PROTOCOL TITLE

The 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

PROTOCOL DATE: 06 August 2018

PROTOCOL VERSION: V3.0

SPONSORED BY: University of Cape Town

SITE PRINCIPAL INVESTIGATOR SIGNATURES OF AGREEMENT FOR PROTOCOL IMPLEMENTATION

_____   _____
SATVI Site PI   Date

_____   _____
Aurum Klerksdorp Site PI   Date

_____   _____
Aurum Rustenberg Site PI   Date

_____   _____
CAPRISA Site PI   Date

_____   _____
Stellenbosch University Site PI   Date

INVESTIGATOR APPROVAL STATEMENT

I have read the protocol and agree that it contains all necessary details for carrying out the trial as described. I will conduct this protocol as outlined therein and will make a reasonable effort to complete the trial within the time designated.

I agree to personally supervise the trial.

I agree to inform all participants that the investigational product is being used for research purposes and I will ensure that the requirements related to obtaining informed consent are in accordance with ICH Guidelines for Good Clinical Practice (GCP) section 4.8 and local requirements.

I agree to report adverse events that occur in the course of the trial to the sponsor in accordance with ICH Guidelines for Good Clinical Practices (GCP) section 4.11 and local requirements.

I agree to promptly report to the Ethics Committee (EC) all changes in the research activity and all unanticipated problems involving risk to the participants. I will not make any changes to the conduct of the trial without the EC and Sponsor approval, except when necessary to eliminate apparent immediate harm to participants.

I agree to maintain adequate and accurate records and make those records available in accordance with ICH guidelines for Good Clinical Practices (GCP) section 4.11 and local requirements.

I agree to ensure that all associates, colleagues and employees assisting in the conduct of the trial are informed about their obligations in meeting the above commitments.

I understand that the trial may be terminated or enrolment suspended at any time by the Sponsor, with or without cause, or by me if it becomes necessary to protect the best interest of the participants.

_____   _____

National Principal Investigator Signature   Date

RESPONSIBILITIES

Sponsor:	University of Cape Town
National Principal Investigator:	Mark Hatherill
Regulatory Functions:	Triclinium Clinical Development Pty LTD
Site Monitoring Functions:	Triclinium Clinical Development Pty LTD
Data Management Functions	Triclinium Clinical Development Pty LTD
Statistical Analysis:	The Statistical Center for HIV/AIDS Research & Prevention (SCHARP)
Clinical Safety Laboratory:	BARC, Johannesburg
Analytical Laboratory:	South African Tuberculosis Vaccine Initiative (SATVI)

PROTOCOL SYNOPSIS

TITLE	**The 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
BACKGROUND	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. 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***. |
| AIMS | ***Primary Aims***
1: Test whether preventive therapy (3HP) reduces the rate of incident TB disease, compared to standard of care (active surveillance), in COR+ persons.
2: Test whether COR status differentiates persons with cumulative prevalent or incident TB disease from persons without TB disease.
Secondary Aims
1: Estimate whether COR status differentiates persons with prevalent TB disease from persons without prevalent TB disease
2: Estimate whether COR status differentiates persons at high risk for incident TB disease from persons at low risk for incident TB disease
3: Compare prognostic performance of the COR for incident TB disease with Interferon-gamma release assay (IGRA).
Exploratory Aims
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. |
| TRIAL SIZE | A maximum of 3,200 participants will be enrolled. |

TRIAL POPULATION	*Inclusion criteria (at time of screening):* 1. Written informed consent 2. Aged ≥18 and ⟨60 years 3. Known COR status (- or +) 4. Known HIV status 5. Women of child-bearing potential who are not surgically sterilized must agree to practice adequate contraception (barrier method or non-hormonal intrauterine device, alone or in addition to systemic hormonal contraceptive method) or abstain from heterosexual intercourse during the first 3 months on study. 6. Likely to remain in follow-up and adhere to protocol requirements *Exclusion criteria (at time of screening):* 1. HIV infection 2. Pregnant or lactating 3. Diagnosed with TB disease within last 3 years 4. Household exposure to a TB patient with known multi-drug resistant (MDR-) TB disease within last 3 years 5. Body weight <40kg 6. Known allergy to INH or Rifamycins 7. Receiving antiarrhythmic, antidepressant, antipsychotic, antihypertensive, anticonvulsant, anticoagulant, or (inhaled or oral) corticosteroid therapy 8. Any medical, surgical, or other condition, including but not limited to known diabetes mellitus (requiring oral or injectable therapy), liver disease, porphyria, peripheral neuropathy, epilepsy, psychosis, or alcoholism, that in the opinion of the Investigator is likely to interfere with COR performance; safety and efficacy of the investigational products (IP); or adherence to protocol requirements.
TRIAL DESIGN	Adult volunteers living in TB hyperendemic communities of South Africa will be consented and screened. Individuals with HIV infection and conditions likely to affect the performance of the COR assay, or the safety and/or efficacy of the 3HP investigational regimen, will not be enrolled. Participants eligible for randomisation who test COR+ at screening will be randomised 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 or they will not be enrolled. A maximum of 3,200 participants will be enrolled in both arms; i.e. the Treatment Arm would include approximately 500 COR+ participants, unblinded to COR status, receiving open-label 3HP; the Observation Arm will include a design-specific mix of approximately 1,000 COR+ and 1,700 COR- participants, blinded to COR status, all undergoing active symptom-targeted TB surveillance. The final number of participants enrolled into the Treatment and Observation Arms, the balance of COR+ and COR- participants, and the total duration of follow-up required to achieve the primary and secondary aims will be adapted, based on 3-monthly operational monitoring reports prepared by the Trial Statistician, using projections of observed COR+ prevalence and TB case accrual. Enrolment into one study arm may be halted prior to the other arm, based on projected ability to achieve the primary and secondary aims, in which case all remaining participants would be enrolled into the remaining arm. Participants enrolled in the first 12 months of recruitment will undergo 15 months of scheduled follow-up. Thereafter, subsequent participants may have follow-up time reduced incrementally, such that individual follow-up would be reduced to a minimum of 3 months, and mean follow-up for all participants is approximately 12 months.

	Treatment efficacy (*TE*) will be evaluated by comparing the incidence of endpoint-defined TB disease through up to 15 months follow-up in treated COR+ versus untreated COR+ participants. The performance of the COR will be evaluated by comparing the incidence of endpoint-defined TB disease through up to 15 months follow-up in untreated COR+ versus untreated COR- participants (RR_{COR}).
INVESTIGATIONS	*COR Assay***:** Whole blood RNA will be collected in PAXgene tubes from all persons screened. Risk of TB disease will be evaluated using the BioMark HD Fluidigm multiplex qRT-PCR machine. Participants with COR result ≥ 60% vote threshold will be classified as COR+, or if < 60% as COR-. *IGRA Assay*: Whole blood will be collected for QuantiFERON-Plus assay, and a serum sample will be stored for proteomic analysis, in all participants at baseline. *Safety Investigations:* Participants in the Treatment Arm will have hepatic function (serum alanine aminotransferase (ALT) and total bilirubin) measured at baseline and repeated if abnormal or symptomatic. *TB Investigations:* All participants will undergo symptom screening and sputum Xpert MTB/RIF at baseline (Day 0). An aliquot of unprocessed sputum will be stored for additional MTB diagnostic tests at the end of the trial, potentially including, but not limited to Xpert MTB/RIF, Mycobacterial Growth Inhibition Test (MGIT) culture, and line probe assay. Thereafter, symptoms consistent with TB disease will be solicited at all study visits; presence of one or more symptoms will trigger TB investigation (paired sputum Xpert MTB/RIF and MGIT culture); participants who are sputum unproductive will be assumed negative; participants who remain symptomatic may undergo additional investigations. All participants will undergo TB investigation at end of study, regardless of presence or absence of symptoms. All participants with confirmed prevalent or incident TB disease will discontinue the study intervention and follow-up and will be referred to the National TB Programme (NTP) for 4-drug curative treatment.
TREATMENT REGIMENS	Participants in the Treatment Arm will receive high dose INH (15mg per kg body weight, rounded up to the nearest 100 mg; maximum dose 900 mg) with Pyridoxine supplementation (25mg), and Rifapentine based on body weight (>32kg – 50kg: 750 mg; >50kg: 900 mg), given weekly as 12 directly observed treatment (DOT) oral doses, ideally with food, over 3 months. Dispensing of IP and Directly Observed Treatment (DOT) field visits in Treatment Arm participants will be performed by staff members not involved in TB symptom screening or investigation. Participants receiving 3HP who develop symptoms of hepatotoxicity will be evaluated by an Investigator.
TRIAL DURATION	Participants enrolled in the first 12 months of the trial will undergo 15 months scheduled follow-up. Thereafter, duration of follow-up required to achieve the primary and secondary aims will be adapted based on 3-monthly operational monitoring reports prepared by the Trial Statistician, using cumulative projections of observed COR+ prevalence and TB case accrual. Subsequent participants may have follow-up time reduced incrementally, such that individual follow-up would be reduced to a minimum of 3 months, and mean follow-up for all participants is approximately 12 months.
SITES	Five (5) clinical trial sites in South Africa.
TRIAL ENDPOINTS	The primary endpoint will be defined as Xpert MTB/RIF and/or MGIT culture positive TB disease, confirmed on two separate sputum samples; or on samples from any other site in the case of extrapulmonary TB disease. Although safety evaluation is not a study-specific aim, Serious Adverse Events (SAEs), including hospitalization or death, as well as severe laboratory toxicities, will be recorded for all participants.
STATISTICAL CONSIDERATIONS	The primary analyses will evaluate TE(15), treatment efficacy, and $RR_{COR}(15)$, relative-risk for TB disease, over up to 15 months follow-up. The primary outcome measure is Relative

	Risk (RR, 95% CI) for TB disease, as per the TB case endpoint definition. Based on a series of trial simulations, it is estimated that a sample size of 3,200 participants (1,500 COR+ and 1,700 COR-) with 500 participants allocated to the Treatment Arm and 1,700 participants to the Observation Arm, would yield approximately 33 COR+ and 7 COR- prevalent and incident TB cases within 27 months of trial start. The study is designed to have 80% power to reject the null-hypothesis, H_0: TE(15) >= 30% if TE(15) = 80%, with a one-sided alpha of 0.05. The study will also have 95% power to reject the null-hypothesis, H_0: RR_{COR}(15) >= 2, with a one-sided alpha of 0.025 based on an alternative hypothesis. In the event that accrual of TB cases is faster than expected and follow-up is reduced from 15 to a minimum of 3 and mean of 12 months, the study is expected to have 70% power to reject the null-hypothesis, H_0: TE(12) <= 20% under the simulated design hypothesis, TE(12) = 80%, with a one-sided alpha of 0.05; and 90% power to reject the null-hypothesis, H_0: RR_{COR}(15) <= 2, with a one-sided alpha of 0.025.
ETHICAL CONSIDERATIONS	New WHO guidelines for provision of INH preventive therapy (IPT) for HIV uninfected adults with LTBI apply to <u>low TB burden countries</u> (annual TB incidence <100 per 100,000)[1]. There is good reason for this distinction, since in high TB burden countries such as South Africa, where annual force of new *M. tuberculosis* infection may exceed 10%[2], there is rapid loss of protection (and some evidence of increased rebound risk) after IPT is completed[3,4]. Since 70-80% of South African adults have LTBI[5], defined by a positive IGRA or tuberculin skin test (TST), and 90% of persons with LTBI would never progress to disease in their lifetime, the balance of protective benefit (transient, and limited to a fraction of IPT recipients) and risk (primarily intolerance, hepatotoxicity, and treatment burden) does not favor preventive therapy for LTBI in <u>high TB burden countries</u>.

