Statistical Analysis Plan

Protocol Title: Correlate of Risk Targeted Intervention Study (CORTIS)

A Randomized, Partially-blinded, Clinical Trial of Isoniazid and Rifapentine (3HP) Therapy to Prevent Pulmonary Tuberculosis in High-risk Individuals Identified by a Transcriptomic Correlate of Risk

Protocol Number: CORTIS-01

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By signing below, I confirm that I have reviewed and approve the above version of the Statistical Analysis Plan.

10-28-2019

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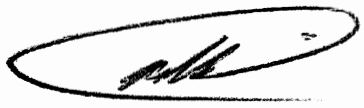

25th October 2019

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1 List of Abbreviations and Definitions of Terms

1.1 Abbreviations

3HP	A 3-month, 12-dose, once-weekly preventive therapy regimen of high dose Isoniazid and Rifapentine
AE	Adverse event
CI	Confidence interval
COR	Correlate of risk biomarker
CRF	Case Report Form
DSMB	Data and Safety Monitoring Board
GCP	Good Clinical Practice
HIV	Human immunodeficiency virus
IGRA	Interferon-gamma release assay
INH	Isoniazid
IPT	INH preventive therapy
ITT	Intention to treat
LTBI	Latent tuberculosis infection
LTFU	Lost to followup
mITT	Modified intention to treat
mRNA	Messenger ribonucleic acid
MTB	Mycobacterium tuberculosis
NNT	Number needed to treat
PP	Per-protocol
PPV	Positive predictive value
QFT	QuantiFERON
RR	Relative risk
RR(15)	Relative cumulative risk for TB disease over 15 months
SAE	Serious adverse event
SAGE	Strategic Advisory Group of Experts on immunization
SAP	Statistical Analysis Plan
SATVI	South African Tuberculosis Vaccine Initiative
SD	Standard deviation
SE	Strategy efficacy
TB	Tuberculosis
TE	Treatment efficacy
TE(15)	Cumulative treatment efficacy over 15 months
TST	Tuberculin skin test
WHO	World Health Organization

2 Study Overview

2.1 Background and rationale

Effective tuberculosis (TB) control requires that people who progress from latent Mycobacterium tuberculosis (MTB) infection (LTBI) to TB disease are identified and treated before they infect others. A prognostic correlate of risk (COR), based on mRNA expression signatures, which prospectively discriminates between TB cases and healthy controls, has been constructed and validated in previous studies *(1)*. Based on published microarray case-control datasets, the COR has 87% diagnostic sensitivity and 97% specificity for prevalent TB disease; and in two nested case-control studies, 70% prognostic sensitivity and 84% specificity for incident TB disease occurring within one year of sampling (HIV uninfected persons). Diagnostic and prognostic performance of the COR has not yet been tested in a prospective cohort.

COR+ status is not directly associated with LTBI; and may, or may not, be amenable to preventive therapy. Although effective in the short-term, preventive therapy is not recommended for treatment of LTBI in HIV uninfected adults living in high TB burden countries, due to rapid loss of protection; and treatment burden. A 3-month, 12-dose, once-weekly preventive therapy regimen of high dose Isoniazid (INH) and Rifapentine (3HP) has been recommended as equivalent to 6 months of daily INH for treatment of LTBI in low TB burden countries by the World Health Organization (WHO).

A “screen & treat” strategy, based on serial mass campaigns to provide targeted, short-course preventive therapy only to COR+ persons at highest risk of TB disease, may offer the solution for durable, community-wide protection in high TB burden countries. The efficacy of 3HP for prevention of incident TB disease in COR+ persons has not yet been tested in a clinical trial.

Adult volunteers living in TB hyperendemic communities of South Africa will be consented and screened. Participants eligible for randomization who test COR+ at screening will be randomized in a 1:2 ratio to either open-label 3HP (Treatment Arm), or active surveillance for TB disease (Observation Arm), including regular symptom screening and symptom-targeted TB investigation (all participants). No placebo will be used for COR+ participants, in order to blind participants in the Observation Arm to COR status. Participants who test COR- will be randomly selected to participate in the Observation Arm (at least 17 COR- participants for each 15 COR+ participants enrolled [block size ≥ 32]), or they will not be enrolled. Thus, the Treatment Arm will include a maximum of 500 COR+ participants, unblinded to COR status, receiving open-label 3HP; the Observation Arm will include a maximum of 1,000 COR+ and 1,700 COR- participants, blinded to COR status, all undergoing active symptom-targeted TB surveillance for a maximum of 15 months.

2.2 Study Aims

2.2.1 Primary Aims

2.2.1.1 Primary Aim 1: Test whether preventive therapy (3HP) reduces cumulative incident TB disease, compared to standard of care (active surveillance), in COR+ persons.

2.2.1.2 Primary Aim 2: Test whether COR status differentiates persons with cumulatve prevalent or incident TB disease from persons without TB disease.

2.2.2 Secondary Aims

2.2.2.1 Secondary Aim 1: Estimate whether COR status differentiates persons with prevalent TB disease from persons without prevalent TB disease

2.2.2.2 Secondary Aim 2: Estimate whether COR status differentiates persons at high risk for incident TB disease from persons at low risk for incident TB disease

2.2.2.3 Secondary Aim 3: Compare prognostic performance of the COR for incident TB disease with IGRA.

2.2.3 Exploratory Aims

2.2.3.1 Exploratory Aim 1: Assess and model the impact of a COR “screen & treat” strategy on reducing the rate of incident TB disease and TB mortality in South Africa.

2.3 Study endpoints

2.3.1 Two-sample endpoint definition

TB disease confirmed by positive Xpert MTB/RIF and/or MGIT culture on two or more separate sputum samples, or samples from another site if extrapulmonary disease.

All aims will be evaluated using this endpoint definition.

2.3.2 One-sample endpoint definition

TB disease confirmed by positive Xpert MTB/RIF and/or MGIT culture on at least one sputum sample, or sample from another site if extrapulmonary disease. As exploratory analyses all aims may also evaluated using this endpoint definition.

2.4 Study design

2.4.1 Design schematic

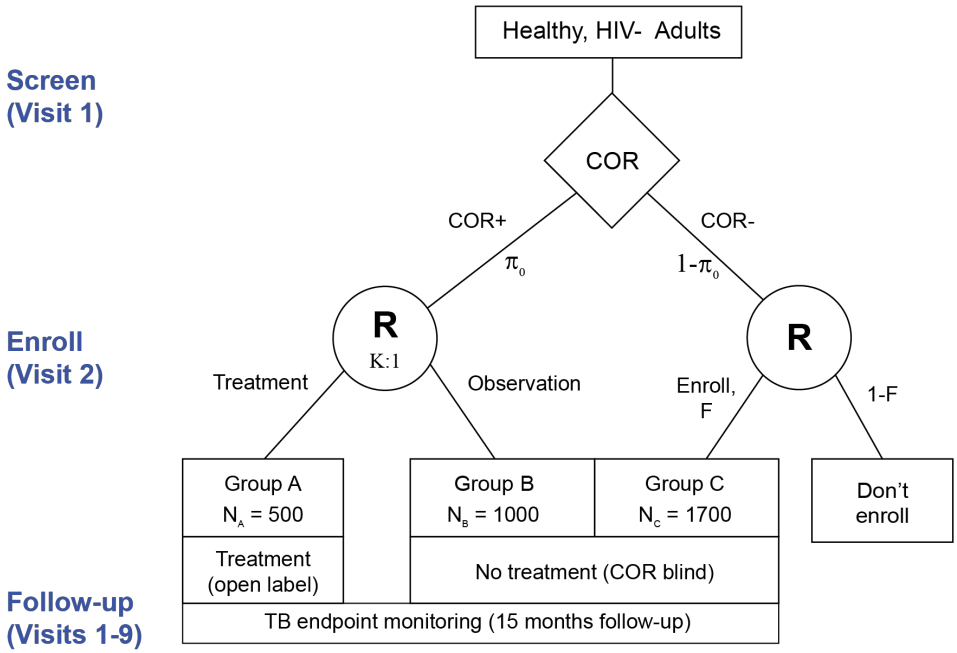

Figure 1. Trial design schematic.

2.5 Design description

This is a randomized, partially blinded clinical trial (**Figure 1**). Adult volunteers living in selected TB hyperendemic areas of South Africa will be recruited and screened for enrolment. Eligible participants will provide a whole blood PAXgene sample for measuring the COR biomarker. Participants that are above a pre-specified biomarker threshold (i.e. COR+) will be enrolled into an open-label 3HP preventive treatment group (Analysis Group A) or an observational group (Analysis Group B). The enrolment will be randomized using a 1:2 treatment ratio. Since we expect COR positivity to be approximately 15% in the study population, only a subset of participants below the pre-specified threshold (i.e. COR-) will be enrolled into an observation group (Analysis Group C). Initially, 17 COR- participants will be selected for enrolment for every 15 COR+ participants enrolled. Since the observed COR prevalence is lower than initially expected the rate of enrollment is reduced. To ensure that all 1700 COR- participants are enrolled the blocksize can be adapted to include >17 COR- for 15 COR+ participants. All participants will be followed, with identical scheduled endpoint evaluation in each group.

The complete cohort will therefore include a maximum of 500 COR+ participants in the Treatment Arm (unblinded to COR status) receiving open-label 3HP; a maximum of 1,000 COR+ participants in the Observation Arm (blinded to COR status) undergoing

active symptom-targeted surveillance, and 1,700 COR- participants in the Observation Arm (blinded to COR status) undergoing active symptom-targeted surveillance.

Enrolment in the different arms will remain balanced at each site and will be managed by a dedicated, unblinded team from the Data Centre.

All enrolled participants will undergo regular TB symptom screening and symptom-targeted TB investigation. No placebo will be used for COR+ participants, in order to blind participants in the Observation Arm to COR status. Active surveillance for incident TB disease will be conducted by trial team members not involved in dispensing or monitoring adherence of investigational product in an identical fashion for participants in both study arms. Participants diagnosed with incident TB disease will discontinue study treatment and follow-up, and will be referred in writing to the NTP for 4-drug curative treatment.

The performance of the biomarker will be evaluated by comparing the incidence of endpoint-defined TB disease over a maximum of 15 months in Group B versus Group C ($RR_{COR(15)}$; **Figure 2**); duration of follow-up may be reduced to a minimum of 3 months for some participants. The screening and enrolment process will ensure that the COR+ and COR- participants in these groups are enrolled contemporaneously, despite the unbalanced prevalence in the population. Participants in these groups, along with site staff and investigators, will be blinded to biomarker status throughout the trial. This ensures that evaluation of biomarker performance will be unbiased.

Treatment efficacy (TE) will be evaluated by comparing the incidence of endpoint-defined TB disease over a maximum of 15 months in Group A versus Group B. The randomization will ensure that all measured and unmeasured covariates are randomly distributed among the groups, aiding in interpretation. Due to the lack of a placebo control, participants in Group A will not be blinded to treatment assignment or their biomarker positivity. Therefore, treatment efficacy will be attributable to this knowledge in addition to the treatment itself. This is a feature of the study design that mirrors how the biomarker may be implemented in a screen and treat strategy. It also reduces sample size by eliminating a COR+ placebo group.

Strategy efficacy (SE) will be evaluated by comparing incidence of endpoint-defined TB disease in Groups A, B and C. The strategy analysis will combine estimates of biomarker performance and treatment efficacy to estimate how efficacious a strategy might be at preventing endpoint-defined TB disease in this population by treating all biomarker positive participants.

