, 42, 48	Suspected TB Visit	Discon Visit[d]	Notes
Subset only: Whole blood for ICS (mL) for CD4 and CD8 T cells		6		6	6	6 (M6 only)			First 80 10- to 12-year-old participants enrolled at SATVI
PBMC and plasma for CoP & CoR (mL)		34			34	26			
Serum for CoP & CoR (mL) (innate and adaptive)		10	10	10	10	10			
Sputum samples or other appropriate samples for smear microscopy, mycobacterial culture, and GeneXpert							X		
Nasal or oropharyngeal sampling for SARS-CoV-2 diagnostic test	X	X	X	X	X	X			Samples collected only if participant presents with suspected COVID-19
SARS-CoV-2 serology (mL)	5					5 at M6, M12, M18 and M24			If enrolled before study pause: collect at the next feasible biannual visit (e.g., M6, M12, etc) and biannually thereafter for 24 months
Per visit approximate phlebotomy volume (vol.) (mL) (includes ICS subset)	19.5	53	13	19	57.0	52 at M6 46 at M12			Vol. at M18, 24, 30, 36, 42, 48 = 46 mL per timepoint, excluding SARS
Cumulative approximate vol. (mL) includes ICS subset	19.5	72.5	85.5	104.5	161.5	259.5 Year (Yr)1[g]			Yr 2=351.5mL Yr 3 =443.5mL Yr 4=535.5mL excluding SARS
Cumulative approximate vol. (mL) excludes ICS subset	19.5	66.5	79.5	92.5	143.5	235.5 Yr 1[h]			Yr 2 =327.5mL Yr 3=419.5mL Yr 4 =511.5mL excluding SARS
Cumulative approximate vol. (mL)	24.5	77.5	90.5	109.5	166.5	269.5			Yr 2=371.5 mL

Study Visit Day (D) or Month (M)	Screen D -28 to D -1	D1	D8[a]	D29[b]	D71[b,c]	M6,12,18, 24,30, 36, 42, 48	Suspected TB Visit	Discon Visit[d]	Notes
after study pause (including SARS-CoV-2 serology) includes ICS subset						Yr 1[g]			Yr 3 =463.5mL Yr 4=555.5mL

X indicates procedure to be performed and number indicates blood volume collected (volumes listed are approximate).

[a] Laboratory testing for innate host responses

[b] Laboratory testing for adaptive host responses

[c] QFT test to determine who to exclude from mITT efficacy analysis (end of wash-out period)

[d] A discontinuation (discon) visit will be scheduled for participants who discontinue or withdraw, whenever possible.

[e] QFT sampling: If the blood sample collected for QFT cannot be evaluated (e.g., insufficient volume; damage, hemolytic or lost sample, etc.), collection of a second (repeat) blood sample is permitted to enable evaluation of the primary efficacy endpoint. If the QFT sample was successfully run and has a reported result, including "indeterminate", collection of a second (repeat) blood sample is not permitted.

[f] If a blood sample collected for screening cannot be evaluated (e.g., insufficient volume; damaged, hemolytic, or lost sample, etc.) a second (repeat) blood collection is permitted to enable evaluation of study eligibility. The repeat blood collection must occur within the protocol-defined screening visit window. If a screening blood sample was successfully run and has a reported result to determine eligibility, a second (repeat) blood collection is not permitted.

[g] Including subset and includes PC visits Table 3: maximum vol. of whole blood collected through M48 = 637.5mL

[h] Participants not in subset, includes PC visits Table 3: maximum approximate vol. of whole blood collected through M48= 613.5mL

Appendix 2 Schedule of Assessments Post QFT Conversion at the Month 6 Visit or thereafter

Study Visit Day, Post Initial QFT conversion	PC Day 28	PC Day 84
Interval history	X	X
Focused physical examination	X	X
Vaccination-related SAEs	X	X
TB symptom screen	X	X
QFT assay		4
Absolute blood cell count (mL)	0.5	0.5
PAXgene tube for RNA (mL)	2.5	2.5
PBMC and plasma for CoPs & CoRs (mL)	34	34
Serum for CoPs & CoRs (mL)	10	10
Per visit phlebotomy volume (mL)	49	53
Cumulative phlebotomy volume (mL)	49	102

PC = post conversion

X indicates procedure to be performed and number indicates blood volume collected.