The COR assay is thought to be a sensitive and specific prognostic test for incident TB disease. However, all current knowledge of COR prognostic performance is based on two nested case-control studies involving less than 600 participants, which may have overestimated COR performance. Since COR performance has never been validated in a prospective cohort, individual risk of COR+ status is not yet known. Although the COR is thought to be more specific than IGRA, most people who test COR+ will likely remain TB disease free and would not benefit from preventive therapy. False positive COR+ participants would only be exposed to potential risks of preventive therapy. Although 3HP is thought to be associated with lower risk of hepatotoxicity than IPT, TB disease associated with COR+ status may reflect a different phenotype from that associated with IGRA/TST+ status; and benefit of preventive therapy for COR+ persons has not been demonstrated, or quantified.

Measures to Ensure Safety: (1) All participants diagnosed with prevalent TB disease at baseline will discontinue study follow-up and will be referred for curative treatment. Thereafter, active symptom-based surveillance and investigation for incident TB disease, in both Treatment and Observation Arms, will allow early diagnosis and effective treatment to prevent severe morbidity; all participants will be investigated for TB at their last study visit; (2) Persons at high risk for hepatotoxicity will not be enrolled; participants in the Treatment Arm will be monitored for hepatotoxicity, so that study drug can be discontinued; (3) a Data & Safety Monitoring Board (DSMB), with the remit to pause/amend the study based on interim unblinded analyses of COR performance, and 3HP efficacy in the COR+ arms, will oversee the conduct of the study. |

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

Abbreviation	Text
3HP	Isoniazid and Rifapentine for 3 months (12 doses; once-weekly)
AE	Adverse event
AFB	Acid-fast bacilli
ALT	Serum alanine aminotransferase
BMI	Body Mass Index (BMI)
cDNA	Copy DNA
CI	Confidence interval
COR	Correlate of Risk
CRA	Clinical research associate
CRF	Case report form
CRO	Clinical Research Organization
DAIDS	NIH Division of AIDS
DSMB	Data and Safety Monitoring Board
DOT	Directly Observed Treatment
eCRF	electronic CRFs
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GIT	Gastrointestinal
H_0	Null hypothesis
HIV	Human Immunodeficiency Virus
IEC	Independent ethics committee
IGRA	Interferon gamma release assay
INH	Isoniazid
IP	Investigational Product
IPT	INH preventive therapy
ITT	Intention-to-treat
LTBI	Latent tuberculosis infection
MCC	Medicines Control Council
MDR-TB	multi-drug resistant tuberculosis
MGIT	Mycobacteria Growth Indicator Tube
mITT	Modified intention-to-treat
mRNA	Messenger RNA
MTA	Material Transfer Agreement
MTB	*Mycobacterium tuberculosis*
NHP	Non-human primate
NTP	National TB Programme
PI	Principal Investigator
PP	Per protocol analysis
QFT	QuantiFERON
RR	Relative risk
$RR_{COR}(15)$	Relative risk for TB disease over 15 months
RIF	Rifampicin
SA	South Africa
SAE	Serious adverse event
SATVI	South African Tuberculosis Vaccine Initiative

SE	Strategy efficacy
TB	Tuberculosis
TE	Treatment efficacy
TE(15)	Treatment efficacy over 15 months
TST	Tuberculin Skin Test
WHO	World Health Organization

1. SCHEDULE OF EVENTS

OBSERVATION ARM

Description	Screening	Enrolment	Follow-up						End of Study
Trial Visit	Visit 1	Visit 2	Contact 3	Contact 4	Visit 5	Visit 6	Contact 7	Visit 8	Visit 9
Day/Month	D-28 to D-1	D0	M1	M2	M3	M6	M9	M12	M15
Window period		None	Day 28 (±3)	Day 56 (±3)	Day 84 (±3)	Day 180 (±7)	Day 270 (±7)	Day 365 (±7)	Day 449 (±7)
Informed consent[1]	x								
Age verification	x								
Screening medical history[7]	x								
Height & weight, BMI	x								
Weight, BMI		x			x	x		x	x
Urine pregnancy test (females)	x	x			x				
HIV counselling & testing[6]	x					x		x	
Phlebotomy COR (Paxgene)[2]	x								
Medical history		x			x	x		x	x
Vital signs (temp, pulse, BP)		x			x	x		x	x
Targeted physical examination		x			x	x		x	x
Verification of eligibility		x							
Randomisation		x							
Phlebotomy IGRA		x							
Phlebotomy serum (store)		x							
TB symptom screen		x	x	x	x	x	x	x	x
TB Investigations		xx[3]	xx[4]	xx[4]	xx[4]	xx[4]	xx[4]	xx[4]	xx[5]
Serious adverse events		x	x	x	x	x	x	x	x
Concomitant Medications	x	x							
Next appointment, check contact details	x	x	x	x	x	x	x	x	x[8]

[1] May be conducted at prior field visit
[2] Only in persons without exclusion criteria
[3] Two sputum samples for Xpert MTB/RIF; store aliquot of unprocessed sputum from each (all participants)
[4] If indicated by positive TB symptom screen, one sputum sample for Xpert MTB/RIF; one sputum sample for MGIT culture
[5] One sputum sample for Xpert MTB/RIF; one sputum sample for MGIT culture (all participants)
[6] HIV Rapid test. If positive, confirm by a second rapid test as per site protocol.
[7] Includes gender, ethnicity, education, household economic factors, risk factors for TB, smoking history, current and past medical and surgical history (and recent febrile episodes)
[8] Check contact details only so that sputum results can be provided, with written TB clinic referral if necessary

TREATMENT ARM

Description	Screening	Enrolment	Follow-up						End of Study
Trial Visit	Visit 1	Visit 2	Contact 3	Contact 4	Visit 5	Visit 6	Contact 7	Visit 8	Visit 9
Day	D-28 to D-1	D0	M1	M2	M3	M6	M9	M12	M15
Window period		None	Day 28 (±3)	Day 56 (±3)	Day 84 (±3)	Day 180 (±7)	Day 270 (±7)	Day 365 (±7)	Day 449 (±7)
Informed consent[1]	x								
Age verification	x								
Screening medical history	x[10]								
Height & weight, BMI	x								
Weight, BMI		x			x	x		x	x
Urine pregnancy test females	x	x			x				
HIV counselling & testing[9]	x					x		x	
Phlebotomy COR (Paxgene)[2]	x								
Medical history		x			x	x		x	x
Vital signs (temp, pulse, BP)		x			x	x		x	x
Targeted physical examination		x			x	x		x	x
Verification of eligibility		x							
Randomisation		x							
Phlebotomy IGRA		x							
Phlebotomy serum (store)		x							
TB symptom screen[3]		x	x	x	x	x	x	x	x
TB Investigations		xx[4]	xx[5]	xx[5]	xx[5]	xx[5]	xx[5]	xx[5]	xx[6]
Serious adverse events		x	x	x	x	x	x	x	x
Phlebotomy ALT, Bilirubin		x[7]							
Prescribe IP		x							
DOT & GIT symptom screen		xxxx[8]	xxxx[8]	xxxx[8]					
Concomitant Medications	x	x	x	x	x				
Next appointment, check contact details	x	x	x	x	x	x	x	x	x[11]

[1] May be conducted at prior field visit; confirm visit procedures clearly documented in source
[2] Only in persons without meeting exclusion criteria
[3] Performed by staff member not involved in dispensing of IP or DOT field visits
[4] Two sputum samples for Xpert MTB/RIF; store aliquot of unprocessed sputum from each (all participants)
[5] If indicated by positive TB symptom screen, one sputum sample for Xpert MTB/RIF; one sputum sample for MGIT culture
[6] One sputum sample for Xpert MTB/RIF; one sputum sample for MGIT culture (all participants)
[7] Repeat if abnormal or if indicated by positive GIT symptom screen. Repeat 2 to 4 weekly until return to baseline

[8] DOT field visit (Weeks 1-11) with GIT symptom screen, performed by staff member not involved in TB symptom screen

[9] HIV Rapid test. If positive, confirm by a second rapid test as per site protocol.

[10] Includes gender, ethnicity, education, household economic factors, risk factors for TB, smoking history, current and past medical and surgical history (and recent febrile episodes)

[11] Check contact details only so that sputum results can be provided, with written TB clinic referral if necessary

Confidential

2. INTRODUCTION

2.1 BACKGROUND

Two billion people worldwide, including the majority of adults in TB endemic countries, are *Mycobacterium tuberculosis* (MTB) infected.[1] These latently infected individuals, identified by a positive tuberculin skin test (TST) or interferon-gamma release assay (IGRA), have higher risk of developing TB disease than uninfected people.[2] Unfortunately, TST and IGRA have poor specificity for incident TB disease in endemic populations, since 90% of people who test IGRA or TST positive will never develop TB disease in their lifetime. Therefore, although prevention of TB disease arising from latent infection is key to achieving WHO elimination targets[6], mass preventive therapy based on IGRA/TST screening in TB endemic countries would need to treat 50-80% of the population, most of them unnecessarily. Mass preventive therapy for all MTB infected people using current tools would not be feasible, affordable, or effective, since reinfection would occur before programmatic coverage was complete.

A more specific predictive screening tool is needed, a COR that identifies those individuals at highest risk of progression from latency to TB disease, thus avoiding unnecessary treatment of people who would remain healthy. A highly specific, risk-targeted prevention strategy would impact the epidemic by interruption of incipient TB disease in infected adults, before onward transmission to susceptible people. A prognostic COR with added value as a triage test for prevalent TB disease would be ideal for this purpose.

Challenges to the development and implementation of this strategy include lack of efficacy data for a risk-targeted therapeutic intervention; i.e. a safe and effective, short-course drug regimen for prevention of TB disease among high-risk individuals identified by COR screening. Further, although HIV infected people bear a considerable burden of global TB morbidity and mortality, proof of concept for a COR targeted intervention would need to be demonstrated also among HIV uninfected persons.