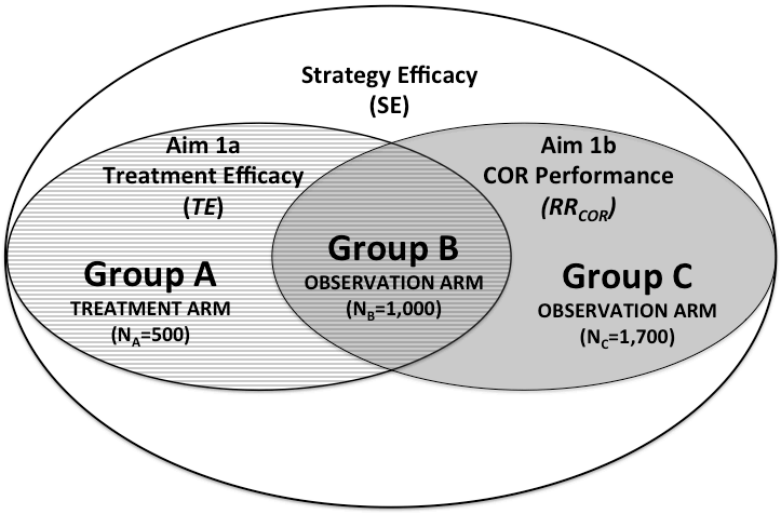

Figure 2. Evaluation of Primary Aims by study group

2.6 Blinding

The trial is partially blinded. Participants in the Observation Arm are double-blinded to COR status. Participants, investigators, and all members of the clinical trial team responsible for performing TB symptom and sputum screening for the purpose of endpoint determination, as well as the medical monitor, Sponsor, and data management personnel, will remain blind to COR status of participants in the Observation Arm from the time of randomization until database lock.

The Treatment Arm is open label. Clinical trial team members responsible for the collection of TB symptom data and sputum samples for TB investigations will not be formally blinded to treatment allocation. Clinical trial team members responsible for dispensing of investigational products or DOT field visits will not take part in collection of TB symptom data and sputum samples for TB investigations. However, if a study staff member involved in dispensing of investigational products or DOT field visits is made aware of possible TB symptoms by a participant, they will immediately refer the participant to an appropriate study staff member. A Delegation of Authority Log will be maintained by the site to identify the individuals authorized to perform these exclusive functions. Investigators responsible for participant safety evaluation and interpretation of laboratory results, including diagnosis and referral for treatment of TB disease, will be unblinded to study arm.

The following personnel will be unblinded to COR status of all participants during the trial: (1) Data Centre personnel responsible for the generation of the randomization schedule, (2) Independent statistician at the Data Centre responsible for the presentation of unblinded safety data to the DSMB, and (3) Statistical programmer at SCHARP who will receive data from the Data Centre and maintain the blind of other SCHARP statisticians, when appropriate. Unblinded personnel will at no time reveal

individual participant COR status or study arm allocation to a blinded member of the clinical trial team.

2.7 Operational monitoring

Operational monitoring performed throughout the study will depend on enrollment rate summaries of participants in each study Group. Though the analysis will be unblinded to COR positivity, only a population-level summary will be presented to the protocol team. The unblinded statistical programmer at SCHARP will perform the analyses to maintain the blind of the study statisticians. Operational analyses will be blinded to TB endpoint status.

2.8 Interim COR Prognostic Efficacy Analysis

An interim efficacy analysis will be performed if there are 40 incident (detected after Visit 2) TB endpoints while there is >6 months of follow-up remaining in the trial. The interim analysis will include estimates of TE and RR_{COR} and will therefore not be blinded to COR positivity and TB endpoint status. If the analysis is triggered, the study statisticians at SCHARP will be fully unblinded and will perform and present the analysis to the DSMB.

In the event that the DSMB decides to continue the study, all participants and protocol team members will remain blinded. An additional blinded statistician at SCHARP will be made available to assist the protocol team with any statistical issues, including study monitoring, throughout the remainder of the trial. The SCHARP statisticians that were unblinded by participation in the interim analysis will cease interactions with the protocol team until database lock at the end of the study.

In the event that the DSMB decides to unblind the study, then all participants and all members of the protocol team will be unblinded to COR positivity and TB endpoint status. The SCHARP statisticians involved in the interim analysis will be permitted to continue working with the protocol team, as all members of the team will be unblinded.

3 Endpoint definition and adjudication

3.1 Requiremet of endpoint adjudication algorithm

This section details how longitudinal Gene Xpert and MGIT results will be used to identify one and two-sample positive endpoints, as described in the protocol. An algorithm is specified below to report on prevalent and incident cases throughout the study, as well as conduct the final Primary analyses. The algorithm is needed to classify each sputum sample as Mtb. positive or negative and subsequently, each participant as TB-negative, one-sample positive or two-sample positive. It also establishes the date at which TB-positive participants will be considered TB-positive in subsequent analyses.

The algorithm makes explicit two basic rules of adjudication: (1) Thirty-day episode window, and (2) “First, worst” case definition. The 30-day episode window implements the concept that assay results from multiple samples will be considered related and therefore combined to indicate a

two-sample positive endpoint if they occur within 30-days of the first positive sample within an episode; samples collected more than 30 days apart will be considered as independent episodes for endpoint adjudication. The “first, worst” rule refers to the concept that a participant will be classified as a two-sample TB-positive endpoint if at any point during the study there is a two-sample positive episode, even if it follows an earlier one-sample positive episode.

3.2 Raw Endpoint Data

Each participant in the study provides a number of sputum samples, which are associated with assay results. The collection date is indicated for each sample by the BARC_MICRO.COL_DATE. We consider three assays: MGIT 960, Gene Xpert and Gene Xpert Ultra. The precise definition of positive and negative results for each assay appear in the following table:

BARC_MICRO.**PROC**	BARC_MICRO. **PROMPT**	BARC_MICRO.**RES**	**Adjudicated result**
MGIT 960 Mycobact Re-Culture	M tuberculosis :	Negative	Neg
MGIT 960 Mycobact Re-Culture	MGIT Re-culture	Mycobacterial culture NEGATIVE after 42 days	Neg
MGIT 960 Mycobact Re-Culture	M tuberculosis :	Positive	Pos
MGIT 960 Mycobacterial Culture	M tuberculosis :	Negative	Neg
MGIT 960 Mycobacterial Culture	MGIT Culture	Mycobacterial culture NEGATIVE after 42 days	Neg
MGIT 960 Mycobacterial Culture	M tuberculosis :	Positive	Pos
MTB PCR GENE EXPERT	NA	M.TB COMPLEX NOT DETECTED	Neg
MTB PCR GENE EXPERT	NA	M.Tb complex Not Detected	Neg
MTB PCR GENE EXPERT	Organism 1	Mycobact tuberculosis complex.	Pos
MTB PCR GENE EXPERT ULTRA	NA	M.Tb complex Not Detected	Neg
MTB PCR GENE EXPERT ULTRA	Organism 1	Mycobact tuberculosis complex.	Pos
MTB PCR GENE EXPERT ULTRA	Organism 1	Mycobact tuberculosis complexu	Pos

3.3 Algorithm

Apply the following steps to each participant’s set of assay results, up until the time of the analysis (or end of study):

Step 1. If there are no positive assay results the participant is classified as TB negative. Proceed to adjudicate the next participant.

Step 2. Begin with the first sputum sample collected that is positive based on any of the criteria above. This sample initiates an episode and defines the episode start date.

Step 3. If there are ≥2 positive samples collected on the episode start date, then classify the participant as two-sample TB-positive on that date. Proceed to adjudicate the next participant.

Step 4. If there is only one positive sample from the episode start date, examine all samples within a 30-day period. If there are any samples within the period that are TB-positive then classify the participant as two-sample TB-positive at the episode start date. Proceed to adjudicate the next participant.

Step 5. If the participant has no subsequent TB-positive results then classify the participant as one-sample TB-positive at the episode start date. Proceed to adjudicate the next participant.

Step 6. If the participant has TB-positive samples remaining, establish a new episode at the next positive sample. Continue with Step 3 to consider this new episode.

If only one-sample positive episodes are identified, the endpoint date will be the collection date of the first episode. A participant classified as a one-sample or two-sample positive TB endpoint at the Enrollment Visit (Visit 2) will be classified as a prevalent case and will be removed from the modified Intent-to-treat (mITT) cohort. Participants classified as a one-sample or two-sample positive TB endpoint at a subsequent visit will be included in both the intent-to-treat (ITT) and mITT cohorts for analysis.

3.4 Endpoint censoring

The Primary objective is to estimate treatment efficacy and COR performance over 15 months. Though follow-up should not be longer than 15 months, in anticipation of visits and samples that may occur more than 15 months after enrollment, a +/- 2 week window is established around the final month 15 timepoint. All endpoints detected after month 15.5 will be right-censored. Censoring depends on whether it is a two or one-sample endpoint. If the censored endpoint is a two-sample endpoint and there is no earlier one-sample endpoint then the participant is censored at the last negative visit. If there is a prior one-sample episode then the participant is censored at the last negative visit for the two-sample endpoint definition, but remains positive for the one-sample endpoint (presuming the one-sample endpoint is within the 15.5 months of follow-up). If the late endpoint is a one-sample endpoint the participant will be censored at the last negative visit.

If a participant has visits after month 15.5 and no TB endpoint is detected then the participant is censored at precisely 15 months. This differs from the censoring strategy for endpoints described above because we can assume that a participant without an endpoint is negative for the entire period between the late visit and the prior visit.

In addition to censoring all participants with follow-up beyond 15.5 months, all event dates (endpoints or censor dates) within the +/- 2 week window around month 15 will be “rounded” to precisely 15 months. This will ensure that the risk pool is stable at the month 15 timepoint for evaluation of the primary objectives. Without this provision the risk pool would shrink rapidly to zero between 14.5 – 15.5 months, leading to unstable estimation of the cumulative incidence at month 15.

4 Analysis Populations

We have defined four populations that will be used in evaluations of the study aims.

4.1 Intention to treat population

The intention-to-treat population will include all enrolled participants who complete the first endpoint evaluation (Visit 2), regardless of COR status or treatment adherence. The evaluation of relative-risk in COR+ vs. COR- (RR_{COR}) for Primary Aim 2 will be performed using the ITT population.

4.2 Modified intention to treat population (mITT)

The modified intention-to-treat cohort will include all participants in the ITT population who complete the first endpoint evaluation (Visit 2), but will omit participants with two-sample endpoint-defined TB disease cases identified at the first endpoint evaluation visit (Visit 2). The evaluation of treatment efficacy (*TE(15)*) for Primary Aim 1 will be performed using the mITT population.

4.3 Per-protocol population

The per-protocol cohort will include all participants in the mITT population who were TB negative at Visit 2 and completed the full treatment regimen (if assigned to Group A). An exploratory re-evaluation of *TE(15)* will be performed using the PP population.

5 Statistical Considerations

5.1 General principles

Unless otherwise specified, descriptive statistics (n, mean, median, standard deviation, interquartile range, minimum, maximum) will be used to describe continuous variables, and frequencies and percentages will be used to describe categorical variables.

Statistical analyses will be generated using R version 3.1.0 or greater. An appendix to the statistical report will list all R packages and versions used in the report generation.

5.2 Method of randomization

Assignment to study arm will be determined by the Data Centre and will be based on COR status at screening. COR+ participants will be randomly assigned to study arm (Treatment or Observation Arm) in a 1:2 ratio in accordance with a randomization schedule generated using SAS® PROC PLAN. COR- participants will be selected randomly for participation in the Observation Arm. The number of COR- participants selected for each COR+ participant (either one or two) will be determined randomly using SAS® PROC PLAN to ensure that at least 17 COR- participants will be selected for each 15 COR+ participants enrolled; the number of COR- participants enrolled per

block may be increased to ensure that the full 1700 participants are enrolled. Allocation to the different arms will therefore remain balanced within enrollment blocks filled at each site.

In order to maintain the partial blind of the trial personnel (blind to COR status in the Observation Arm), the randomization schedule will be prepared by an independent, unblinded statistician, who will not be involved in the conduct of the trial or analysis of the trial data. The randomization process will be managed by a dedicated, unblinded randomization team from the Data Centre. The Data Centre will provide each site with a list of participants to bring back for Visit 2 (D0, Enrolment) after receiving COR assay results for each batch of samples assayed. Upon eligibility confirmation and successful enrollment of the participants, the site staff will be unblinded and will use the list for study arm allocation. Participants in the list who do not meet the eligibility criteria or are not enrolled will be replaced by participants from a subsequent batch of COR assay results as determined by the Data Centre.

Participants who are withdrawn or LTFU after enrolment will not be replaced.

5.3 Missing Data

In spite of the best efforts to obtain complete data and to follow all enrolled participants, data may be missing upon completion of the trial. The reasons for any missing data will be ascertained and appropriate statistical methods will be used to accommodate these absences in the analyses of trial data that minimize potential biases and maximize efficiency, conditional on the causes for data being missing. Data values that are identified by quality control procedures to be spurious will be completely documented, and will not be used in the final analyses of trial data. Prior to any analysis we will evaluate the quantity and nature of the missing data in its entirety and specify an appropriate strategy to address the issue, possibly including: (1) complete-case analysis under a missing-completely-at-random assumption, (2) multiple imputation under a missing-at-random assumption, and/or (3) sensitivity analyses under a missing-not-at-random assumption.