Note that participants who become QFT positive will continue to follow procedures in Appendix 1 through the end of the study

Appendix 3 Study Sites and Quintiles

Site Number	Site Name	Quintile	Schools Included [a]
101	Be Part Yoluntu Centre		
102	Emavundleni Research Centre		
103	SATVI	1	Alfred Stamper Primary; Bonne Esperance Primary; Iingcinga Zethu Secondary; Nduli Primary; Nkqubela Primary; P.J.B Cona Primary; Sibabalwe Primary; Siyafuneka Primary; St. Mark's Primary; Vusisizwe Secondary; Zwelethemba High School
		2	De Villiers Laerskool; F.J. Conradie Primary; Hexvallei Sekondêr; Masakheke Combined; Worcester Sekondêr
		3	Dagbreek Laerskool; Esselenpark Primary; Hexpark Primary; Langeberg Sekondêr; Roodewal Primary; Vergesig Primêr
		4	Avian Park Primary; Bella Vista Hoërskool; Breërivier Hoërskool; Ceres Primêr; Ceres Sekondêr; Esselenpark Sekondêr; F.D. Conradie Laerskool; Rawsonville Primêr; Riverview Primary; Somerset High School; Victoriapark Primêr; W.F. Loots Primêr; Wolseley Sekondêr; Worcester Moslem Primêr, Worcester NGK Oefen Primêr; Worcester RK Primêr
		5	Bella Vista Primêr; Ceres Lions Pre-Primary; Charlie Hofmeyer Hoërskool; De Tuinen Primer; Drostdy HTS; Gericke Laerskool. Goudini Hoërskool; Lanner House; Lifestyle Christian Academy; Montana Hoërskool, Mooi-Uitsig Primer; Morrisdale Primêr; Robertson Hoërskool; Robertson Logos Christian School; Robertson Voorb; Witzenberg Primêr; Wolseley Laerskool; Worcester Gimnasium; Worcester Laerskool; Worcester Voorb.; Worcester-Noord Primêr; Worcester-Oos Laerskool.

104	Centre for Aids Programme of Research in South Africa (CAPRISA)		
105	Wits Reproductive Health and HIV Institute (RHI) Shandukani Research Centre		
a: Only displayed for Site 103.			

Appendix 4 Study Visit Intervals

Study Visits	Length of Interval	Allowed Interval
Screening	Day -28 to Day -1	Day -28 to Day -1
Day 1	NA	Day 1
Day 8	Day 1 plus 7 days	Day 8 through Day 11
Day 29	Day 1 plus 28 days	Day 29 to Day 35
Day 71	Day 1 plus 70 days	Day 71 to Day 78
Month 6, M12, 18 …M48,	Day 1 plus 6 (12, 18, …) calendar months	6 (12, 18, …48) calendar months from Day 1 ±14 days
PC28	Date of QFT conversion plus 28 days	Day 28 to Day 35 post QFT conversion
PC84	Date of QFT conversion plus 84 days	Day 84 to Day 98 post QFT conversion

NA = not applicable PC = post-conversion.

Note that after Day 71, timepoints and intervals will be measured in calendar months.

Refer to Section 7.4 of the protocol for intervals based on COVID-19 contingency plans.