University of Cape Town investigators have constructed a COR classifier based on mRNA expression signatures from RNA-seq data that discriminates between TB cases and healthy controls prospectively, more than one year before disease (*Penn-Nicholson, Zak, Scriba, Hanekom, et al, Lancet submitted*). This COR transcriptomic signature has been transferred to a high-throughput, microfluidic, real-time PCR platform (Biomark system; Fluidigm), which can simultaneously test 96 samples and provide results within 3-5 days. COR assay robustness, accuracy, precision, range and linearity have been qualified. The optimal COR model (PSVM.1) is parsimonious (48 transcripts) and has excellent potential for transfer to a simplified testing platform for implementation at local clinic or laboratory level, with re-engineering of existing, available technology.

Detection of prevalent TB disease
Sensitivity and specificity of the COR for detection of TB disease is maximal nearest the time of diagnosis. Diagnostic performance of the COR for prevalent TB disease has been validated against published microarray datasets[7-10]. Analysis of data
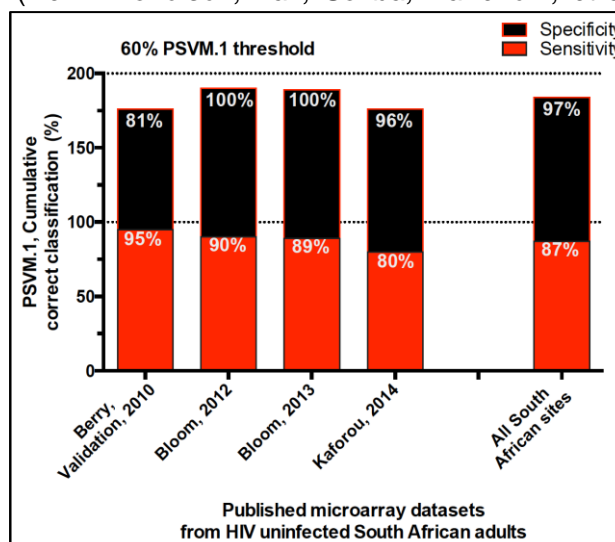

Figure 1: Cumulative percentage correct classification by the COR at 60% vote threshold for diagnosis of prevalent TB disease in HIV uninfected South African adults (published datasets). Sensitivity shown in red and specificity in black.

from HIV uninfected South African adults in four case-control studies, including 130 prevalent TB cases and 230 controls, showed 87% sensitivity and 97% specificity for active TB disease (**Figure 1**)[7-10]. It is notable that COR sensitivity for diagnosis of prevalent TB in HIV infected people was reduced by <10% compared to HIV uninfected patients, based on analysis of published data[7]. These performance characteristics suggest the COR may have added value as a triage tool to detect prevalent cases of undiagnosed TB disease during mass screening.

Prediction of incident TB disease
Prevalence of COR+ status in young HIV uninfected South Africans (80% MTB infected) is approximately 15%; and is not associated with IGRA/TST+ status. In two nested case-control studies, including 119 cases and 408 controls, the COR was 70%

Figure 2: Hazard ratio (HR) for incident TB with 95% confidence intervals (shaded area), among COR+ compared to COR- individuals, by time of sampling prior to diagnosis. HR is weighted and unweighted for case control matching (solid lines).

sensitive and 84% specific for incident TB disease occurring within one year of sampling. COR prognostic performance was time-sensitive. Sensitivity increased consistently, from 18 - 21 months prior to disease, and was maximal at time of diagnosis. Relative risk (RR) for TB disease in COR+ compared to COR- people was ≈15 at time of diagnosis; averaged RR was ≈7 for the 18-month period preceding diagnosis, when the COR would be most useful as a prognostic test (**Figure 2**). Thus, the COR has potential both as a triage test, to identify persons who should be investigated for prevalent TB disease and offered curative treatment; and as a prognostic test for incident TB, to identify persons who should be offered preventive therapy.
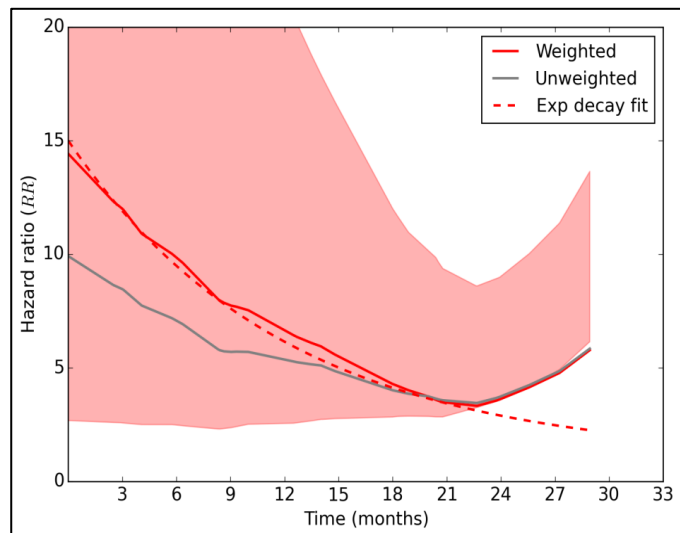
2.2 RATIONALE

A mass campaign to halt TB transmission in a community, by identifying both persons with undiagnosed TB and persons at high risk of progressing from latency to active TB disease, would require that COR screening is used in combination with a curative regimen and a short-course, sterilizing preventive regimen, respectively. The historical TB preventive regimen, 6 months of daily isoniazid preventive therapy (IPT), is inadequate for this purpose. Studies in mining communities have shown that long-term impact of mass IPT campaigns is negated by low adherence and slow coverage, which are inherent problems of the 6-month daily IPT regimen, leading to high rates of reinfection disease before complete coverage can be achieved[4]. A shorter, simple, sterilizing preventive regimen (3 months of high dose 900mg INH and 900mg Rifapentine, given once-weekly as directly observed doses) (3HP) was non-inferior to 9 months IPT among almost 8,000 participants in a large Phase 3 trial[11]. 3HP is now recommended as an alternative regimen to IPT for treatment of latent MTB infection (LTBI) in low TB burden, mid- and high-income countries, by the World Health Organization (WHO)[1].

Importantly, based on estimated COR+ prevalence, only 15% of people in a TB hyperendemic community would need 3HP preventive therapy targeted by COR screening, allowing a several-fold reduction in treatment burden compared to conventional IGRA/TST screening, in which 50-80% of all people would need preventive therapy. The 3HP regimen has three major implementation benefits compared to conventional IPT. A shorter, once-weekly regimen has better rates of treatment completion[11]; and 12 doses can be directly observed to ensure adherence. The third factor, crucial to the success of a mass preventive therapy campaign,[4] is that the 3-month regimen can achieve rapid coverage, reducing the risk of reinfection of susceptible people. Ultra-short, 1-month preventive regimens are now being tested, which would have even greater potential for rapid coverage in community-wide, mass campaigns.

The CORTIS trial will test a "screen & treat" strategy, based on this highly specific COR, to identify persons with undiagnosed TB disease to be offered curative therapy; and persons at highest risk of progression to active TB disease to be offered preventive therapy. Applied at community level, this COR targeted strategy has the potential to interrupt TB disease before transmission to susceptible people, and accelerate reductions in TB incidence and mortality.

Development Pathway: The goal of this project is to collect evidence to support a WHO policy recommendation for the COR targeted screen & treat strategy that would lead to implementation. In particular, the following evidence is lacking: (1) COR prognostic data from prospective cohorts; (2) comparison with IGRA as the prognostic gold standard; and (3) efficacy data for protection against TB disease arising in COR+ persons. This proof-of-concept trial addresses the first steps in the development pathway, by evaluating the COR as a prognostic test for incident disease; and by evaluating efficacy of 3HP for prevention of incident TB disease arising in COR+ persons. Additionally, we will take advantage of baseline TB investigations to evaluate COR performance as a test to detect prevalent TB disease. The next steps would be evaluation of COR prognostic performance and demonstration of treatment efficacy in other high-risk groups, particularly HIV infected individuals, since inclusion of HIV infected people in the "screen & treat" strategy will be crucial for population-level impact.

2.3 SUMMARY OF POTENTIAL RISKS AND BENEFITS

New WHO guidelines for provision of TB preventive therapy for HIV uninfected adults with LTBI apply to <u>low TB burden countries</u> (annual TB incidence <100 per 100,000)[1]. There is good reason for this distinction, since in high TB burden countries such as South Africa, where annual force of new MTB infection may exceed 10%[2], there is rapid loss of protection (and some evidence of rebound increased risk) after preventive therapy is completed[3]. Since 70-80% of South African adults have LTBI, defined by a positive IGRA or TST[5], and 90% of persons with LTBI would never to progress to disease in their lifetime, the balance of protective benefit (transient, and limited to a fraction of recipients) and risk (primarily intolerance, hepatotoxicity, and treatment burden) does not favor preventive therapy for LTBI <u>in high TB burden countries</u>.

Should COR+ participants receive preventive therapy? All current knowledge of COR prognostic performance is based on two nested case-control studies, involving less than 600 participants. Since COR performance has never been validated in a prospective cohort, ***individual risk of COR+ status is not yet known***.

It is our hypothesis that the COR has better prognostic specificity for TB disease than IGRA/TST, but like IGRA/TST, most people who test COR+ will remain disease free and would not benefit from preventive therapy. '***False positive' COR+ participants would only be exposed to potential risk of preventive therapy***.

COR+ status is not directly associated with IGRA/TST+ status. TB disease associated with COR+ status may reflect a different phenotype from that associated with IGRA/TST+ status, which may or may not respond to preventive therapy. ***Benefit of preventive therapy for COR+ persons has not been demonstrated or quantified***.

It is possible that COR+ participants require a full course of 4-drug curative TB treatment rather than 3HP to prevent progression to TB disease, but evidence of (1) good prognostic COR performance, and (2) poor efficacy of 3HP preventive therapy, would be needed to justify such a major intervention for otherwise healthy people (*see risks associated with 'false positive' COR+ status*). It follows that, ***based on current knowledge, the balance of potential risk and benefit associated with preventive and curative therapy for COR+ participants is in equipoise***. The CORTIS-01 trial will address this knowledge gap.

RISKS

Risk of Incident TB Disease: Average incidence of TB disease in South Africa is 834 per 100,000 (all ages; HIV infected and uninfected)[12]. Participants will be recruited from selected TB hyperendemic communities, where TB incidence is expected to exceed 1,000 per 100,000 (1%) in HIV uninfected adult participants. Further, it is our hypothesis that TB cases will be enriched in COR+ persons, who comprise almost half of the study population, and approximately 40 prevalent and incident TB cases might be expected among 3,200 COR+ and COR- participants.