6 Treatment Efficacy Analysis

An evaluation of treatment efficacy will be performed for the Final Efficacy Report as well as the Interim Efficacy Report. The method for both reports are detailed in this section.

6.1 Time-dependent endpoint

We will evaluate treatment efficacy based on the cumulative hazard of endpoint-defined TB among COR+ participants randomized to Groups A (preventive therapy) and B (observation). Treatment efficacy will be evaluated cumulatively over 15 months of follow-up, according to the formula:

$$TE(15) = 1 - \frac{1-S_A}{1-S_B} \quad (1)$$

where S_X is the Breslow estimate of the survival function estimated for group X using the Nelson-Aalen product-limit estimator of cumulative hazard and it's associated variance *(2)*. These are given by the following equations:

$$H(t) = \sum_{t_i \le t} \frac{d_i}{Y_i} \quad (2)$$

$$\sigma^2(H(t)) = \sum_{t_i \le t} \frac{d_i}{Y_i^2} \quad (3)$$

where d_i is the number of endpoints occurring at time t_i and Y_i is the number of participants at risk at time t_i. As specified in the protocol a 90% confidence interval and a two-sided Wald-based p-value for H_0: *TE(15)* ≤ 20% will be provided; $p < 0.1$ will be considered significant. As an exploratory analysis a 95% confidence interval and two-sided p-value for H_0: *TE(15)* = 0% will also be provided. No adjustments will be made for study site, baseline or demographic variables. A plot of cumulative incidence ($1 - S_x$) with 95% confidence interval will be provided for each group.

6.2 Binary endpoint

An additional exploratory analysis of TE will be performed based on a binary TB endpoint.

		TB disease at or after Visit 3	
		Yes	**No**
Group	**A**	*a*	b
	B	c	d

Probability of developing TB after enrollment for each group over the 15 month follow-up period will be estimated as the cumulative number of endpoints observed after enrollment (e.g. *a* for Group A) divided by the number of enrolled participants in the mITT cohort (i.e. excluding participants with an endpoint at enrollment/Visit 2, e.g. *a* + *b* for Group A), adding ½ to each cell of the table above to stabilize the estimate*(3)*:

$$RR_{bin}(15) = \frac{(a+0.5)/(a+b+1)}{(c+0.5)/(c+d+1)} \quad (4)$$

$$TE_{bin}(15) = 1 - RR_{bin}(15) \quad (5)$$

The 90% and 95% confidence intervals will be computed based on the score statistic for risk ratios developed by Koopman*(4)*, improved by Nam*(5)* and implemented in the R package *PropCIs*.

See **Supporting Tables and Figures 11.1**

7 COR Performance Analysis

7.1 Cumulative incidence ratios

A performance of the COR biomarker will be performed for the Final Efficacy Report as well as the Interim Efficacy Report. The method for both reports are detailed in this section.

We will evaluate the relative risk of endpoint-defined TB over the duration of follow-up $RR_{COR}(15)$, in COR+ (Group B) versus COR- (Group C) participants using the cumulative incidence ratio (CIR). Previous studies have shown that the relative risk of TB disease among COR+ versus COR- decreases over time *(1)*, therefore using a Cox model, which assumes constant proportional hazards through time, would not be appropriate. A cumulative incidence approach is powerful, interpretable and robust to time-varying hazard ratios. We will provide the point estimate based on the formula:

$$RR_{COR}(15) = \frac{1-S_B}{1-S_C} \quad (6)$$

where S_X is the Breslow estimate of the survival function for group X using the Nelson-Aalen product-limit estimator of cumulative hazard *(2)* (see eqns. (2) and (3) above). The 95% confidence interval and a two-sided Wald-based p-value for H_0: $RR(15) \leq 1$ will be provided; $p < 0.05$ will be considered significant. As specified in the protocol, a 90% confidence interval will also be provided. No adjustments will be made for study site, baseline or demographic variables. A plot of cumulative incidence ($1 - S_x$) with 95% confidence interval will be provided for each group.

7.2 Analysis of binary endpoints

An additional exploratory analysis of RR will be performed based on a binary TB endpoint.

		TB disease at or after Visit 2	
		Yes	**No**
Group	**B**	*a*	b
	C	c	d

Probability of developing TB over the 15 month follow-up period within each group will be estimated as the cumulative number of endpoints (e.g. *a* for Group B) divided by the number of enrolled participants (e.g. *a* + *b* for Group B), adding ½ to each cell of the table above to stabilize the estimate*(3)*:

$$RR_{bin}(15) = \frac{(a+0.5)/(a+b+1)}{(c+0.5)/(c+d+1)} \quad (7)$$

The 95% confidence interval will be computed based on the score statistic for risk ratios developed by Koopman*(4)*, improved by Nam*(5)* and implemented in the R package *PropCIs*.

7.3 Varying COR thresholds: Receiver-operator curve (ROC) analysis

Exploratory analyses will include estimates of TE and RR using alternative thresholds for defining COR positivity. For TE, only thresholds higher than COR = 60% can be evaluated since no participants with COR < 60% were given prophylactic treatment. These analyses will also include evaluation of the sensitivity, specificity, positive predictive value (PPV), negative predictive value and number needed to treat (NNT) for the continuous COR biomarker in its ability to predict TB disease progression. Sensitivity is defined as the number of TB endpoints that were COR+, while specificity is the percentage of participants without an endpoint that were COR-. The PPV is the percentage of COR+ participants that developed TB. In the context of CORTIS-01, the NNT is the number of COR+ participants that would have to be treated to prevent one TB endpoint, assuming treatment could be 100% effective at preventing an endpoint; it is also the inverse of the absolute reduction in risk for COR- participants relative to COR+. Since the study is artificially enriched for COR+ participants by design, participant-specific weights in the analysis are required to recover estimates that are applicable to the screened population, as opposed to the enrolled cohort. The COR- participants up-weighted according to the empirical inverse probability of enrolling COR- participants that were screened (i.e. inverse probability weighting, IPW):

$$w_{COR^+} = \left(\frac{n_{COR^+\ enrolled}}{n_{COR^+\ screened}}\right)^{-1}$$

$$w_{COR^-} = \left(\frac{n_{COR^-\ enrolled}}{n_{COR^-\ screened}}\right)^{-1}$$

The weights, *w*, for COR- or COR+ participants are a function of the number, *n*, of COR- or COR+ participants enrolled and screened; $w_{COR+} \approx 1$ since the plan is to enroll all COR+ participants. No adjustment is needed for estimating CIR or RR. The 95% confidence interval will be provided for each performance metric using a non-parametric bootstrap, with sampling stratified by COR status, since the number of COR+ and COR- enrolled is fixed by the study design.

7.4 Time-dependent ROC analyses

In addition to performing protocol specified analyses of TB detected at enrollment and cumulative TB detected over 15 months, we will also evaluate the changes in biomarker performance over time, including sensitivity, specifity, RR, PPV and NPV. Plots of each of these measures as a function of follow-up time will aid interpretation of the primary results at month 15. These analyses will make use of methods and R packages developed by Zheng, Heagerty, Pepe and others *(6)*.

8 Operational Monitoring Reports

Throughout the trial we will periodically perform group-blinded analyses based on the rate of screening and enrolment and on the total number of accrued endpoints. The monitoring report will contain summaries of screening rates, enrolment rates, COR positivity (blinded to treatment assignment) and TB incidence (blinded to COR positivity and treatment assignment). The report will be presented to the protocol team and the sponsor, to inform operational decisions and increase efficiency.

Based on simulations of the trial, we initially expect to accrue a total of 40 endpoints (IQR [33, 47]) over 27 months from the date of the first screening (though the accrual, in accordance with the enrolment, is expected to be slow at first and catch up later). With each operational analysis we will conduct simulations of the remaining follow-up. The parameters of the simulation are pre-specified in this SAP and will not be updated based on observations from the trial, with three exceptions involving group blinded summary data: (1) number and accumulated follow-up duration of participants enrolled, (2) number of endpoints observed, (3) number of participants lost-to-followup (LTFU).

8.1 Timing of the analyses

The first operational analysis will occur after 6 months of follow-up and will be repeated every 3 months thereafter.

8.2 Study simulations

The trial simulation is based upon data from the Adolescent Cohort Study, which was conducted in a high TB burden area in Worcester, South Africa *(7–9)*. The biomarker was measured in all incident cases of TB disease (N = 47) and a set of 2:1 covariate-matched non-cases (N = 105). The relative-risk of TB disease for COR+ versus COR- was evaluated longitudinally, adjusting for the stratified case-control design. The analysis showed that relative-risk is initially high, but decreases over time. Since this analysis included only QuantiFERON-positive (QFT+) individuals, the results were re-weighted for translation to a mixed QFT+/- population, such as the target population in the current study. The re-weighting was based on QFT prevalence in the target population and also conservatively assumed that the biomarker is ineffective (RR_{COR} = 1) in QFT- individuals. The final result indicates that upon measuring the biomarker, relative-risk for COR+ is initially RR_{COR} = 15, but decreases exponentially with a decay time constant of approximately 12 months (**Figure 3**).

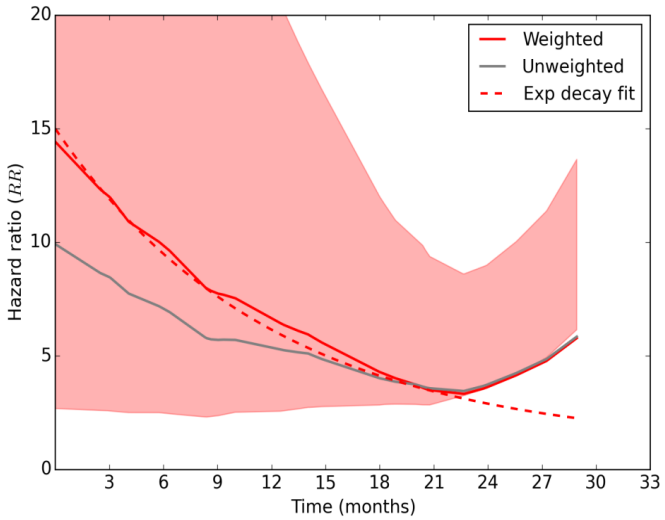

Figure 3. Declining cumulative relative-risk (RR) of incident TB with 95% CI.

Values of the simulation parameters were estimated from data when possible or were selected based on the expertise and experience of the protocol team and sponsors (**Table 1**).

Table 1. Simulation parameters	
1500	COR+ enrolled
1700	COR- enrolled
15 months	Follow-up period
10%	Lost to follow-up rate (per year)
1 : 2	Treatment randomization ratio for COR+ (Rx : No-Rx)
15%	COR prevalence
210	Enrollment rate (participants screened per week)
1% per year	TB incidence in the screened population
80%	Treatment efficacy (TE) among COR+
$RR_{COR}(t = 0)$	15
RR_{decay}	12 month decay time constant

8.3 Monitoring analyses

For each report the simulation will be initialized with the current state of the trial, including the: (1) number of participants enrolled and the date of enrolment, (2) total number of endpoints observed (group blinded), (3) total number of participants LTFU (group blinded). The remainder of the trial will be simulated 1000 times to project the duration of the trial and the total number of endpoints accrued. For the purposes of initialization, the observed endpoints and LTFU censoring will be randomly assigned to enrolled participants in each simulated trial. The simulation parameters will not be updated to reflect the data; for example, population incidence will continue to be projected at 1% per year, without regard to the actual incidence observed among trial participants. Similarly, the enrolment rate, which depends directly on COR prevalence, will also not be updated for the simulated projections.

Tables will be used to report the following variables as counts and as counts per unit of study time (i.e. rates) with 95% CI, for each study site and for the study overall: (1) participants screened, (2) COR+/- participants enrolled, (3) treatment initiated/completed, (4) participants LTFU (group blinded), (5) primary/secondary endpoints observed (prevalent and incident; group blinded). From the simulations we will report the projected total duration of the trial (i.e. first-participant-in to last-participant-out) and the total number of endpoints observed with 5^{th}, 10^{th}, 50^{th}, 90^{th} and 95^{th} percentiles. The fraction of simulated trials that trigger an interim efficacy analysis and its timing will also be reported for reference.