Appendix 5 Prior and Concomitant Medications Date Imputation

Imputation Rules for Partial Dates (D=day, M=month, Y=year)			
Parameter	**Missing**	**Additional Conditions**	**Imputation**
Start Date	D only	M and Y same as M and Y of date of vaccination	Date of vaccination
		M and/or Y not the same as date of vaccination	First day of month
	M and D	Y same as Y of date of vaccination	Date of vaccination
		Y not the same as date of vaccination	Jan 01 of Y
	M, D, and Y	Non-date completely missing	Day prior to date of vaccination
Stop Date	D only	M and Y same as M and Y of date of discontinuation/completion of study	Date of discontinuation/ completion of study
		M and/or Y not the same as date of discontinuation/completion of study	Last day of month
	M and D	Y same as Y of date of discontinuation/completion of study	Date of discontinuation/ completion of study
		Y not the same as date of discontinuation/completion of study	Dec 31 of Y
	M, D, and Y	None – date completely missing and NOT ongoing	Date of discontinuation/ completion of study

Appendix 6 Time to Event Derivation Details

Initial QFT Conversion/ Month 3 post initial conversion/Month 6 post initial conversion[1]	Event/ Censored	Date of Event/Censoring
Sustained conversion prior to date of data cut-off (i.e. Positive/Positive/Positive: -/-/-/…/+/+/+/any/any)	Event	Date of Initial Conversion to QFT positive
No initial conversion prior to date of data cut-off (-/-/-/…/-/-)	Censored	Minimum (date of last non-missing QFT result, date of data cut-off)
Initial converters with a 3-month positive QFT and missing 6-month results prior to date of data cut-off (i.e. Positive/ Positive/missing: -/-/-/…/+/+/-/+/+/Missing)	Censored	Date of initial conversion to QFT positive
Initial converters with a 3-month negative QFT and missing 6-month result prior to date of data cut-off (i.e. Positive/ Negative/Missing: -/-/-/…/+/-/Missing)	Censored	Date of initial conversion to QFT positive
Initial converters with a missing 3-month and positive 6-month result prior to date of data cut-off (i.e., Positive/Missing/Positive: -/-/…/+/Missing/+)	Censored	Date of initial conversion to QFT positive
Initial converters with a missing 3-month and negative 6-month results prior to date of data cut-off (i.e. Positive/Missing/Negative: -/-/-/…/+/Missing/-)	Censored	Date of initial conversion to QFT positive
Initial converters with missing 3-month and missing 6-month results prior to date of data cut-off (i.e., Positive/Missing/Missing: -/-/-/…/+/Missing/Missing)	Censored	Date of initial conversion to QFT positive

[1]indeterminate QFT results are counted a negative test result.

Appendix 7 SAS Code

SAS code for all Kaplan-Meier analysis:

```
proc lifetest data = <dataset>;
    time time*censor(1);

    strata agegrp sex / group = Treatment test = (logrank);

run;
```

Hazard ratios and 95% confidence intervals will be estimated using a stratified Cox proportional hazard regression model. The following SAS code will be utilized.

```
proc phreg data = <dataset>;

    model time to event (days) * censor (1) = Treatment / risklimits ties=efron;

    strata agegrp sex;

run;
```

Proportional hazards assumption will be tested using the following code. Statistical significance of the coefficient associated with the interaction of survival time and treatment group will be assessed at the 0.10 level.

```
proc phreg data = <dataset>;

    model time to event (days) * censor (1) = Treatment trt_time /risklimits ties=efron;

    strata agegrp sex;

    trt_time=treatment*log(time to event);

run;
```

If the coefficient associated with the function of time is nominally significant at the 0.10 level, then we can use robust sandwich estimate of Lin and Wei (1989) for the covariance matrix.

```
proc phreg data = <dataset> covs;

    model time to event (days) * censor (1) = Treatment /risklimits ties=efron;

    strata agegrp sex;

run;
```

Interval censoring will be used as sensitivity analysis (based on sustained conversion using 0.35 IU/mL threshold). The following SAS code will be implemented:

```
proc icphreg data = <dataset>;
    model (left, right) = Treatment / b=pch(INTERVAL=X);
run;
```

The following SAS code will be implemented to **compile CI's based on the mid-p method**:

```
proc freq data=<dataset> order=freq;
    tables category / binomial (CL=MIDP);
    weight Count;
run;
```

The following SAS code will be implemented to **compile CI's based on the Miettinen and Nurminen method without stratification**:

```
proc freq data=<dataset>;
    tables  treatment*rate / nocol nopct missing riskdiff (CL=mn);
run;
```