Measures to Minimize Risk of TB Disease: Persons with additional risk factors for TB disease, including, but not limited to HIV infection and Diabetes Mellitus, will not be enrolled. Symptom screening will be performed and two sputum samples will be collected for Xpert MTB/RIF in all participants at baseline. Participants diagnosed with prevalent TB at baseline will discontinue follow-up; if already allocated to a study arm (Treatment or Observation), the study intervention will be stopped, and the participant will be referred in writing with a copy of their TB results to start a curative 4-drug treatment course, as per NTP standard of care. Thereafter, active symptom-based surveillance and investigation for incident TB disease (paired sputum Xpert MTB/RIF and MGIT culture), in both Treatment and Observation Arms, will allow early TB diagnosis and effective treatment to prevent severe TB morbidity. Symptoms will be solicited at every follow-up visit and presence of one or more symptoms characteristic of TB will trigger investigation. In addition, sputum will be collected from all participants at end of study, regardless of presence or absence of symptoms. Participants who remain symptomatic in the absence of microbiological confirmation of TB disease may undergo additional investigations.

Incident TB case accrual will be monitored continuously throughout the study. It is estimated that sufficient incident TB endpoint cases will have accumulated 27 months after study start to determine whether statistically significant differences exist in RR for incident TB disease between COR+ and COR- participants; and between COR+ participants who have received or not received 3HP. To guard against the possibility of early imbalance in incident TB case accrual between study arms, which might have allowed statistically valid conclusions about COR prognostic and 3HP risk/benefit to be drawn prior to end of study, we will conduct an interim unblinded analysis of prognostic COR performance and 3HP efficacy, as soon as 40 incident TB cases have accrued. The Data & Safety Monitoring Board (DSMB) will review the findings of the interim analyses and make a recommendation on whether the study should continue and/or whether the protocol should be amended.

Risk of 3HP: The primary risk of TB preventive therapy, including 3HP and 6- and 9-month INH regimens (6H and 9H), is hepatotoxicity. Hepatotoxicity related to INH is more frequent in older persons, pregnant and post-partum women, persons who consume alcohol on a daily basis, and those with chronic liver disease[13]. INH hepatotoxicity is usually reversible if INH is stopped when clinical signs and symptoms of hepatotoxicity develop. Risk of hepatotoxicity due to 3HP has been studied primarily in HIV infected persons, in whom 3HP compared to 9H was tolerable and had higher completion rates (88% vs. 64%) [*Sterling T; Int AIDS Conference 2012; Abstract MOAB0302*] [*Sterling T; CROI 2014; Abstract P-R3-817*]. The 3HP regimen was also compared to 6H in HIV infected, ART naïve, TST positive South African adults. In the intention- to- treat (ITT) analysis the incidence of active TB or death in the 3HP and 6H arms was similar (3.1 vs. 3.6 per 100 person-years respectively, crude incidence rate ratio: 0.87 (0.54–1.39)).[14] The recent WHO Expert Panel on management of LTBI concluded that the 3HP regimen was associated with fewer hepatotoxicity events compared to a 6-month and 9-month INH regimen[1]. Note that 3HP is now a WHO-recommended TB preventive therapy regimen and evaluation of safety of 3HP is not a primary aim of this study[1]. However, safety data will be collected for all Serious Adverse Events (SAEs), including hospitalization, or death; and severe laboratory toxicities.

Other risks associated with INH include peripheral neuropathy, which may be prevented by pyridoxine supplementation, and gastrointestinal symptoms including nausea, vomiting and loss of appetite. Other risks reported with Rifapentine include hypersensitivity reactions, orange discoloration of body fluids, *Clostridium difficile*-associated diarrhea (CDAD), and porphyria (*see Package Insert*).

Rifapentine may reduce the effectiveness of hormonal contraceptives and drugs metabolized via the Cytochrome P450 3A4 and 2C8/9 enzyme systems.

Measures to Minimize Risk of 3HP: Persons with known chronic liver disease, alcoholism, or porphyria; and those receiving drugs metabolized via the Cytochrome P450 3A4 and 2C8/9 enzyme systems, will not be enrolled. Female participants receiving a systemic hormonal contraceptive may only be enrolled if used in addition to another acceptable method of contraception. Participants in the Treatment arm will receive pyridoxine supplementation with each dose of INH. Hepatic function (serum alanine aminotransferase (ALT) and total bilirubin) will be measured at baseline in Treatment Arm participants and if abnormal (Grade 1 or higher; DAIDS Toxicity Table), or if participants become symptomatic, will be repeated 2-4 weekly until return to baseline. Participants receiving 3HP who develop symptoms or signs of hepatic dysfunction, including nausea, malaise, vomiting, loss of appetite or jaundice will be evaluated by an investigator. Participants who develop Grade 3 or higher toxicity while receiving 3HP will have therapy discontinued.

BENEFITS

*Benefits of 3HP for Prevention of TB Disease: **It is not known whether 3HP protects against incident TB arising in COR+ persons.*** Rifapentine is a Rifamycin with a long half-life and greater potency against MTB than Rifampicin. In mouse models of LTBI, Rifapentine has a greater sterilising effect than INH[15] and weekly high dose rifapentine and INH for three months (3HP) had greater efficacy than INH alone[16]. The TB Trials Consortium (TBTC) Study 26 compared 3 months of high dose once-weekly INH (900mg) and Rifapentine (900mg) (3HP) to 9 months of daily INH (300mg) (9H) in a non-inferiority study design.[11] The study was conducted in low to medium TB and HIV burden settings (United States, Canada, Brazil, and Spain). Participants were aged 12 years and above and the vast majority were HIV uninfected. Study 26 showed that 3HP was non inferior to 9H in the modified intention to treat (mITT) and per protocol (PP) analysis and there was a trend towards superiority in reducing TB incidence (TB incidence: 9H:16/100 persons-years, 3HP:7/100 person-years).[11] The 3HP, compared to the 9H, study arm had a higher treatment-completion rate (82% vs 69%).[11] Based on this evidence, a recent WHO Expert Panel agreed that 3HP is equivalent to 6-month or 9-month INH regimens for the purpose of preventing incident TB arising in persons with LTBI in low TB burden countries[1]. However, preventive therapy for persons with LTBI (IGRA/TST+) is not indicated in high TB burden countries, including South Africa, due to a combination of factors including: rapid loss of protection (and some evidence of rebound increased risk) after preventive therapy is completed[3,4]; rates of MTB infection that may exceed 10% per year[2]; rates of prevalent LTBI in the range of 70-80% among adults[5]; and the fact that 90% of persons with LTBI would never progress to disease in their lifetime. ***The balance of protective benefit (transient, and limited to a fraction of recipients) and risk (primarily intolerance, hepatotoxicity, and treatment burden) does not favor preventive therapy for all IGRA/TST+ persons in high TB burden countries***. Note that this proof-of-concept study will address the question of whether 3HP can provide short-term protection against incident TB arising in COR+ persons. If proof-of-concept efficacy were demonstrated, larger studies with longer follow-up would be needed to evaluate the magnitude and durability of protection in COR+ persons.

Benefits of Active Case-finding and Active Surveillance for TB Disease: All participants, in both the Treatment and Observation Arms, will benefit from active case finding for undiagnosed prevalent TB disease at baseline, by symptom screening and collection of sputum for investigation. Similarly, all participants will benefit from TB education and active surveillance for incident TB disease; by active symptom screening and symptom-triggered TB investigation during follow-up; and by repeat sputum screening for undiagnosed TB disease in all participants at end of study. Earlier diagnosis of previously undiagnosed and pre-symptomatic or incipient TB disease will allow earlier, effective treatment, reduced morbidity, and reduced MTB transmission to susceptible contacts.

Benefits of Participation in Research: Persons with previously undiagnosed medical, surgical, or other conditions identified at screening, including but not limited to HIV infection, will benefit from early

diagnosis, referral and rapid access to treatment systems. Similarly, participants who develop new conditions during follow-up will also benefit from early diagnosis and linkage to care.

2.4 AIMS

2.4.1 PRIMARY AIMS

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

2: Test whether COR status differentiates persons with cumulative prevalent or incident TB disease from persons without TB disease.

2.4.2 SECONDARY AIMS

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

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

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

2.4.3 EXPLORATORY AIMS

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.

3. TRIAL DESIGN

Figure 3: Design Schematic
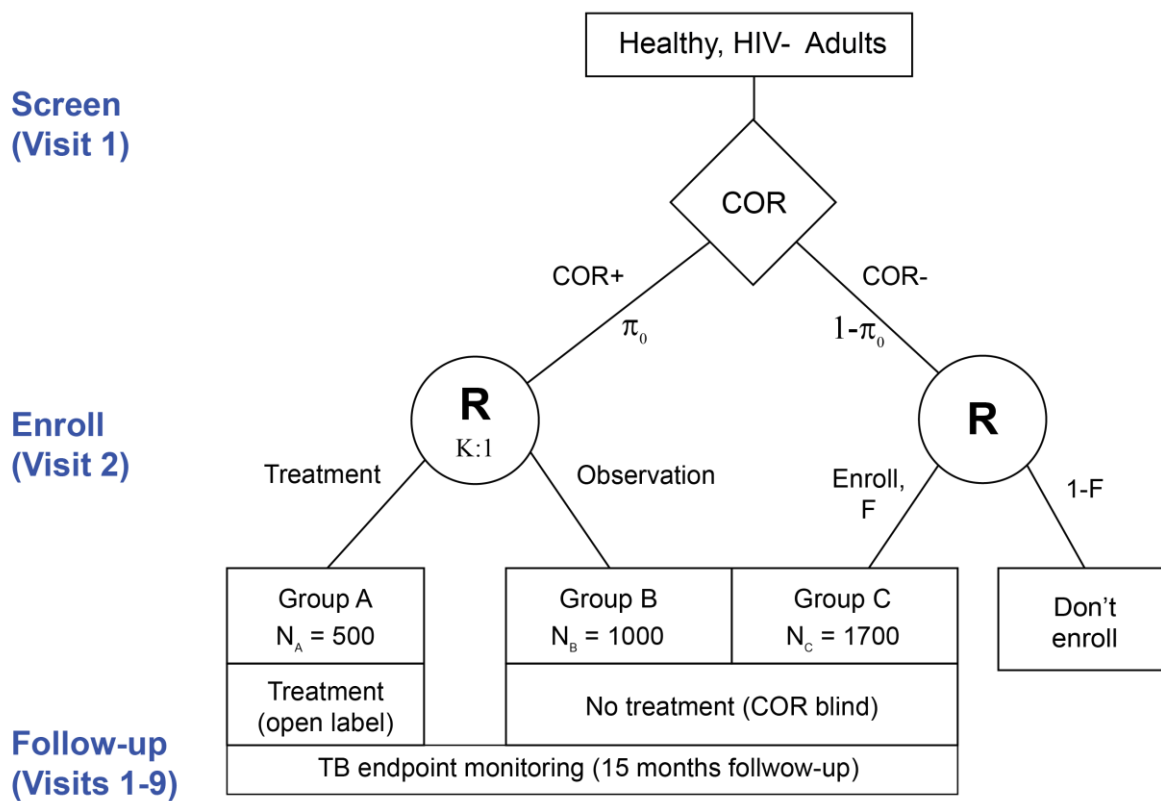
This is a randomised, partially blinded clinical trial. Adult volunteers living in selected TB hyperendemic areas of South Africa will be identified and recruited by community sensitization, word-of-mouth, and telephonic or home or workplace contact.