Safety data will not be presented in the operational monitoring report.

See **Supporting Tables and Figures 9.1** for additional information.

9 Interim COR Prognostic Efficacy Analysis Report

9.1 Analysis objectives

An unblinded interim analysis of the primary objectives will be performed after identification of 40 incident (detected after Visit 2) endpoint-defined cases of TB, as long as there is at least 6 months remaining in the trial. The analysis is designed to detect two scenarios: (A) The possibility of high biomarker performance in the presence of high treatment efficacy, and (B) The possibility of high biomarker performance in the presence of low treatment efficacy (**Table 2**). To detect these scenarios, cumulative treatment efficacy (*TE(X)*) and biomarker performance ($RR_{COR}(X)$) will be estimated within the mITT cohort (i.e. excluding prevalent cases). We use *X* to represent the average time in months over which cumulative incidence will be estimated. We expect that X will be less than 15 months as many participants will not have completed follow-up. In the analysis all TB disease-free participants will be right-censored at the time of the last documented visit. If the criteria are met for Scenario A then the trial will be unblinded and COR+ participants under active surveillance (Group B) may be offered the preventive therapy (3HP). If the criteria are met for Scenario B then the trial will be unblinded and all COR+ participants (Groups A and B) may be referred for a more effective therapy. Note that power for both scenarios is quite low. This is acceptable because the main objective is to complete the trial except under extreme conditions.

Table 2. Criteria and power for interim efficacy analysis.

	Scenario A	**Scenario B**
Null-hypothesis (H_0)	$RR_{COR}(X) \leq 5$ & $TE(X) \leq 60\%$	$RR_{COR}(X) \leq 5$ & $TE(X) \geq 60\%$
Joint power to reject H_0 under H_1	30%	20%
Est. months to 40 endpoints	10.7	8.6

Under the simulated design hypothesis for the Primary Analysis we expect to accrue a median total of 40 endpoints. Therefore, it is likely that the interim analysis will be triggered with minimal follow-up remaining or may not be triggered at all. In the event that we observe 40 endpoints with <6 months of follow-up remaining for the last participant enrolled, we will not perform the interim analysis. As a substitution, the interim analysis will be performed on the complete dataset immediately following trial closing.

The analysis will be performed by the unblinded statistician at SCHARP who will prepare a report for the DSMB that will be pre-specified in the Statistical Analysis Plan. No adjustment for the unblinded interim analyses will be made to the final analysis of the Primary Aims. This is justified as the stopping criteria under both scenarios are highly unlikely to be met except for trials in which the null-hypotheses of the Primary Aims would also be rejected.

9.2 Timing of the analysis

The 40th incident case of endpoint-defined TB confirmed by two-samples will trigger the Interim efficacy analysis, if there is at least six months before the last scheduled visit of the last enrolled participant. The dataset will include all data up to and including data collected on the day of the 40th endpoint.

9.3 Testing for Scenario A

We will compute point-estimates and confidence intervals for TE(X) and $RR_{COR}(X)$ as described in **Sections 5-7**, respectively. We will test the two hypotheses of Scenario A independently:

$$H_0: RR_{COR}(\mathrm{X}) \leq 5$$

$$\mathrm{H}_0: \mathrm{TE}(\mathrm{X}) \leq 60\%$$

A two-sided p-value will be computed for each hypothesis using a Wald test. If both p-values are less than 0.025 then the criteria for Scenario A will be met.

9.4 Testing for Scenario B

We will compute point-estimates and confidence intervals for TE(X) and $RR_{COR}(X)$ as described in Sections 5 and 6, respectively. We will test the two hypotheses of Scenario B independently:

$$H_0: RR_{COR}(\mathrm{X}) \leq 5$$

$$\mathrm{H}_0: \mathrm{TE}(\mathrm{X}) \geq 60\%$$

A two-sided p-value will be computed for each hypothesis using a Wald test. If both p-values are less than 0.025 then the criteria for Scenario B will be met.

10 Interim COR Diagnostic Performance Analysis and Incidence Projection

It is possible that participant follow-up will be extended to a maximum of 15 months. A decision is expected before end of recruitment in November 2018. To inform this decision a group-unblinded interim analysis of COR diagnostic performance and a group-blinded projection of TB incidence based on observed endpoints will be performed. The diagnostic analysis will be based solely on prevalent TB endpoints

detected at Visit 2 up until the date of data transfer. It is critical to the integrity of the Primary diagnostic analyses, at the end of the enrollment period, that no decision be made about ending the study before the study is fully enrolled. Therefore, results from this analysis will not have any impact on study enrollment and no statistical adjustment of the Primary diagnostic analysis will be necessary to account for this interim analysis.

The incidence projection will be based on observed incident TB (Visit 3 and later), however data will remain group-blinded for this analysis.

To maintain study integrity, results of these interim analyses will be shared only with the Principal Investigators, Study Sponsor, and the DSMB.

10.1 Diagnostic performance analysis

The performance of the COR, measured at screening, will be evaluated on its ability to predict TB disease detected at Visit 2 using the following performance measures: relative-risk of COR+ vs. COR- (RR_{COR}), sensitivity, specificity, positive predictive value (PPV) and the number needed to treat to prevent one case (NNT). Since the study is enriched for COR+ by design, participants will be re-weighted in the analyses to make population estimates of these metrics (see **Section 7.3** for details).

A confidence interval will be provided for each metric using a non-parametric bootstrap. The estimates and confidence intervals will be provided in a table (**Table 4**) along side the minimum and optimal Target Product Profiles (TPP), provided by the WHO, for a community-based triage or referral test to identify people suspected of having TB (WHO, “High-priority target product profiles for new tuberculosis diagnostics: report of a consensus meeting”, April 2014).

Table 3. Diagnostic endpoint contingency table

		TB disease at Visit 2	
		Yes	**No**
COR status	**Positive**	True-positives (*a*)	False-positives (*b*)
	Negative	False-negatives (*c*)	True-negatives (*d*)

Table 4. Diagnostic performance results

Performance measure	Estimate	Bootstrap 95% confidence interval		Target product profile (TPP)	
		Lower bound	Upper bound	Minimum	Optimal
Relative-risk (RR)	-	-	-	-	-
Sensitivity	-	-	-	90%	95%
Specificity	-	-	-	70%	80%
Positive-predictive value	-	-	-	-	-
Number-needed-to-treat (NNT)	-	-	-	-	-

10.2 Incidence projection

Simulations will be used to estimate the number of incident cases expected for the final analysis of COR prognostic performance. The simulation is similar to that which was used for study design and power calculations, however the incident rate of TB for the simulation will be estimated from the observed incident TB endpoints and accrued follow-up at the time of analysis. Estimates of incidence will be based on the two-sample definition, though a sensitivity analysis may be presented that would include both two-sample and one-sample endpoints. Screening rates and COR prevalence parameters will also be estimated from the accrued CORTIS-01 data. However, the relative-risk and treatment efficacy parameters will be the same as those used for study design (**Table 1**). The simulation will be run 1000 times to provide the median number of projected incident cases along with the 25th and 75th percentile. Incidence projection estimates will be provided through the end of enrollment (expected in November 2018) and at three month intervals through February 2020 when the last participant will have completed 15 months of follow-up.

11 Final Efficacy Report

See **Supporting Tables and Figures 11.6**

11.1 Participant summaries and baseline predictors of COR positivity and TB incidence

The participant disposition will be summarized. Trial completion, trial withdrawals, exclusions and protocol non-compliances will be summarized. A CONSORT diagram will be used to describe the number of subjects: screened, enrolled by study group, with a positive COR, completing the treatment regimen, and completing all follow-up visits. The diagram will be supplemented with a table summarizing the number and percentage of those not completing the preventive treatment series or who withdrew from the study prior to completion of the endpoint evaluation visits accompanied by the reasons for withdrawal. A listing will be prepared detailing the reasons for missed or out-of-window visits.

Data for baseline and demographic variables will be listed by study group. Descriptive statistics will be provided. The baseline variables will include:

- Demographics: age, height, weight, BMI, race, sex, socioeconomic variables
- Pre-existing conditions that may influence the COR or TB risk including, prior TB, smoking, TB risk factors, TB contact (including number and proximity of TB contacts if present), febrile illness
- Clinical laboratory values and vital signs including normal ranges: concomitant medications, heart rate, systolic/diastolic blood pressure, body temperature

Fisher's Exact test (categorical data) or ANOVA (continuous data) will be used to test for any statistically noticeable differences ($p < 0.05$) in categorical demographic or baseline data between the treatment groups. A test will be performed comparing: (1) Group A vs. Group B (randomized; relevant for TE estimation), (2) Group B vs. Group C (non-randomized; relevant for RR estimation) and (3) Group A+B vs. Group C (non-randomized; relevant for comparison of COR+/-).

Additional relevant variables that are collected at each point of contact with the participant will be summarized and presented in tabular format. These variables may include: concomitant medication, medical history, pregnancy, vital signs, liver function and specific TB symptoms elicited at visits.

11.2 TB prevalence and incidence

A plot of cumulative incidence ($1 - S_x$) with 95% confidence interval will be provided for each group. A table accompanying the plot will provide the numbers of participants enrolled, diagnosed with TB, at-risk and LTFU at baseline and at the conclusion of each Study Visit. The primary figure and table will present data that includes all participants included in the ITT cohort and will use the two-sample TB endpoint definition. Additional figures and tables will be limited to either the mITT or per-protocol populations.

Prevalent/early incident TB disease will be shown using a table of the number and fraction of participants (with 95% CIs) in each group with and without endpoint-defined TB at Visit 2.

All figures and tables reporting incident and prevalent TB will be provided for the entire study population as well as by study site.

11.3 Primary Aim 1: Treatment Efficacy

Treatment efficacy over 15 months of follow-up (*TE(15))* will be estimated using the two-sample TB endpoint definition in the mITT population that excludes prevalent TB diagnosed at Visit 2. See the relevant sections about endpoint-defined TB (**Section 3**), the definition of the mITT population (**Section 4**) and the computation of *TE(15)* (**Section 6**) for details. The following null hypothesis will be tested using a two-sided $\alpha < 0.1$ threshold:

$$H_0: TE(15) \leq 20\%$$

Cumulative TE will be presented with point-estimates and the 90% confidence interval plotted as a function of follow-up time. A p-value will only be presented for the final timepoint, *TE(15)*. A table will contain the number of participants enrolled, the numbers of participants with endpoint-defined TB disease and the average, annualized incidence of TB in Groups A and B, with 95% confidence intervals. The table will also contain a point-estimate and 90% CI for TE(15). No adjustments for study site, baseline or demographic variables will be performed. All figures and tables will also be generated for the population enrolled at each study site, though a p-value for the null-hypothesis will only be presented for the entire study population.

An additional figure and table will show cumulative TE among participants that adhered to TB treatment according to the protocol.

11.4 Primary Aim 2: COR Performance for All Endpoint-defined TB

The primary analysis of $RR_{COR}(15)$ will be estimated using the two-sample TB endpoint definition in the ITT population. See the relevant sections about endpoint-defined TB (**Section 3**), the definition of the ITT population (**Section 4**) and the computation of $RR_{COR}(15)$ (**Section 7**) for details. The following null hypothesis will be tested using a two-sided $\alpha < 0.05$ threshold:

$$H_0: \mathrm{RR}_{COR}(15) \leq 1$$

Cumulative RR_{COR} will be presented with point-estimates and the 90% confidence intervals plotted as a function of follow-up time. A p-value will only be presented for the final timepoint, $RR_{COR}(15)$. A table will contain the number of participants enrolled, the numbers of participants with endpoint-defined TB disease and the average, cumulative incidence of TB in Groups B and C, with 95% confidence intervals. The table will also contain a point-estimate and 95% CI for $RR_{COR}(15)$. No adjustments for study site, baseline or demographic variables will be performed. All figures and tables will also be generated for the population enrolled at each study site, though a p-value for the null-hypothesis will only be presented for the entire study population.

A table will quantify the performance of the COR to predict and prevent TB disease in the ITT population based on its relative-risk (RR_{COR}), sensitivity, specificity, positive predictive value (*PPV*), and number needed to treat (*NNT*). These metrics will be computed using final tallies of the TB endpoints observed in each group and will assume that all enrolled participants were at-risk for the full duration of the study. For this reason, the estimate of RR_{COR} may not be equivalent to that of $RR_{COR}(15)$, which takes the timing of endpoints and censoring into account. The sensitivity and specificity metrics will be adjusted to reflect the screened population as opposed to the COR+ enriched participants that were enrolled (see **Section 7.3** for details). An exploratory analysis may use time-dependent methods to estimate these performance metrics with confidence intervals over time.

To estimate the diagnostic performance of the COR biomarker, a table will present the number and fraction of participants (with the 95% CI) in Groups B and C with and without endpoint-defined TB at Visit 2. The table will also show the point-estimate and confidence interval for RR_{COR} as well as sensitivity, specificity, PPV and NNT for prevalent TB.

11.5 Secondary Aim 1: COR Performance for Detection of Prevalent TB

To evaluate the diagnostic performance of the COR biomarker we will estimate the relative-risk of endpoint-defined TB detected at enrollment (Visit 2), $RR_{COR}(V2)$. Endpoints will be analyzed as binary indicators of TB at Visit 2 using methods described in **Section 7.2**. Results will be presented for the entire study population as well as for each study site.

11.6 Secondary Aim 2: COR Performance for Prediction of Incident TB

To evaluate the prognostic performance of the COR biomarker we will estimate the relative-risk of endpoint-defined TB over 15 months, $RR_{COR}(15)$, in COR+ (Group B) versus COR- (Group C) participants in the mITT cohort that excludes TB cases observed at Visit 2. Tables and figures will parallel those used in **Section 11.4** to evaluate $RR_{COR}(15)$ in the ITT population. Results will be presented for the entire study population as well as for each study site.

11.7 Secondary Aim 3: IGRA Performance for Prediction of TB

All participants will provide a sample for use in the QuantiFERON GIT (QFT) interferon gamma release assay (IGRA) that tests for TB-specific T-cell responses that are indicative of a latent TB infection. We will evaluate the relative-risk of endpoint-defined TB in IGRA+ versus IGRA- participants, over 15 months ($RR_{QFT}(15)$). Participants will be pooled from Groups B and C who were both under active surveillance for TB and were blinded to their group assignment and COR status. The primary analysis will evaluate $RR_{QFT}(15)$ on endpoints in the mITT cohort using the two-sample endpoint definition and according to the cumulative-incidence based approach for $RR_{COR}(15)$ described for Primary Aim 2. One notable exception is that the inverse probability weighting, described in **Section 7.3** will be required to recover population estimates of IGRA performance, including RR. See the relevant sections about endpoint-defined TB (**Section 3**), the definition of study populations (**Section 4**) and the computation of $RR_{COR}(15)$ (**Section 7.2**) for details. Tables and figures presenting results will parallel those for evaluation of $RR_{COR}(15)$ described in **Section 11.4**. In each plot of RR_{QFT} a line indicating RR_{COR} will also be shown for comparison.

We will also present an analysis of the IGRA as a diagnostic biomarker for Visit 2 TB, as well as a prognostic TB biomarker in the mITT population.

A comparison of the concordance of the COR biomarker and the IGRA will be summarized in a table. The table will show the number and fraction of participants in the pooled Groups B and C that were IGRA+/- or COR+/-.

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13 Supporting Tables and Figures

This section contains mock tables, listings, and figures illustrating specific details for the analyses described above.

13.1 Operational Monitoring

The figures and tables describing the progress of the trial (**Sections 11.1.1 – 11.1.4**) will be presented for each study site and for the study as a whole. The simulation will not

distinguish between study sites and therefore tables and figures will be presented only for the study as a whole.

13.1.1 Figure: CONSORT diagram

Diagram indicating screening, randomization, and enrolment.

13.1.2 Table: Participant disposition

Summary table of screening, enrolment, visit completion, and LTFU presented by study site and for the study as a whole.

Table 11.1.2: Participant Disposition
All Screened Subjects

		Site 1	Site 2	Site 3	Total
Screened	N	*NA*	*NA*	*NA*	*N*
Enrolled	N	*N*	*N*	*N*	*n (%)*
Not Enrolled	N	*NA*	*NA*	*NA*	*n (%)*
Reason not Enrolled[1]					
Withdrawal of Informed Consent	N	*NA*	*NA*	*NA*	*n (%)*
Inclusion/Exclusion Criteria Not Met	N	*NA*	*NA*	*NA*	*n (%)*
Other	N	*NA*	*NA*	*NA*	*n (%)*
Enrolled[2]	N	*N*	*N*	*N*	*n (%)*
All scheduled visits attended	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*
Missed visits but no early termination	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*
Early termination or LTFU	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*
Trial Completion	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*

Footnote 1: Percentages in this group are computed using total number not enrolled as denominator.
Footnote 2: Percent enrolled is computed as fraction of N screened. Subsequent percentages in this group are computed as a fraction of N enrolled.

13.1.3 Table: Group blinded endpoint accrual

Rows for all, prevalent (Visit 2 diagnosis) and mITT cohort (i.e. Visit 3 or later) TB endpoints.

Table 11.1.3: Group blinded endpoint accrual
All Screened Subjects

		Site 1	Site 2	Site 3	Total
ITT cohort	N	*N*	*N*	*N*	*N*
Subjects diagnosed with TB at Visit 2[1]					
1. Based on two-sample detection	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*
+ve Xpert MTB/RIF	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*
+ve MGIT culture	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*
+ve Xpert MTB/RIF & MGIT culture	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*

2. Based on one-sample detection	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*
+ve Xpert MTB/RIF	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*
+ve MGIT culture	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*
+ve Xpert MTB/RIF & MGIT culture	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*
Subjects diagnosed with TB at/after Visit 2[1]					
Based on two-sample detection	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*
+ve Xpert MTB/RIF	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*
+ve MGIT culture	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*
+ve Xpert MTB/RIF & MGIT culture	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*
Based on one-sample detection	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*
+ve Xpert MTB/RIF	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*
+ve MGIT culture	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*
+ve Xpert MTB/RIF & MGIT culture	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*
mITT cohort	N	*N*	*N*	*N*	*N*
Subjects diagnosed with TB at/after Visit 3[2]					
1. Based on two-sample detection	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*
+ve Xpert MTB/RIF	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*
+ve MGIT culture	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*
+ve Xpert MTB/RIF & MGIT culture	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*
2. Based on one-sample detection	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*
+ve Xpert MTB/RIF	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*
+ve MGIT culture	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*
+ve Xpert MTB/RIF & MGIT culture	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*

Footnote 1: Percentages in this group are computed using total number in ITT cohort as denominator.
Footnote 2: Percentages in this group are computed using total number in mITT cohort as denominator.

13.1.4 Figure: Group blinded endpoint accrual

Plot of endpoint accrual by study time (i.e. Visit number), with multiple lines indicating the one/two sample endpoint definition.

13.1.5 Table: Simulation parameters

Rows for each of the relevant parameters needed to run the trial simulations and project trial completion.

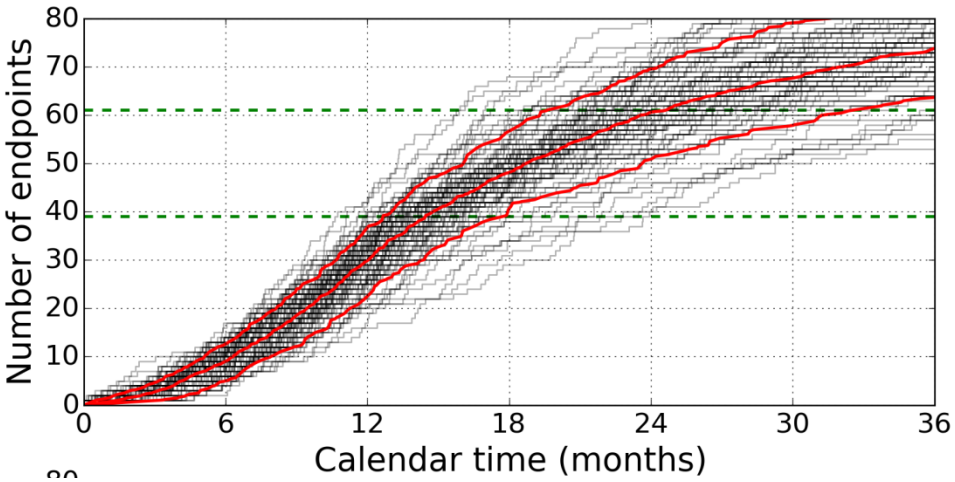
Table 11.1.5: Simulation parameters

	Total

Parameters based on current state of the trial			
1.	No. of participants enrolled	n	*n*
2.	Total no. of endpoints observed	n	*n*
3.	Total no. of participants lost to follow-up	n	*n*

13.1.6 Figure: Endpoint accrual in simulated trials

Blinded endpoint accrual will be plotted as a function of calendar time in months. The initial section of the trial that has already passed will be represented by a single line, while simulated trials from that point onward will be plotted as a "cloud" of lines annotated with relevant percentiles. The plot will indicate the full duration and the time until the 20th and 40th endpoint of the 90th percentile trial. A draft example is provided below.



13.1.7 Table: Projected endpoint accrual

Rows for the observed endpoints as well as projected endpoints at 6 month intervals through completion of the 90th percentile trial. Columns for the 5th, 10th, 50th, 90th, and 95th percentile of endpoints observed at each time point.

Table 11.1.7: Projected endpoint accrual at 6 month intervals through completion of 90th percentile trial

		Projected Quantiles				
	Observed	**5th**	**10th**	**50th**	**90th**	**95th**
Observed endpoints	x	.	.	.	.	.
Projected endpoints accrued through 6 mos	.	x	x	x	x	x
Projected endpoints accrued through 12 mos	.	x	x	x	x	x

Projected endpoints accrued through 18 mos	.	x	x	x	x	x

13.1.8 Table: Projected trial duration

Rows for completion of screening, time to 40 endpoints (i.e. interim analysis trigger), and trial completion. Columns for the 5th, 10th, 50th, 90th, and 95th percentile of each duration.

Table 11.1.8: Projected trial duration

	Projected Quantiles				
	5th	**10th**	**50th**	**90th**	**95th**
Completion of screening	x	x	x	x	x
Time to 40 endpoints	x	x	x	x	x
Trial completion	x	x	x	x	x

13.2 Interim Efficacy Analysis

All figures and tables describing unblinded results of the trial up to and including the 40th observed primary endpoint will be presented by study site in addition to the study as a whole. Results will be presented for the ITT, mITT and PP cohorts (PP cohort for Group A and TE results only). No safety data will be presented in the Interim Efficacy Report.

13.2.1 Figure: CONSORT diagram

Diagram indicating screening, randomization, enrolment, LTFU, endpoints, treatment initiation/completion and followup completion.

13.2.2 Table: Participant disposition

Summary table of screening, enrolment, group assignment, visit completion, LTFU and participant demographics presented by study site and for the study as a whole. See **Section 11.3.15 and 11.3.16** for an example.

13.2.3 Table: Unblinded endpoint accrual

Table will include row for all TB cases by group, as well as prevalent (Visit 2 diagnosis) and those identified in the mITT cohort (i.e. Visit 3 or later). Table will also differentiate between one vs. two sample detection and will indicate whether the endpoint was Xpert MTB/RIF and/or MGIT positive.