A maximum of 3,200 participants (approximately 1,500 COR+ and 1,700 COR-) will be enrolled and followed for up to 15 months for TB disease. Depending on observed rates of TB disease accrual during the course of the trial, the final number of participants enrolled into the Treatment and Observation Arms, the final balance of COR+ and COR- participants, and the duration of follow-up will be adapted, based on 3-monthly operational monitoring reports prepared by the Trial Statistician, using cumulative projections of observed COR+ prevalence and TB case accrual. Enrolment into one study arm may be halted prior to the other arm, based on projected ability to achieve the primary and secondary aims, in which case all remaining particiants would be enrolled into the remaining arm. All participants enrolled in the first 12 months of recruitment will undergo 15 months of scheduled follow-up, but thereafter, subsequent participants may have follow-up time reduced incrementally, such that individual follow-up would be reduced to a minimum of 3 months, with mean follow-up of all participants a minimum of 12 months).

Individuals with HIV infection and any conditions likely to affect the performance of the COR assay, or the safety and/or efficacy of 3HP, will not be enrolled. Participants eligible for randomisation who test COR+ at screening will be randomised in a 1:2 ratio to either open-label 3HP (Treatment Arm), or active surveillance for TB disease (Observation Arm). Participants who test COR- will be randomly selected to participate in the Observation Arm or they will not be enrolled. Approximately seventeen (17) COR- participants will be selected for enrolment for every 5 COR+ participants.

The maximum cohort of 3,200 participants will therefore include:
- 500 COR+ participants in the Treatment Arm (unblinded to COR status) receiving open-label 3HP;
- 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 be managed by a dedicated, unblinded team from the Data Centre.

Participants in both study arms 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.

Socio-demographic characteristics of participants randomized to the Treatment and Observation Arms will be tabulated and monitored by site throughout the enrolment period.

Participants in the Treatment Arm will receive open-label 3HP: high dose INH (15mg per kg body weight, rounded up to the nearest 100 mg; maximum dose 900 mg) with Pyridoxine supplementation (25mg), and Rifapentine based on body weight (>32kg – 50kg: 750 mg; >50kg: 900 mg), given weekly as 12 directly observed treatment (DOT) oral doses, ideally with food, over 3 months. Participants in the Observation Arm will undergo active symptom-targeted TB surveillance.

Efficacy of 3HP will be evaluated for prevention of incident TB, in COR+ participants in the Treatment and Observation Arms. The COR will be evaluated for detection of prevalent TB in participants who undergo symptom screening and TB investigation at baseline (Visit 2). Thereafter, the COR will be evaluated, singly and in comparison with IGRA, as a prognostic test for incident TB, in Observation Arm participants only.

The outcomes of interest include undiagnosed prevalent TB disease in participants at baseline; and incident TB disease, occurring in participants without prevalent disease through up to 15 months of follow-up. Participants with baseline TB disease, confirmed by positive Xpert MTB/RIF on two separate sputum samples, will be included in the evaluation of COR performance for prevalent TB, but will not be included in evaluation of 3HP treatment efficacy. If only one test is positive, a third sputum sample will be collected for Xpert MTB/RIF and MGIT culture. Participants with prevalent TB disease diagnosed at baseline will have a chest radiograph performed, discontinue study treatment, cease study follow-up, and will be referred in writing to the NTP for 4-drug curative treatment, which is provided free of charge.

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 with any one or more symptoms consistent with TB disease, including persistent unexplained cough, fever, night sweats, weight loss, or any hemoptysis, detected at study contacts or visits will undergo standardized investigation for TB disease, including two sputum samples, one for Xpert MTB/RIF assay and one for MGIT culture. If only one test is positive, a chest radiograph will be performed and a third sputum sample will be collected for Xpert MTB/RIF and MGIT culture. Participants who are sputum unproductive will be assumed sputum negative in the first instance. Participants who test negative for TB, but remain symptomatic, may have additional investigations performed, including sputum induction or sampling from an extrapulmonary site, if clinically indicated. Sputum sampling will be repeated at the final scheduled study visit, regardless of presence or absence of symptoms, in all participants.

Participants with incident TB disease, confirmed by positive Xpert MTB/RIF and/or MGIT culture on two separate sputum samples, will be included in the evaluation of COR prognostic performance for

incident TB (Observation Arm only) and evaluation of 3HP treatment efficacy (COR+ participants in Treatment and Observation Arms).

Participants diagnosed with incident TB disease will have a chest radiograph performed, discontinue study treatment, and will be referred in writing to the NTP for 4-drug curative treatment. After referral for TB treatment all participants diagnosed with TB disease will attend a final (End of Study) visit, to confirm that they have accessed TB treatment, at which they will be withdrawn from the study. Participants with a positive sputum test at the final scheduled study visit will be asked to return for an unscheduled visit to confirm the diagnosis of TB disease and to complete a written referral to the NTP for 4-drug curative treatment.

HIV counselling and testing will be repeated at 6 and 12 months for all participants on study; and for all participants diagnosed with incident TB disease; or if otherwise clinically indicated. HIV infected participants will be withdrawn from the study and referred to the health services for further management, including antiretroviral therapy and IPT as per South African national guidelines.

4. TRIAL POPULATION

A maximum of 3,200 HIV uninfected adult volunteers of known COR status (1,500 COR+ and 1,700 COR-) residing in TB hyperendemic communities will be enrolled at 5 study sites in South Africa.

4.1 ELIGIBILITY CRITERIA

A participant will be eligible for enrolment in the trial if all inclusion criteria are met. A participant will not be eligible for trial enrolment if any of the exclusion criteria are met.

4.1.1 Inclusion criteria (at time of screening):

1. Written informed consent
2. Aged ≥18 and <60 years
3. Known COR status (- or +)
4. Known HIV status
5. Women of child-bearing potential who are not surgically sterilized must agree to practice adequate contraception (barrier method or non-hormonal intrauterine device, alone or in addition to systemic hormonal contraceptive method) or abstain from heterosexual intercourse for 3 months on study.
6. Likely to remain in follow-up and adhere to protocol requirements

4.1.2 Exclusion criteria (at time of screening):

1. HIV infection
2. Pregnant or lactating
3. Diagnosed with TB disease within last 3 years
4. Household exposure to a TB patient with known multi-drug resistant (MDR-) TB disease within last 3 years
5. Body weight <40kg
6. Known allergy to INH or Rifamycins
7. Receiving antiarrhythmic, antidepressant, antipsychotic, antihypertensive, anticonvulsant, anticoagulant, or (inhaled or oral) corticosteroid therapy
8. Any medical, surgical, or other condition, including but not limited to known Diabetes Mellitus (requiring oral or injectable therapy), liver disease, porphyria, peripheral neuropathy, epilepsy, psychosis, or alcoholism, that in the opinion of the Investigator is likely to interfere with COR performance; safety and efficacy of the investigational products (IP); or adherence to protocol requirements.

4.2 CONCOMITANT MEDICATIONS

Concomitant medications will be recorded for all participants at Visit 1 (screening period) and Visit 2 (Day 0) and for the first 3 months in participants on the treatment arm. Details to be recorded, if known, include the specific medication trade name, the dose and unit, frequency and route of administration, as well as the start and stop dates of the therapy and the indication for its use. The investigator will instruct the participant to notify the trial site about any new medications that he or she uses during this period prior to their administration whenever possible.

4.3 PARTICIPANT IDENTIFIER

All participants who are screened for eligibility to participate in the trial will be allocated a unique participant identifier. The number will consist of a 1-digit site identifier followed by a 4-digit participant

identifier which will be allocated sequentially in accordance with the order in which participants present for screening i.e. the first, second and third participants presenting for screening at Site 1 will be 10001, 10002 and 10003 etc. This number will be used as the participant's primary identifier throughout the study and will be used for all labelling purposes.

5. INVESTIGATIONAL PRODUCTS

5.1 NAME PRIFTIN® (RIFAPENTINE) TABLETS

The U.S. Food and Drug Administration (FDA) has approved Priftin® (Rifapentine) in combination with INH for the treatment of LTBI in patients two years of age and older at high risk of progression to TB disease.

Manufacturer Sanofi

Dosage form Priftin® is supplied as 150 mg round normal convex dark-pink film-coated tablets debossed "Priftin" on top and "150" on the bottom, packaged in aluminium formable foil blister strips inserted into an aluminium foil laminated pouch.

Carton of 32 tablets (4 strips of 8 tablets) NDC 0088-2100-03

Carton of 24 tablets (3 strips of 8 tablets) NDC 0088-2100-XX

Table 1: Weight based dose of PRIFTIN in the treatment of latent tuberculosis infection

Weight range	PRIFTIN dose	Number of PRIFTIN tablets
10-14 kg	300 mg	2
14.1-25 kg	450 mg	3
25.1- 32 kg	600 mg	4
32.1-50 kg	750 mg	5
> 50 kg	900 mg	6

Active Ingredient Priftin® (Rifapentine) for oral administration contains 150 mg of the active ingredient Rifapentine per tablet. Rifapentine is a Rifamycin derivative antimicrobial and has a similar profile of microbiological activity to Rifampicin. The molecular weight is 877.04. The molecular formula is $C_{47}H_{64}N_4O_{12}$.

Dose Priftin® should be administered once-weekly in combination with INH 15 mg/kg (900 mg maximum). Adults and children 12 years and older: The recommended dose of Priftin® should be determined based on weight of the patient up to a maximum of 900 mg once-weekly, for 3 months (12 doses) (**Table 1**).

Route of administration Oral, ideally with food. Administration of Priftin® with a meal increases oral bioavailability and may reduce the incidence of gastrointestinal upset, nausea, and/or vomiting.

Indication Treatment of LTBI. Priftin® is indicated in adults and children 2 years and older for the treatment of LTBI caused by MTB in patients at high risk of progression to TB disease (including those in close contact with active TB patients, recent conversion to a positive TST, HIV-infected patients, or those with pulmonary fibrosis on radiograph).