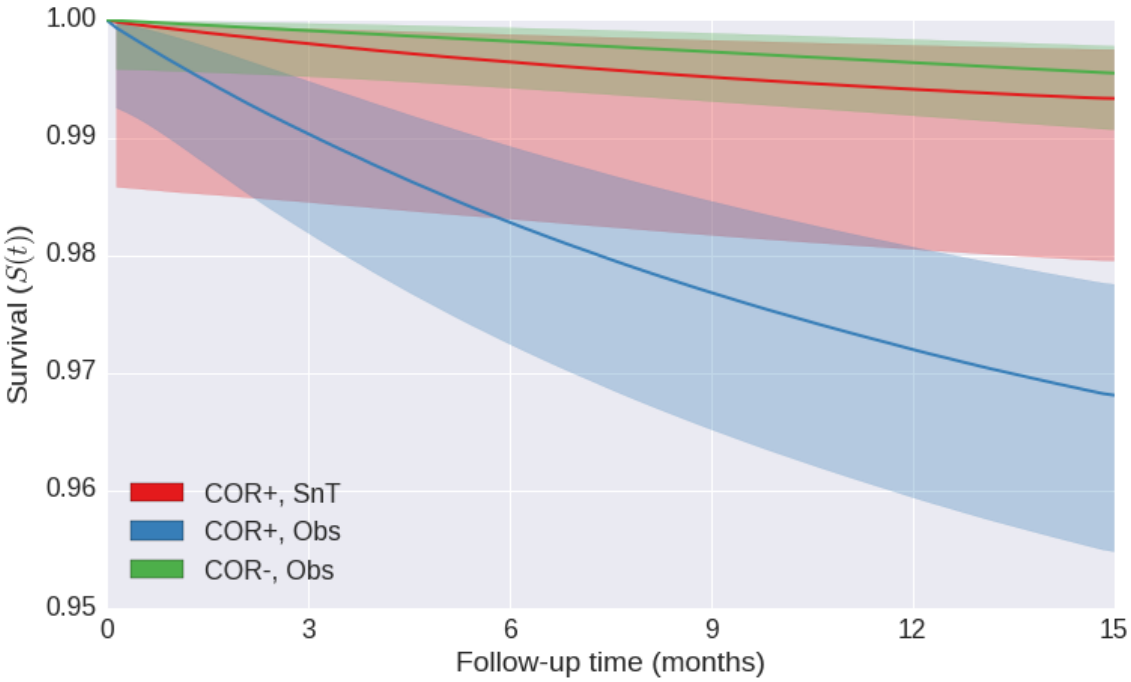
Table 11.2.3: Unblinded endpoint accrual

		Group 1	**Group 2**	**Group 3**	**Total**
ITT cohort	N	*N*	*N*	*N*	*N*
Subjects diagnosed with TB at Visit 2[1]					
1. Based on two-sample detection	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*
+ve Xpert MTB/RIF	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*
+ve MGIT culture	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*
+ve Xpert MTB/RIF & MGIT culture	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*
2. Based on one-sample detection	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*
+ve Xpert MTB/RIF	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*
+ve MGIT culture	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*
+ve Xpert MTB/RIF & MGIT culture	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*
Subjects diagnosed with TB at/after Visit 2[1]					
Based on two-sample detection	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*
+ve Xpert MTB/RIF	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*
+ve MGIT culture	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*
+ve Xpert MTB/RIF & MGIT culture	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*
Based on one-sample detection	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*
+ve Xpert MTB/RIF	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*
+ve MGIT culture	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*
+ve Xpert MTB/RIF & MGIT culture	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*
mITT cohort	N	*N*	*N*	*N*	*N*
Subjects diagnosed with TB at/after Visit 3[2]					
1. Based on two-sample detection	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*
+ve Xpert MTB/RIF	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*
+ve MGIT culture	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*
+ve Xpert MTB/RIF & MGIT culture	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*
2. Based on one-sample detection	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*
+ve Xpert MTB/RIF	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*
+ve MGIT culture	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*
+ve Xpert MTB/RIF & MGIT culture	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*

Footnote 1: Percentages in this group are computed using total number in ITT cohort as denominator.
Footnote 2: Percentages in this group are computed using total number in mITT cohort as denominator.

13.2.4 Figure: Unblinded endpoint accrual

Survival plots with multiple lines indicating the groups and the one/two sample endpoint definition.



13.2.5 Table: Point estimates and confidence intervals for TE(X) and $RR_{CoR}(X)$

Estimates of TE(X) and 95% CIs will be presented for the ITT, mITT and PP cohorts. Estimates of RR(X) and 95% CIs will be presented for the ITT, mITT cohorts as well as for prevalent (Visit 2) endpoints only. Confidence intervals will be calculated using the Greenwood variance estimator of the survival function.

Table 11.2.5.1: Point estimates and CIs for TE(X)

		Group A	**Group B**
Total subjects diagnosed with TB at time of interim efficacy report	n^3/N^4 = %	*n/N = %*	*n/N = %*
S_X (X)[1]	x	*x*	*x*
TE(X) (95% CI)[2]	x (x, x)	*x (x, x)*	

Footnote 1: Product-Limit estimator of Nelson-Aalen based on survival function
Footnote 2: TE evaluated cumulatively over 15 months of follow-up with 95% CI calculated using the Greenwood variance estimator. Subjects not completing 15 months of follow-up and not reporting TB disease are right-censored.
Footnote 3: n = Number of subjects diagnosed with TB by 15 months
Footnote 4: N = Number of subjects at risk at study start (will differ for ITT, mITT and PP cohorts)

Table 11.2.5.2: Point estimates and CIs for $RR_{CoR}(15)$

		Group B	**Group C**
Total subjects diagnosed with TB at time of interim efficacy report	n^3/N^4 = %	*n/N = %*	*n/N = %*
S_X (X)[1]	x	*x*	*x*
RR_{CoR} (X) (95% CI)[2]	x (x, x)	*x (x, x)*	

Footnote 1: Survival based on the Nelson-Aalen Product-Limit estimator
Footnote 2: RR_{CoR} evaluated cumulatively over 15 months of follow-up with 95% CI calculated using the Greenwood variance estimator. Subjects not completing 15 months of follow-up and not reporting TB disease are right-censored.
Footnote 3: n = Number of subjects diagnosed with TB by 15 months
Footnote 4: N = Number of subjects at risk at study start (will differ for ITT, mITT and PP cohorts)

13.2.6 Table: Scenario A and Scenario B Hypothesis Testing

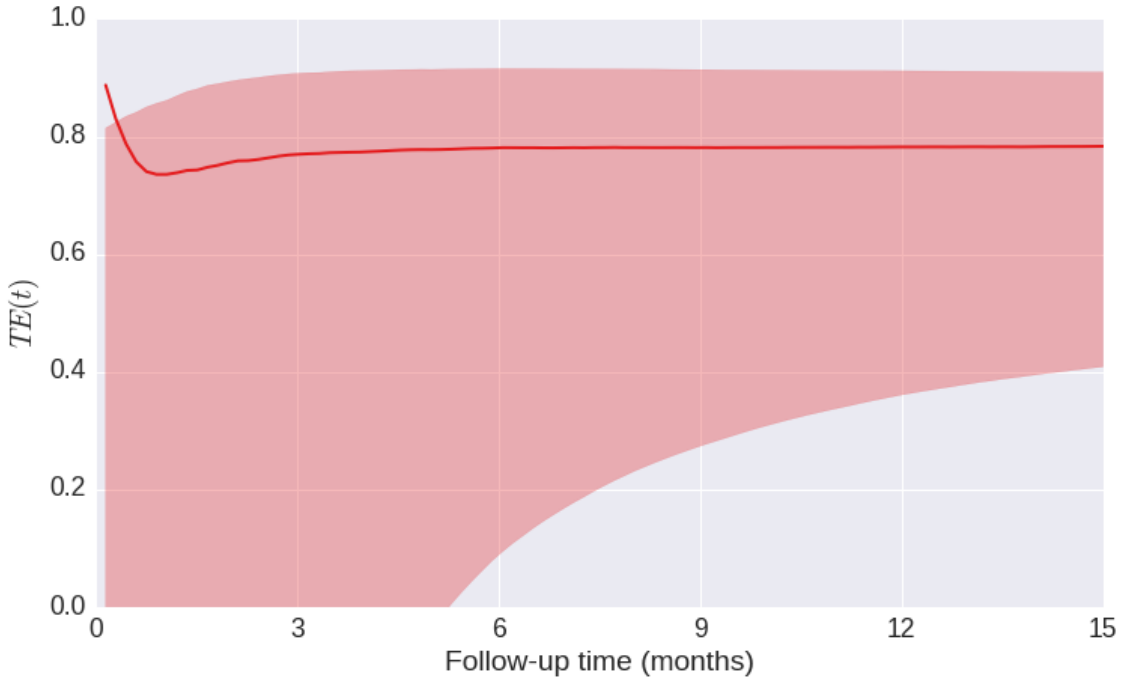
Table indicating the null hypothesis for each Scenario and the associated Wald test p-values for *TE(X)* and $RR_{COR}(X)$.

Table 11.2.6: Hypothesis Testing for Scenarios A and B
mITT cohort

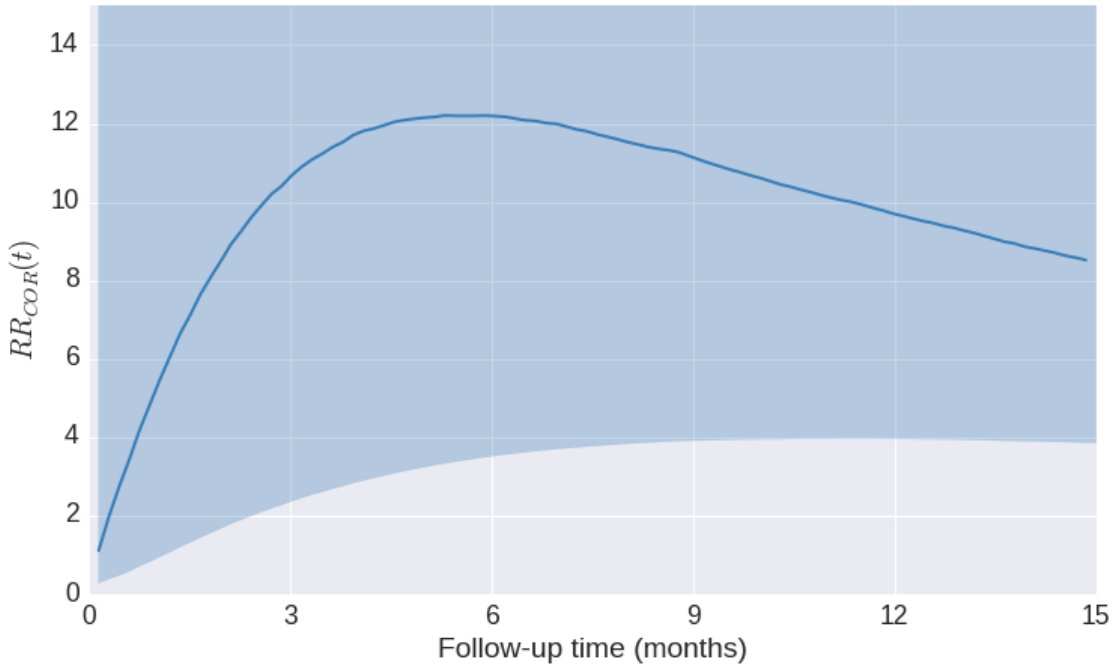
	Null	N[1]	p-value[2]
Scenario A	$RR_{COR}(X) \leq 5$	*N*	*x.xxx*
	$TE(X) \leq 60\%$	*N*	*x.xxx*
Scenario B	$RR_{COR}(t) \leq 5$	*N*	*x.xxx*
	$TE(t) \geq 60\%$	*N*	*x.xxx*

Footnote 1: Number of subjects in mITT cohort
Footnote 2: Two-sided pvalue computed for each hypothesis independently using a Wald test.

13.2.7 Figure: Cumulative treatment efficacy



13.2.8 Figure: Cumulative COR relative risk



13.3 Final Efficacy Analysis

All figures and tables describing unblinded results of the completed trial will be presented by study site in addition to the study as a whole. Results will be presented for the ITT, mITT and PP cohorts (PP cohort for Group A and TE results only). Summaries of non-severe adverse events will appear in the Final Safety Report provided by the Data Centre.

13.3.1 Figure: CONSORT diagram

Diagram indicating number of subjects screened, randomized, enrolled by study group, with a positive COR, LTFU, endpoints, treatment initiation/completion and follow-up completion.

13.3.2 Table: Participant disposition

Summary table of screening, enrolment, group assignment, visit completion, LTFU and participant demographics presented by study site and for the study as a whole. See **Section 11.3.15 and 11.3.16** for an example.

13.3.3 Table(s): Baseline variables by Group

A summary of each relevant variable measured at baseline will be included in tables presented by group and for the study overall (ITT cohort only). To assess the balance of each variable across the groups, three p-values will be presented for each variable: (1) Group A vs. Group B (randomized; relevant for TE estimation), (2) Group B vs. Group C (non-randomized; relevant for RR estimation) and (3) Group A+B vs. Group C (non-randomized; relevant for comparison of COR+/-). Normal ranges for each variable will be presented from the most recent DAIDS toxicity table.

13.3.4 Table: Endpoint accrual by Study Group

Table will include row for all TB cases, as well as prevalent (Visit 2 diagnosis) and those identified in the mITT (i.e. Visit 3 or later) or PP cohorts. Table will also differentiate between one vs. two sample detection and will indicate whether the endpoint was Xpert MTB/RIF and/or MGIT positive (see **Section 11.2.3** for draft example).

I. TB prevalence and incidence (Sections 11.3.5 and 11.3.6)

13.3.5 Figure: Survival by Study Group

Survival plots with multiple lines indicating the Study Groups and the one/two sample endpoint definition (see **Section 11.2.4** for draft example).

13.3.6 Table: Subjects diagnosed with TB and at-risk at each study visit

A table providing the number of participants enrolled, diagnosed with TB using the two-sample TB endpoint definition (including 95% CI), at-risk and LTFU at baseline and at the conclusion of each Study Visit will be presented for the ITT cohort by study group. Additional figures and tables will be limited to either the mITT or per-protocol populations and/or using the one-sample TB endpoint definition.

All figures and tables reporting incident and prevalent TB will be provided for the entire study population as well as by study site.

Table 11.3.6: Subjects diagnosed with TB and at-risk at each study visit for ITT cohort[4]

		Group A	**Group B**	**Group C**
No. of subjects enrolled (ITT cohort)	N	*N*	*N*	*N*
Visit 2	n^1/N^2 = %; n^3	*n/N = %; n*	*n/N = %; n*	*n/N = %; n*
Contact 3	n/N = %; n	*n/N = %; n*	*n/N = %; n*	*n/N = %; n*
Contact 4	n/N = %; n	*n/N = %; n*	*n/N = %; n*	*n/N = %; n*
Visit 5	n/N = %; n	*n/N = %; n*	*n/N = %; n*	*n/N = %; n*
Visit 6	n/N = %; n	*n/N = %; n*	*n/N = %; n*	*n/N = %; n*
Contact 7	n/N = %; n	*n/N = %; n*	*n/N = %; n*	*n/N = %; n*
Visit 8	n/N = %; n	*n/N = %; n*	*n/N = %; n*	*n/N = %; n*
Visit 9	n/N = %; n	*n/N = %; n*	*n/N = %; n*	*n/N = %; n*
Cumulative	n/N = %; n	*n/N = %; n*	*n/N = %; n*	*n/N = %; n*

Footnote 1: Number of subjects diagnosed with TB
Footnote 2: Number of subjects at-risk
Footnote 3: Number of subjects lost to follow-up
Footnote 4: This table could be prepared for mITT/PP cohort and/or with one-sample TB endpoint definition.

II. Primary Aim 1: Treatment Efficacy (Sections 11.3.7 and 11.3.8)

13.3.7 Table: Point estimates and confidence intervals for TE(15)

Estimates of TE(15) will be presented for the mITT and PP cohorts. Estimates will be accompanied by 95% confidence intervals and p-values for the null-hypotheses specified above. The table and figure below will be prepared for the PP cohort as well as for each site (but without a p-value).

Table 11.3.7: Point estimates and CIs for TE(15) for mITT cohort[4]

		Group A	**Group B**
Subjects diagnosed with endpoint-defined TB at/after Visit 3	n/N	*n/N*	*n/N*
Average, annualized incidence of TB with 95% CI	x (x, x)	*x (x, x)*	*x (x, x)*
S_X (15)[1]	x	*x*	*x*
TE(15) (95% CI)[2]	x (x, x)	*x (x, x)*	
p-value[3]		*x.xxx*	

Footnote 1: Product-Limit estimator of Nelson-Aalen based on survival function
Footnote 2: TE evaluated cumulatively over 15 months of follow-up with 95% CI calculated using the Greenwood variance estimator.
Footnote 3: p-value calculated using a one-sided alpha < 0.05 threshold and tests null of TE(15) less or equal to 20%.
Footnote 4: This table will also be prepared for each site but without a p-value

13.3.8 Figure: Cumulative treatment efficacy

See **Section 11.2.7** for draft example.

III. Primary Aim 2: COR Performance (Sections 11.3.9, 11.3.10 and 11.3.11)

13.3.9 Table: Point estimates and confidence intervals for $RR_{CoR}(15)$

Estimates of RR(15) will be presented for the ITT cohorts well as for prevalent (Visit 2) endpoints only. Estimates will be accompanied by 95% confidence intervals and p-values for the null-hypotheses specified above. All tables and figures will be generated for the population enrolled at each study site but inference made only for the entire study population.

Table 11.3.9: Point estimates and CIs for $RR_{CoR}(15)$ for subjects diagnosed with endpoint-defined TB at/after Visit 2 for ITT cohort[4]

		Group B	**Group C**
Subjects diagnosed with endpoint-defined TB at/after Visit 2	n/N	*n/N*	*n/N*
Average, annualized incidence of TB with 95% CI	x (x, x)	*x (x, x)*	*x (x, x)*
S_X (15)[1]	x	*x*	*x*
RR_{CoR} (15) (95% CI)[2]	x (x, x)	*x (x, x)*	
p-value[3]		*x.xxx*	

Footnote 1: Product-Limit estimator of Nelson-Aalen based on survival function
Footnote 2: RR_{CoR} evaluated cumulatively over 15 months of follow-up with 95% CI calculated using the Greenwood variance estimator.
Footnote 3: p-value calculated using a one-sided alpha < 0.025 threshold and tests null of RR_{CoR} (15) less or equal to 1.
Footnote 4: This table will also be prepared for each site but without a p-value

13.3.10 Figure: Cumulative COR relative risk

See **Section 11.2.8** for draft example.

13.3.11 Table: Biomarker performance

Table of endpoints in each Study Group along with estimates of relative risk, sensitivity, specificity, positive predictive value (PPV), number needed to treat (NNT) and other relevant metrics. Each row will summarize performance of either the CoR or IGRA/QFT biomarker in the ITT, mITT cohorts and among prevalent case detection (Visit 2).

Table 11.3.11.1: Point estimates and CIs for RR_{CoR} for subjects diagnosed with endpoint-defined TB at/after Visit 2 for ITT cohort

		Group B	**Group C**
Subjects diagnosed with endpoint-defined TB at/after Visit 2	n/N	*n/N*	*n/N*
RR_{CoR} (95% CI)[1]	x (x, x)	*x (x, x)*	
Sensitivity		*x.xx*	
Specificity		*x.xx*	
PPV		*x.xx*	
NNT		*x*	

Footnote 1: RR_{CoR} with 95% CI assumes that all enrolled participants were at-risk for the full duration of the study.

Table 11.3.11.2: Point estimates and CIs for RR_{CoR} for subjects diagnosed with endpoint-defined TB "at" Visit 2 for ITT cohort

		Group B	**Group C**
Subjects diagnosed with endpoint-defined TB "at" Visit 2	n/N	*n/N*	*n/N*
RR_{CoR} (95% CI)[1]	x (x, x)	*x (x, x)*	
Sensitivity		*x.xx*	
Specificity		*x.xx*	
PPV		*x.xx*	
NNT		*x*	

Footnote 1: RR_{CoR} with 95% CI assumes that all enrolled participants were at-risk for the full duration of the study.Footnote 2: This table made only for ITT cohort, not for mITT cohort.

IV. Secondary Aim 1: Prognostic COR performance for prediction of incident TB

Tables and Figures in Primary Aim 2 will be made for the mITT cohort for entire study population and each study site. No inference will be made in these results.

V. Secondary Aim 2: IGRA performance for prediction of incident TB and concordance between COR and IGRA (Sections 11.3.12 and 11.3.13)

13.3.12 Table: IGRA performance

Estimates of $RR_{QFT}(15)$ will be presented for the mITT cohort using two-sample endpoint definition and according to the cumulative-incidence based approach for $RR_{COR}(15)$. Participants from Groups B and C will be pooled for this analysis. Tables and Figures will be similar to ones in Primary Aim 2.

For each plot of RR_{QFT}, a line indicating RR_{COR} in the matched study population will also be shown for comparison. Results will show IGRA performance as a diagnostic biomarker for Visit 2 TB, as well as a prognostic TB biomarker in the mITT population.

13.3.13 Table: Biomarker concordance

Table showing the number and fraction of participants with COR+/- and IGRA/QFT+/- to assess the concordance of the biomarkers.

Table 11.3.13: Number and fraction of participants in pooled groups B and C that were +/- for IGRA or COR in ITT cohort

	IGRA +ve	**IGRA -ve**	**Total**
COR +ve	*n (x.xx)*	*n (x.xx)*	*n (x.xx)*
COR -ve	*n (x.xx)*	*n (x.xx)*	*n (x.xx)*
Total	*n (x.xx)*	*n (x.xx)*	*n (x.xx)*

13.3.14 Participant disposition

Summary table of screening, enrolment, group assignment, visit completion, LTFU and participant demographics presented by study site and for the study as a whole.

Table 11.3.15: Participant Disposition
All Screened Subjects

		Group A	**Group B**	**Group C**	**Total**
Screened	N	*NA*	*NA*	*NA*	*N*
Enrolled	N	*N*	*N*	*N*	*n (%)*
Not Enrolled	N	*NA*	*NA*	*NA*	*n (%)*
Reason not Enrolled[1]					
Withdrawal of Informed Consent	N	*NA*	*NA*	*NA*	*n (%)*
Inclusion/Exclusion Criteria Not Met	N	*NA*	*NA*	*NA*	*n (%)*
Other	N	*NA*	*NA*	*NA*	*n (%)*
Enrolled[2]	N	*N*	*N*	*N*	*n (%)*
Positive COR	n (%)	*n (%)*	*n (%)*	*NA*	*n (%)*
Received any DOT	n (%)	*n (%)*	*NA*	*NA*	*n (%)*
Received all DOTS	n (%)	*n (%)*	*NA*	*NA*	*n (%)*
All visits attended	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*
Missed visits but no early termination	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*
Early termination	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*
Trial Completion	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*
Reasons for early termination:	N	*N*	*N*	*N*	*N*
Withdrawal of informed consent	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*
SAE /Severe AE	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*
Adverse event	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*
Failure to comply with protocol requirements	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*
Lost to follow-up	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*
Death	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*
Discretion of investigator	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*
Other	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*

Footnote 1: Percentages in this group are computed using total number not enrolled as denominator.
Footnote 2: Percent enrolled is computed as fraction of N screened. Subsequent percentages in this group are computed as a fraction of N enrolled.

13.3.15 Tables: Additional relevant variables

Tables will present any additional variables that may be relevant to the interpretation of treatment efficacy or biomarker performance. This may include concomitant medication, pre-existing conditions and medical history, pregnancy or vital signs, throughout the trial.