Limitations of Use Active TB disease should be ruled out before initiating treatment for LTBI. Priftin® must always be used in combination with INH as a 12-week once-weekly regimen for the treatment of LTBI. Priftin® in combination with INH is not recommended for individuals presumed to be exposed to rifamycin- or – INH-resistant MTB.

Storage Priftin® should be stored at room temperature (20 – 25°C)

5.2 NAME WINTHROP ISONIAZID (INH) 100mg/300mg TABLETS

Manufacturer Sanofi

Dosage form Winthrop INH is supplied as 100mg white, biconvex, scored tablets and as 300mg light yellow, flat, scored tablets with bevelled edges.

100mg tablets: 28

100mg tablets: 84 and 1000
300mg tablets: 28 and 1000

Active Ingredient The active ingredient INH is rapidly active against actively dividing MTB and bacteriostatic against semi-dormant organisms.

Dose The dose for treatment of active TB is 3-5 mg per kg body weight in single or divided doses up to a maximum of 300mg daily. The recommended dose for treatment of LTBI in combination with Priftin® is 15mg per kg body weight, rounded up to the nearest 100 mg; maximum dose 900 mg) with Pyridoxine supplementation (25mg) with each dose[1], given once weekly for 3 months (12 doses).

Route of administration Oral

Indication INH is indicated alone for the prophylaxis of TB and in combination with other antituberculosis medicine for the treatment of active TB.

Limitations of Use INH is contraindicated for persons with known hypersensitivity to isoniazid or related medication such as ethionamide, pyrazinamide and niacin. Safety in pregnancy and lactation has not been established. Risk-benefit ratio should be considered for persons with alcoholism, hepatic or renal impairment, convulsive disorders, history of psychosis.

Storage Store below 25°C in closed container protected from light.

5.3 RECEIPT AND STORAGE

The investigational products will be shipped to the sites from a central distributor (Lekoko, Johannesburg) appointed by the Sponsor. Upon receipt of the investigational product supply, the site pharmacist will inspect the shipment for damage. Any damage or discrepancies from the packing list will be documented and discussed with the Sponsor and the trial monitor to determine the appropriate action. The Principal Investigator (PI) is responsible for ensuring that the IP is stored at the specified temperature in a locked cabinet or other secure storage facility with no access to unauthorised personnel and in accordance with any other instructions on the investigational product labels.

5.4 PACKAGING AND LABELLING

The IP containers will be identified by protocol number, storage requirements and contents. Preparation and labelling of the IP will be the responsibility of the distributor appointed by the Sponsor. The IP will be labelled with trial-specific information meeting all of the applicable regulatory requirements and in accordance with the current version of the Guide to Good Manufacturing Practice for Medicines in South Africa.

5.5 DRUG ACCOUNTABILITY

The IP will only be administered to participants in this trial. The site pharmacist is required to maintain accurate IP accountability records. These include records of the product's delivery to the site, the inventory at the site, the product dispensed to and used by each participant and the return to the Sponsor or destruction of any unused product.

IP will be dispensed by the site pharmacist or authorized site staff member licensed to dispense. Each dose will be administered and directly observed, ideally with food, by a designated study staff member at each DOT visit. DOT visits may be conducted as field visits or study clinic visits.

Drug accountability records will be reviewed by the trial monitor during interim site visits and upon completion of the trial. Information regarding any IP that was unusable, lost or stolen will be documented and reported to the Sponsor and appropriate regulatory agencies as required.

5.6 DISPOSAL OF THE INVESTIGATIONAL PRODUCT

After completion of the trial, and upon written authorisation from the Sponsor, any remaining unused or partially used IP will either be returned to the Sponsor or destroyed as pharmaceutical waste in accordance with South African practice. Details of the final disposition of the IP including a copy of the destruction certificate as relevant, will be documented in the trial master file.

5.7 SELECTION OF DOSES

Participants in the Treatment Arm will receive:

INH (15mg per kg body weight, rounded up to the nearest 100 mg; maximum dose 900 mg) with Pyridoxine supplementation (25mg) with each dose.

Rifapentine based on body weight (>32kg – 50kg: 750 mg; >50kg: 900 mg)

5.8 DOSING SCHEDULE AND DURATION OF TREATMENT

INH and Rifapentine will be given weekly as 12 directly observed treatment (DOT) oral doses, ideally with food, over 3 months.

The dosing interval will be defined by a calendar week. Any dose missed in that calendar week will result in an additional week being added to the treatment course, to a maximum of 16 completed weeks. Completion of therapy will be defined as receiving a minimum of 11 doses within a maximum of 16 weeks. Participants who have not completed a minimum of 11 doses within 16 weeks, but who leave the study for any reason, will not have follow-up extended in order to complete therapy. Participants who leave the study before completion of therapy will return for a final unscheduled safety visit whenever possible.

5.9 ASSIGNMENT TO STUDY ARM

Assignment to study arm will be managed by a dedicated, unblinded randomisation team from the Data Centre and will be based on COR status at screening.

The Data Centre randomisation team will provide each site with a list of participants to bring back for enrolment at Visit 2 (Day 0, Enrolment) after receiving COR assay results for each batch of samples assayed. Participants that satisfy the eligibility criteria at Visit 2 will then be enrolled. The study arm to which participants have been randomised will be revealed at the time of enrolment. Participants who are ineligible for inclusion at Visit 2 or who fail to present for this visit, will be replaced by participants identified from a subsequent batch of COR assay results as determined by the Data Centre.

Participants who are withdrawn or lost to follow-up after enrolment will not be replaced.

5.10 BLINDING

The trial is partially blinded.

The Observation Arm is 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 randomisation 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 authorised 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 will be the only personnel unblinded to COR status of all participants during the trial:
The Data Centre personnel responsible for the generation of the randomisation schedule.
The independent statistician responsible for unblinded analyses for DSMB closed sessions.

Unblinded personnel will at no time reveal individual participant COR status or study arm allocation to a blinded member of the clinical trial team. Planned unblinding of the trial team members will only occur after conclusion of the trial and database lock.

5.11 EMERGENCY OR ACCIDENTAL UNBLINDING OF COR STATUS

If there is an urgent clinical requirement for a participant's COR status to be known (i.e. if knowledge of COR status was thought to impact on the participant's medical care), the investigator (in consultation with the Sponsor) will put forward a written request to the Data Centre code holder for urgent unblinding of the participant's COR status. The unblinding request must include the participant's treatment number, the date, clinical justification, and the investigator's signature. The request will be kept in the trial master file. The unblinded treatment allocation will not be recorded in the participant's Case Report Form (CRF). Any accidental unblinding of COR status should also be reported immediately to both the Sponsor and Clinical Research Organization (CRO). The reason for the unblinding and the steps taken to ensure that the risks of this happening again in the future are minimised, must be documented.

6   VISIT SCHEDULE

After successful screening and enrolment, each participant will undergo up to seven (7) study contacts or visits, including three (3) study contacts (telephonic or field visits) and four (4) study clinic visits, through a maximum of 15 months of follow-up. Study participants whose individual follow-up time is reduced would undergo between 12 months and a minimum of 3 months of follow-up. Study participants whose individual follow-up time is reduced would be informed at least 3 months prior to their final study visit, at which end of study procedures and TB investigations would be performed. Participants with a positive TB investigation at the end of study visit will return for an additional visit to ensure referral for TB treatment.

6.1 VISIT 1 (SCREENING PERIOD): DAY -28 TO DAY -1

Potential participants must provide written informed consent for participation in the trial prior to performing any screening assessments or procedures. If necessary, the participant may take the trial information document away with them and return at a later stage for screening examinations. The 28-day screening period commences with the first screening assessment. All screening assessments need to occur within the 28 days prior to randomisation.

The following information will be obtained and procedures and assessments performed during this time:
- Written informed consent for trial participation
- Verification of age
- Screening medical history
- Review of concomitant medications
- Measurement of height and weight
- Urine pregnancy test (women of child-bearing potential only)
- Blood will be collected for:
  - HIV rapid test (with pre- and post-test counselling)
  - COR assay (PAXgene tube)

6.2 VISIT 2: DAY 0

Potentially eligible participants as identified by the randomisation team from the Data Centre will return to the trial site for Visit 2 enrolment procedures. Participants can only be enrolled if all screening activities are complete, including receipt of HIV rapid test and COR assay results, within the 28-day screening window period.

The following procedures/assessments will take place prior to the final assessment of eligibility by the investigator:
- Medical history
- Concomitant medications
- Vital signs
- Measurement of weight
- Targeted physical examination
- Urine pregnancy test (women of child-bearing potential only)
- Review of inclusion and exclusion criteria

The investigator will review all available information to assess whether or not the participant is eligible for trial participation. Persons who are not eligible for inclusion will be immediately logged as screening failures and will not be eligible to be re-screened at a later stage.

All eligible participants will be enrolled and will undergo the following assessments and procedures:
Blood will be collected for:
  - IGRA
  - Serum (to be stored for proteomics)
- TB symptom screen questionnaire

- Two sputum samples will be collected for Xpert MTB/RIF; two aliquots of unprocessed sputum will be stored for additional MTB diagnostic tests at the end of study (potentially including, but not limited to Xpert MTB/RIF, MGIT culture, and line probe assay).

Treatment Arm participants will undergo the following additional assessments and procedures:
Blood will be collected for:
   o ALT and Total Bilirubin
- Prescription of IP
- Treatment education and dispensing of first dose (DOT)
- Appointment and confirmation of contact details for next DOT visit

All participants will be given an appointment and contact details confirmed for the next study contact (Month 1).

6.3 DOT VISITS (TREATMENT ARM ONLY): WEEKS 1-11

Treatment Arm participants will undergo the following additional assessments and procedures at DOT visits:
- Gastrointestinal (GIT) symptom screen questionnaire
- If indicated by one or more GIT symptoms, the dose of IP will be withheld and the participant will be referred to an investigator for review
- Review concomitant medications
- Record any SAEs
- Treatment education and administration of next dose, ideally with food, under DOT
- Appointment and confirmation of contact details for next DOT visit

6.4 CONTACT 3: DAY 28 (+/- 3)

All participants will undergo the following assessments and procedures:
- TB symptom screen questionnaire (telephonic contact or field visit)
- If indicated by one or more TB symptoms, two sputum samples will be collected, one for Xpert MTB/RIF and one for MGIT culture (field or study clinic visit)
- Review concomitant medications (for treatment arm participants only)
- Record any SAEs
- All participants will be given an appointment and contact details confirmed for the next study contact (Month 2)

6.5 CONTACT 4: DAY 56 (+/- 3)

All participants will undergo the following assessments and procedures:
- TB symptom screen questionnaire (telephonic contact or field visit)
- If indicated by one or more TB symptoms, two sputum samples will be collected, one for Xpert MTB/RIF and one for MGIT culture (field or study clinic visit)
- Review concomitant medications (for treatment arm participants only)
- Record any SAEs
- All participants will be given an appointment and contact details confirmed for the next study visit (Month 3)

6.6 VISIT 5: DAY 84 (+/- 3)

All participants will undergo the following assessments and procedures:
- Medical history
- Review concomitant medications (for treatment arm participants only)
- Vital signs
- Measurement of weight
- Targeted physical examination

- Urine pregnancy test (women of child-bearing potential only)
- TB symptom screen questionnaire
- If indicated by one or more TB symptoms, two sputum samples will be collected, one for Xpert MTB/RIF and one for MGIT culture
- Record any SAEs
- All participants will be given an appointment and contact details confirmed for the next study visit (Month 6).