Table 11.3.16.1: Demographic characteristics by group
Intention to Treat Population (annotated with p-value from exact test/ANOVA for differences among groups)

			Group A (N)	**Group B (N)**	**Groups A & B (N)**	**Group C (N)**	**Total (N)**	**Pvalue (A vs B; B vs C; A+B vs C)**
Gender	Male	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*	*n (%)*	*x.xxx; x.xxx; x.xxx*
	Female	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*	*n (%)*	
	Missing	n (%)	*n (%)*	n *(%)*	n *(%)*	n *(%)*	n *(%)*	*x.xxx; x.xxx; x.xxx*
Age (years)	N	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*	*n (%)*	
	Mean (SD)	x.x (x.x)	*x.x (x.x)*	*x.x (x.x)*	*x.x (x.x)*	*x.x (x.x)*	*x.x (x.x)*	*x.xxx; x.xxx; x.xxx*
	Median (Q1, Q3)	x.x (x.x, x.x)	*x.x (x.x, x.x)*	*x.x (x.x, x.x)*	*x.x (x.x, x.x)*	*x.x (x.x, x.x)*	*x.x (x.x, x.x)*	
	Range (min, max)	(x, x)	*(x, x)*	*(x, x)*	*(x, x)*	*(x, x)*	*(x, x)*	
Ethnicity	Caucasian	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*	*n (%)*	*x.xxx; x.xxx; x.xxx*
	Asian	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*	*n (%)*	*x.xxx; x.xxx; x.xxx*
	Black	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*	*n (%)*	*x.xxx; x.xxx; x.xxx*
	Mixed	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*	*n (%)*	*x.xxx; x.xxx; x.xxx*
	Other	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*	*n (%)*	*x.xxx; x.xxx; x.xxx*
	Missing	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*	*n (%)*	*x.xxx; x.xxx; x.xxx*
Height (cm)	N	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*	*n (%)*	
	Mean (SD)	x.x (x.x)	*x.x (x.x)*	*x.x (x.x)*	*x.x (x.x)*	*x.x (x.x)*	*x.x (x.x)*	*x.xxx; x.xxx; x.xxx*
	Median (Q1, Q3)	x.x (x.x, x.x)	*x.x (x.x, x.x)*	*x.x (x.x, x.x)*	*x.x (x.x, x.x)*	*x.x (x.x, x.x)*	*x.x (x.x, x.x)*	
	Range (min, max)	(x.x, x.x)	*(x.x, x.x)*	*(x.x, x.x)*	*(x.x, x.x)*	*(x.x, x.x)*	*(x.x, x.x)*	
Weight (kg)	N	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*	*n (%)*	
	Mean (SD)	x.x (x.x)	*x.x (x.x)*	*x.x (x.x)*	*x.x (x.x)*	*x.x (x.x)*	*x.x (x.x)*	*x.xxx; x.xxx; x.xxx*
	Median (Q1, Q3)	x.x (x.x, x.x)	*x.x (x.x, x.x)*	*x.x (x.x, x.x)*	*x.x (x.x, x.x)*	*x.x (x.x, x.x)*	*x.x (x.x, x.x)*	
	Range (min, max)	(x.x, x.x)	*(x.x, x.x)*	*(x.x, x.x)*	*(x.x, x.x)*	*(x.x, x.x)*	*(x.x, x.x)*	

BMI (kg/m2)	N	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*	*n (%)*	*x.xxx; x.xxx; x.xxx*
	Mean (SD)	x.x (x.x)	*x.x (x.x)*	*x.x (x.x)*	*x.x (x.x)*	*x.x (x.x)*	*x.x (x.x)*	
	Median (Q1, Q3)	x.x (x.x, x.x)	*x.x (x.x, x.x)*	*x.x (x.x, x.x)*	*x.x (x.x, x.x)*	*x.x (x.x, x.x)*	*x.x (x.x, x.x)*	
	Range (min, max)	(x.x, x.x)	*(x.x, x.x)*	*(x.x, x.x)*	*(x.x, x.x)*	*(x.x, x.x)*	*(x.x, x.x)*	

Footnote 1: All continuous variables measured at baseline .
Footnote 2: Similar table will be made for mITT and PP cohorts.

Table 11.3.16.2: Socioeconomic characteristics by group
Intention to Treat Population (annotated with p-value from exact test/ANOVA for differences among groups)

			Group A (N)	**Group B (N)**	**Groups A & B (N)**	**Group C (N)**	**Total (N)**	**Pvalue (A vs B; B vs C; A+B vs C)**
Highest level of education	Primary School	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*	*n (%)*	*x.xxx; x.xxx; x.xxx*
	High School	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*	*n (%)*	*x.xxx; x.xxx; x.xxx*
	Tertiary Diploma	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*	*n (%)*	*x.xxx; x.xxx; x.xxx*
	Tertiary Degree	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*	*n (%)*	*x.xxx; x.xxx; x.xxx*
	No Schooling	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*	*n (%)*	*x.xxx; x.xxx; x.xxx*
	Missing	n (%)	*n (%)*	n *(%)*	n *(%)*	n *(%)*	n *(%)*	*x.xxx; x.xxx; x.xxx*
Household economic indicators	Unemployed	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*	*n (%)*	*x.xxx; x.xxx; x.xxx*
	Casual employment	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*	*n (%)*	*x.xxx; x.xxx; x.xxx*
	Formal employment	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*	*n (%)*	*x.xxx; x.xxx; x.xxx*
	Missing	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*	*n (%)*	*x.xxx; x.xxx; x.xxx*
Household main breadwinner	Yes	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*	*n (%)*	*x.xxx; x.xxx; x.xxx*
	Missing	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*	*n (%)*	*x.xxx; x.xxx; x.xxx*
Number of romos in household	N	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*	*n (%)*	
	Mean (SD)	x.x (x.x)	*x.x (x.x)*	*x.x (x.x)*	*x.x (x.x)*	*x.x (x.x)*	*x.x (x.x)*	*x.xxx; x.xxx; x.xxx*

	Median (Q1, Q3)	x.x (x.x, x.x)	*x.x (x.x, x.x)*	*x.x (x.x, x.x)*	*x.x (x.x, x.x)*	*x.x (x.x, x.x)*	*x.x (x.x, x.x)*	
	Range (min, max)	(x.x, x.x)	*(x.x, x.x)*	*(x.x, x.x)*	*(x.x, x.x)*	*(x.x, x.x)*	*(x.x, x.x)*	
Number of adults in household	N	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*	*n (%)*	
	Mean (SD)	x.x (x.x)	*x.x (x.x)*	*x.x (x.x)*	*x.x (x.x)*	*x.x (x.x)*	*x.x (x.x)*	*x.xxx; x.xxx; x.xxx*
	Median (Q1, Q3)	x.x (x.x, x.x)	*x.x (x.x, x.x)*	*x.x (x.x, x.x)*	*x.x (x.x, x.x)*	*x.x (x.x, x.x)*	*x.x (x.x, x.x)*	
	Range (min, max)	(x.x, x.x)	*(x.x, x.x)*	*(x.x, x.x)*	*(x.x, x.x)*	*(x.x, x.x)*	*(x.x, x.x)*	
Number of children in household	N	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*	*n (%)*	
	Mean (SD)	x.x (x.x)	*x.x (x.x)*	*x.x (x.x)*	*x.x (x.x)*	*x.x (x.x)*	*x.x (x.x)*	*x.xxx; x.xxx; x.xxx*
	Median (Q1, Q3)	x.x (x.x, x.x)	*x.x (x.x, x.x)*	*x.x (x.x, x.x)*	*x.x (x.x, x.x)*	*x.x (x.x, x.x)*	*x.x (x.x, x.x)*	
	Range (min, max)	(x.x, x.x)	*(x.x, x.x)*	*(x.x, x.x)*	*(x.x, x.x)*	*(x.x, x.x)*	*(x.x, x.x)*	

Footnote 1: All continuous variables measured at baseline .
Footnote 2: Similar table will be made for mITT and PP cohorts.

Figure 11.3.16.3: Boxplots of demographic characteristics (age, height, weight and BMI) by group
ITT Population

[placeholder]

Footnote containing relevant explanation will be included.

Table 11.3.16.4: Pre-existing conditions and their balance across study groups (annotated with p-value from exact test/ANOVA for differences among groups)

Baseline Variable	**Level**	**Group A (N)**	**Group B (N)**	**Groups A & B (N)**	**Group C (N)**	**Total (N)**	**Pvalue (A vs B; B vs C; A+B vs C)**
Prior TB	Yes	*n (%)*	*n (%)*	*n (%)*	*n (%)*	*n (%)*	*x.xxx; x.xxx; x.xxx*
Smoking	Yes	*n (%)*	*n (%)*	*n (%)*	*n (%)*	*n (%)*	*x.xxx; x.xxx; x.xxx*
TB risk factors: 1. Family TB history 2. 3.	Yes	*n (%)*	*n (%)*	*n (%)*	*n (%)*	*n (%)*	*x.xxx; x.xxx; x.xxx*
Any person with active TB disease in householdTB contact 1. Number () 2. Proximity/Relationship to participant 3. Sleeping in same room as participant	Yes	*n (%)*	*n (%)*	*n (%)*	*n (%)*	*n (%)*	*x.xxx; x.xxx; x.xxx*
Febrile Illness	Yes	*n (%)*	*n (%)*				*x.xxx; x.xxx; x.xxx*

Footnote: Fisher's Exact test and ANOVA are used to derive p-values for categorical and continuous data respectively.

Table 11.3.16.5: Baseline (Day 0) vital signs by group
ITT Population

Parameter	Unit			Group A (N)	Group B (N)	Group A + B (N)	Group C (N)	Total (N)	Pvalue (A vs B; B vs C; A+B vs C)
Weight	xx	Within Normal Range	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*	*n (%)*	
		Outside Normal Range	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*	*n (%)*	
		Mean (SD)[2]	x.x (x.x)	*x.x (x.x)*	*x.x (x.x)*	*x.x (x.x)*	*x.x (x.x)*	*x.x (x.x)*	*x.xxx; x.xxx; x.xxx*
		Median (Q1, Q3)[2]	x.x (x.x, x.x)	*x.x (x.x, x.x)*	*x.x (x.x, x.x)*	*x.x (x.x, x.x)*	*x.x (x.x, x.x)*	*x.x (x.x, x.x)*	
		Range (min, max)[2]	(x.x, x.x)	*(x.x, x.x)*	*(x.x, x.x)*	*(x.x, x.x)*	*(x.x, x.x)*	*(x.x, x.x)*	
[…repeat for Systolic BP, Diastolic BP, Heart Rate, Body Temp]									

Footnote 1: Percentage is percent of total number outside normal range
Footnote 2: Mean, median, and range describe values outside normal range

Table 11.3.16.6:
Table 11.3.16.11: Time Interval (in days) between DOTS for Group A
ITT Population

	n (%)	Mean (SD)	Median (Q1, Q3)	Range (min, max)
	n (%)	x.x (x.x)	x (x, x)	x (x, x)
1st DOT (N)	*n (%)*	*x.x (x.x)*	*x (x, x)*	*x (x, x)*
2nd DOT (N)	*n (%)*	*x.x (x.x)*	*x (x, x)*	*x (x, x)*
3rd DOT (N)	*n (%)*	*x.x (x.x)*	*x (x, x)*	*x (x, x)*
4th DOT (N)	*n (%)*	*x.x (x.x)*	*x (x, x)*	*x (x, x)*
5th DOT (N)	*n (%)*	*x.x (x.x)*	*x (x, x)*	*x (x, x)*
6th DOT (N)	*n (%)*	*x.x (x.x)*	*x (x, x)*	*x (x, x)*
7th DOT (N)	*n (%)*	*x.x (x.x)*	*x (x, x)*	*x (x, x)*
8th DOT (N)	*n (%)*	*x.x (x.x)*	*x (x, x)*	*x (x, x)*
9th DOT (N)	*n (%)*	*x.x (x.x)*	*x (x, x)*	*x (x, x)*
10th DOT (N)	*n (%)*	*x.x (x.x)*	*x (x, x)*	*x (x, x)*
11th DOT (N)	*n (%)*	*x.x (x.x)*	*x (x, x)*	*x (x, x)*
12th DOT (N)	*n (%)*	*x.x (x.x)*	*x (x, x)*	*x (x, x)*

Figure 11.3.16.12: Histogram of the time interval (in days) between DOTS in Group A
ITT Population

[placeholder]

Listing 11.3.16.13: Urine pregnancy test results for those with a positive test on study
ITT population

Group	**Subject**	**Day**	**Result**
A	2002	*84*	*Positive*

[*repeat for all positive urine test results*]

Table 11.3.16.14: Results from HIV rapid test at Visits 6 and 8
ITT Population

Visit			**Group A (N)**	**Group B (N)**	**Group C (N)**	**Total (N)**
Visit 6 (Day 180)	+ve	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*
	-ve	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*

Visit 8 (Day 365)	+ve	n (%)	*NA*	*n (%)*	*n (%)*	*n (%)*
	-ve	n (%)	*NA*	*n (%)*	*n (%)*	*n (%)*

13.3.16 Protocol deviations

Listing 11.3.17.1: Reasons for missed visits
Intention to Treat Population

Group	Subject	Visit	Reason
A	1001	Day 0	Text
	1010	Day 0	Text
	…	…	
B	2021	Day 0	Text
	2034	Day 28	Text
	…		
[…repeat for all subjects missing a vaccination…]			

Listing 11.3.17.2: Out of window visits
Intention to Treat Population

Group	Subject	Visit	Reason
A	1001	Day 0	Text
	1010	Day 0	Text
	…	…	
B	2021	Day 0	Text
	2034	Day 28	Text
	…		
[…repeat for all subjects missing a vaccination…]			

Listing 11.3.17.3: Reasons for missed treatments in Group A
Intention to Treat Population

Group	Subject	Visit	Reason
A	1001	Day 0	Text
	1010	Day 0	Text
	…	…	

…

[…repeat for all subjects missing a vaccination…]