6.7 VISIT 6: DAY 180 (+/- 7)

All participants will undergo the following assessments and procedures:
- Medical history
- Vital signs
- Measurement of weight
- Targeted physical examination
- TB symptom screen questionnaire
- If indicated by one or more TB symptoms, two sputum samples will be collected, one for Xpert MTB/RIF and one for MGIT culture
- Record any SAEs
- Blood will be collected for HIV rapid test (with pre- and post-test counselling)
- All participants will be given an appointment and contact details confirmed for the next study visit (Month 9).

6.8 CONTACT 7: DAY 270 (+/- 7)

All participants will undergo the following assessments and procedures:
- TB symptom screen questionnaire (telephonic contact or field visit)
- If indicated by one or more TB symptoms, two sputum samples will be collected, one for Xpert MTB/RIF and one for MGIT culture (field or study clinic visit)
- Record any SAEs
- All participants will be given an appointment and contact details confirmed for the next study visit (Month 12)

6.9 VISIT 8: DAY 365 (+/- 7)

All participants will undergo the following assessments and procedures:
- Medical history
- Vital signs
- Measurement of weight
- Targeted physical examination
- TB symptom screen questionnaire
- If indicated by one or more TB symptoms, two sputum samples will be collected, one for Xpert MTB/RIF and one for MGIT culture
- Record any SAEs
- Blood will be collected for HIV rapid test (with pre- and post-test counselling)
- All participants will be given an appointment and contact details confirmed for the next study visit (Month 15).

6.10 VISIT 9 (END-OF-STUDY VISIT): DAY 449 (+/- 7)

All participants leaving the study, including those who complete less than 15 months follow-up, will return to the trial site for a final end-of-study evaluation for safety and TB screening. Every attempt will be made to ensure that participants are not lost to follow-up prior to this visit and the clinical trial team will attempt to trace participants who fail to present for this visit. All participants, except those

who have already been confirmed to have TB disease at an earlier visit and who will not have TB screening repeated, will undergo the following assessments and procedures at end of study:

- Medical history
- Vital signs
- Measurement of weight
- Targeted physical examination
- TB symptom screen questionnaire
- Two sputum samples will be collected, regardless of presence or absence of symptoms, one for Xpert MTB/RIF and one for MGIT culture
- Record any SAEs

Contact details will be confirmed so that sputum results can be provided, with written TB clinic referral if necessary. If a sputum sample from the end of study visit tests positive, an unscheduled follow-up visit must be conducted for safety purposes to ensure the participant is referred for TB treatment.

6.11 EARLY WITHDRAWAL FROM THE TRIAL

Participants will be advised that they are free to withdraw from the trial at any time, for any reason, without prejudice. Every reasonable effort should be made by the study staff to keep participants in the trial. Participants must, however, be withdrawn from the trial for any of the following reasons:

- At the request of the participant (withdrawal of informed consent), irrespective of the reason;
- At the discretion of the investigator if he or she believes that continuation in the trial would be detrimental to the participant's well-being;
- Any protocol non-conformance or adverse event such that continuation on trial would pose a significant risk to the participant's safety.

For participants with missed study visits who are thought to be lost to follow-up, study staff should make at least three documented attempts to contact the participant for each visit. In the case of missed visits, an out-of-window (unscheduled) visit may be performed for TB screening, provided that the interval between the missed scheduled visit and the planned out-of-window visit is less than the interval between the planned out-of-window visit and the next scheduled visit. In other words, if less than half of the inter-visit period has elapsed, an out-of-window visit should be performed. Participants with multiple consecutive missed visits are only considered lost to follow-up if they fail to attend the end of study visit. Unless lost to follow-up, withdrawn participants will attend an early discontinuation visit (procedures and assessments conducted as for End of Study Visit). Reason for withdrawal from the study will be documented to ascertain whether toxicity or treatment burden contributed to early termination.

7   TRIAL ASSESSMENTS

7.1 SCREENING DATA

Screening data will be collected during screening (Visit 1) and prior to enrolment on Day 0 (Visit 2).

7.1.1 AGE VERIFICATION

Age of potential participants at date of screening will be verified by identification document, passport, or driver's license, copy of which to be kept in the participant file and checked at each visit.

7.1.2. SCREENING MEDICAL HISTORY

Potential participants will provide a targeted medical history, with a focus on socio-demographic data (gender, ethnicity, education level, & household economic indicators), risk factors for TB (including TB contact and smoking history), current and past medical and surgical conditions (including recent febrile episodes), and concomitant medications, using a standardised questionnaire.

7.1.3. WEIGHT AND HEIGHT

Height in centimetres (cm) and body weight (to the nearest 0.1 kg in indoor clothing, but without shoes) will be measured at screening. Body Mass Index (BMI) will be calculated using the formula:

BMI = weight (kg) / height (m)^2.

Body weight but not height will be measured at each subsequent study visit.

7.1.4. URINE PREGNANCY TEST

To confirm eligibility at screening, a urine β-hCG test will be performed for all females of child-bearing potential. The pregnancy test will be repeated at Day 0 and at the Month 3 visit.

7.1.5. HIV RAPID TEST

Following appropriate pre-test counselling, evaluation for HIV seropositivity will be performed by rapid test, and, if positive, will be confirmed by a second rapid test as per site protocol. Appropriate post-test counselling will be made available by the investigator, and participants will be referred for ongoing HIV management in the event of a positive test. HIV testing will be repeated at 6 and 12 months, and in the event that TB disease is diagnosed during follow-up.

7.1.6. COR ASSAY

Whole blood RNA will be collected in PAXgene tubes from all potentially eligible persons at screening (1 tube of 2.5mL blood, stored at room temperature for 2-18 hours, then frozen at -20°C) and shipped frozen to the South African Tuberculosis Vaccine Initiative (SATVI) Cape Town Laboratory on a weekly basis. PAXgene tubes will be processed in batches of 93 (plus 3 internal assay controls), allowing for handling by standard assay plate format. cDNA synthesis and pre-amplification will be automated, and up to 6 Fluidigm chips will be run weekly. In order to extract high quality RNA and complete the first amplification steps of the COR assay using whole blood collected in PAXgene tubes in a high-throughput, standardized, reproducible and cost-effective manner, a fully automated procedure using the TECAN EVO Freedom robotic platform will perform RNA extraction, cDNA-synthesis and pre-amplification steps on up to 465 samples per week.

Participants will be evaluated for risk of TB disease using the PSVM.1 model on the BioMark HD Fluidigm multiplex qRT-PCR machine. COR analysis will be conducted by a locked-down R script, which includes Quality Control filters and gives a vote threshold as the COR score. Participants with a PSVM.1 progressor vote ≥ 60% will be classified as COR+, whereas progressor votes ≤ 60% will

be classified as COR-. Screening COR results will be made available for participant randomization within 21 days of sampling.

7.2 BASELINE EVALUATIONS

Baseline data will be collected on Day 0 (Visit 2)

7.2.1. MEDICAL HISTORY

The investigator will review the screening medical history and confirm eligibility. An abbreviated medical history will be collected at each subsequent study visit.

7.2.2. VITAL SIGNS & PHYSICAL EXAMINATION

A targeted physical examination will be performed at the enrolment visit on Day 0 (Visit 2), including recording of vital signs (temperature, pulse rate, blood pressure); general examination including lymph nodes and skin; detailed examination of the respiratory system; and other systems as indicated on the basis of medical history or other physical findings. At all other visits, vital signs and an abbreviated physical examination will be performed if directed by presence of symptoms or occurrence of adverse events. Physical examination data will be recorded in the source documentation at the trial site. Significant findings present prior to the first administration of the investigational product will be recorded.

7.2.3. IGRA

A whole blood sample will be collected for IGRA on Day 0 in all enrolled participants (QuantiFERON-Plus; 4mL total, incubated at 37$°$C for 16-24 hours, then spun and supernatants stored at -80$°$C).

7.2.4. SERUM PROTEOMICS

A clotted blood sample will be collected on Day 0 in all enrolled participants; spun and serum stored at -80$°$C for future proteomic analysis. Serum may be stored for up to 10 years before being destroyed.

7.3 SAFETY LABORATORY EVALUATIONS

Clinical chemistry: Hepatic function (serum alanine aminotransferase (ALT) and total bilirubin) will be measured at baseline in Treatment Arm participants and if abnormal (Grade 1 or higher; DAIDS Toxicity Table), or if participants become symptomatic, will be repeated 2-4 weekly until return to baseline.

7.4. TB EVALUATIONS

Investigation for TB disease will be conducted in all participants at baseline; in symptomatic participants during follow-up; and in all participants at the end of study visit.

7.4.1. TB SYMPTOM SCREENING

All participants will be asked about any new household or other close contact with a recently diagnosed TB patient, and about symptoms consistent with TB disease, at all study contacts and visits from Day 0 through end of study. Symptoms will be solicited using a standardized questionnaire and will include loss of weight or persistent unexplained cough, chest pain, fever, or night sweats for longer than two weeks; or any hemoptysis.

7.4.2. TB INVESTIGATIONS

Two sputum samples will be collected from all participants at baseline, regardless of presence or absence of symptoms, for Xpert MTB/RIF testing. An aliquot of unprocessed sputum from each sample will be stored for additional MTB diagnostic tests at the end of the trial, potentially including, but not limited to Xpert MTB/RIF, MGIT culture, and line probe assay. Thereafter, TB investigation will be symptom-triggered throughout follow-up. A participant with any one or more symptoms consistent with TB disease will be asked to provide two sputum samples, one for Xpert MTB/RIF and one for MGIT culture. If only one test is positive, a third sputum sample will be collected for Xpert MTB/RIF and MGIT culture. If a participant cannot produce a sputum sample spontaneously, this will be recorded in the source notes and no sample will be sent to the laboratory. Participants who are unproductive of sputum will be deemed Xpert MTB/RIF and MGIT culture negative. However, if clinical suspicion of TB disease persists in any participant, additional samples may be obtained, including induced sputum, or samples from other sites in the case of suspected extrapulmonary disease. Participants with a positive sputum MTB/RIF or MGIT culture will have a chest radiograph performed before referral for treatment.

7.5 SERIOUS ADVERSE EVENTS

SAEs will be recorded for all participants from Day 0 to end of study. The definition, evaluation, recording and reporting of adverse events is described in detail in Section 9.

8   REPORTING OF ADVERSE EVENTS

8.1 DEFINITIONS

8.1.1. ADVERSE EVENTS

An adverse event (AE) is the appearance, or worsening from baseline, of any undesirable sign, symptom, or medical condition occurring in a participant administered an investigational product, which does not necessarily have a causal relationship to the investigational product. Investigational product includes the investigational product under evaluation. Medical conditions/diseases present before the first dose of the investigational product are only considered adverse events if they worsen after the investigational product is administered. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, or are considered clinically significant, or require therapy. Day-to-day fluctuations in pre-existing conditions that do not represent a clinically significant change in the participant's status will not necessarily be reported as adverse events.

AEs should only be reported for participants enrolled in the treatment arm of CORTIS-01.

Hypersensitivity reactions in participants in the Treatment Arm are termed Adverse Events of Special Interest (AESI). Hypersensitivity reactions may include one or more of the following: hypotension, urticaria, angioedema, acute bronchospasm, conjunctivitis, thrombocytopenia, neutropenia or 'flu-like illness' (syndrome including one or more of weakness, fatigue, muscle pain, nausea, vomiting, headache, fever, chills, aches, rash, itching, sweats, dizziness, shortness of breath, chest pain, cough, syncope, palpitations). There have been reports of anaphylaxis.

Adverse events in Treatment Arm participants that fall under the definition of AESI should be reported as related or unrelated to investigational product. For example, symptoms of 'flu-like illness' in combination with clinical evidence of a respiratory tract infection might be reported as unrelated; whereas symptoms of flu-like illness in absence of clinical evidence of a respiratory tract infection, especially if temporally associated with IP, might be reported as related.

Treatment Arm participants who experience an unrelated AESI should be treated supportively and continue to receive IP. Participants who experience a related AESI should be treated supportively and should discontinue IP; and remain on study follow-up for safety and efficacy per protocol.

8.1.2. SERIOUS ADVERSE EVENTS

A serious adverse event (SAE) is an AE that meets any of the following criteria:
- Is fatal or life-threatening
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
- Requires inpatient hospitalisation or prolongation of existing hospitalisation, unless hospitalisation is for:
    - elective or pre-planned treatment for a pre-existing condition that is unrelated to the trial and has not worsened since the start of the investigational product
    - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of an SAE given above and not resulting in hospital admission
    - social reasons and respite care in the absence of any deterioration in the participant's general condition

- Is medically significant (i.e. it does not meet any of the above serious criteria, but based on appropriate medical judgment, may jeopardize the participant and require medical or surgical intervention to prevent one of the serious outcomes listed above).

All SAEs will be monitored continuously and are subject to special reporting requirements (refer to Section 9.4) and should be reported for all trial participants, both in the treatment and observation arms.

8.2 ASSESSMENT AND DOCUMENTATION OF SERIOUS AND SEVERE LABORATORY ADVERSE EVENTS

The occurrence of any Grade 3 or 4 laboratory hepatotoxicity and all SAEs will be assessed by the investigator and recorded throughout the trial; whether spontaneously reported by the participant, observed by the investigator (either directly or by laboratory or other assessments), or elicited by general, non-leading questioning. At screening and again at each follow-up visit, participants will be instructed to report any changes in normal health that they experience to the investigator. Adverse events that are not a laboratory hepatotoxicity or SAE will not be recorded.

All SAEs will be recorded in the adverse event section of the CRF with the following information:
- The event name or term
- When the SAE first occurred (start date)
- When the SAE stopped (stop date) or whether it is "ongoing"
- The assessment of severity of the event (graded according to the Common Terminology Criteria for Adverse Events [CTCAE version 4.03, June 2010])[19]
- The investigator opinion regarding the relationship to the investigational product
- The action taken in response to the SAE
- The action taken on the investigational product in response to the SAE
- The outcome of the SAE
- If classified as an SAE, the reason for classification as such
- The expectedness of the adverse event, if the relationship to the investigational drug is considered to be certain, probable or possible.

8.2.1 DEFINITION OF RELATIONSHIP TO INVESTIGATIONAL DRUG(S)

The categories for classifying the Investigator's opinion regarding the relationship of an AE to investigational drug(s) are listed below:

Definite: An AE occurring in a plausible time relationship to investigational drug administration and which cannot be explained by a concurrent disease or other drugs or events. The response to withdrawal of the drug (dechallenge) is clinically reasonable.

Probable (likely): An AE with a reasonable time sequence to administration of the investigational drug and which is unlikely to be attributed to concurrent disease or other drugs or events. The response to withdrawal of the investigational drug (dechallenge) is clinically reasonable.

Possible: An AE with a reasonable time sequence to administration of the investigational drug, but which could also be explained by concurrent disease or other drugs or events. Information may be lacking or unclear.

Unlikely: An AE, including laboratory test abnormality, without a temporal relationship to investigational drug administration that makes a causal relationship improbable and/or, in which other drugs, events, or underlying disease provide plausible explanations.

Not related: An AE with sufficient evidence to accept that there is no causal relationship to investigational drug administration (eg, no temporal relationship to drug administration; another cause was proven; etc.).

Unclassifiable: An AE where the relationship to the investigational drug cannot be judged because information is insufficient or contradictory and cannot be supplemented or verified.

8.2.2 DEFINITION OF EXPECTEDNESS

If an AE is considered related to the investigational product (relationship to investigational drugs considered to be Definite, Probable or Possible), the expectedness of the event will be assessed and recorded by the investigator. An expected AE is an AE for which the nature or severity of the event is consistent with the known AE profile of the investigational product as per the Investigator brochure or package insert. An unexpected AE is an AE that is not listed in the Investigator Brochure or package insert, or that is listed, but not at the specificity or severity of the current event under observation.

8.3 FOLLOW-UP OF SERIOUS ADVERSE EVENTS

Each SAE will be followed to a satisfactory resolution, until it becomes stable, or until it can be explained by another known cause(s) (e.g. concurrent condition or concomitant medication use) and clinical judgment indicates that further evaluation is not warranted. All findings relevant to the final outcome of an AE must be reported in the participant's medical record.

8.4 SERIOUS ADVERSE EVENT REPORTING

To ensure participant safety, every SAE, regardless of suspected causality, occurring after Day 0 until end of study, must be reported using an SAE Report Form to the CRO (Triclinium), the Sponsor and to SANOFI. Severe (Grade 3 or 4) laboratory toxicities and severe Adverse Events of Special Interest (AESI), including hypersensitivity reactions and flu-like illness occurring during this period must also be reported.

This report must be forwarded by the PI or his/her designee within 24 hours (one calendar day) of the clinical site becoming aware of the event. Investigators must not wait to collect additional information required to fully describe the event before forwarding this report, but should simply document all information available to them at the time.

The initial notification should include the following:
- Protocol number
- Name and contact number of the investigator
- Participant's screening and treatment numbers
- Participant's date of birth
- Participant's gender
- The AE term
- Date of first dose of investigational drug(s), if applicable
- Date of last dose of investigational drug(s), if applicable
- The reason why the event was classified as an SAE
- Concomitant medications that were taken at the time of the event onset
- Medical history relevant to the event
- Relevant laboratory test findings (if available)
- The investigator's opinion of the relationship of the event to the investigational product
- The current status of the participant

Any missing or additional relevant information regarding the SAE should be provided in a written follow-up report(s).

Fatal or life-threatening serious adverse events that the investigator suspects are related to the investigational product should be reported telephonically to Triclinium and SANOFI immediately upon the investigator becoming aware of the event. Contact information for all safety personnel are contained in the Clinical Trial Team Contact List which will be stored on site.

Recurrent episodes, complications, or progression of the initial SAE must be reported using follow-up SAE Report Forms. These reports must be submitted to the same parties as the initial report, within 24 hours of the investigator receiving the follow-up information. The follow-up information should describe whether the event has resolved or is continuing, if and how it was treated, whether or not

the treatment blind was broken, and whether or not the participant was withdrawn from trial participation. Each SAE must be followed up until resolution or until stabilization of the event (if considered chronic or a permanent condition), or until it can be explained by another known cause(s).

The sponsor has authorized Triclinium to execute its responsibilities for safety report submission to the national regulatory authority (Medicines Control Council; MCC) within specific time periods of being notified of the event. The PI is required to comply with applicable regulations regarding the notification of the site Independent Ethics Committee (IEC) of the event.

The sponsor will notify all members of the DSMB of any related SAE within 24 hours of becoming aware of the event and will continue to provide all follow-up information in a timely manner.

8.5 IMMEDIATELY REPORTABLE ADVERSE EVENTS

Hypersensitivity reactions in participants in the Treatment Arm are termed Adverse Events of Special Interest (AESI). AESIs are Immediately Reportable Adverse Events (IRE) and must be reported using an IRE Report Form to the CRO (Triclinium), the Sponsor and to SANOFI.

This report must be forwarded by the PI or his/her designee within 7 working days of the clinical site becoming aware of the event. If the IRE is an SAE, the event is to be reported per SAE reporting criteria detailed in Section 8.4. Investigators must not wait to collect additional information required to fully describe the event before forwarding this report, but should simply document all information available to them at the time.

The initial notification should include the following:
- Protocol number
- Name and contact number of the investigator
- Participant's screening and treatment numbers
- Participant's date of birth
- Participant's gender
- The AE term
- Date of first dose of investigational drug(s), if applicable
- Date of last dose of investigational drug(s), if applicable
- The reason why the event was classified as an AESI
- Concomitant medications that were taken at the time of the event onset
- Medical history relevant to the event
- Relevant laboratory test findings (if available)
- The investigator's opinion of the relationship of the event to the investigational product
- The current status of the participant

Any missing or additional relevant information regarding the IRE should be provided in a written follow-up report(s).

8.6 REPORTING PREGNANCIES

If a participant in either study arm becomes pregnant during the trial, she will be withdrawn from the trial. Follow-up should continue in order to monitor the outcome of the pregnancy, including premature terminations. These data are to be included in the safety reports. The investigator should attempt to maintain contact with the participant to obtain information after delivery. The health status of the mother and child, the date of delivery, the child's sex and birth weight should be reported after delivery. All pregnancies will be followed to birth unless there are clinically significant abnormalities in the infant at birth, in which case further follow-up will be required to document their outcome.

Any pregnancies must be reported by the investigator to Triclinium. The report must be forwarded to the relevant parties even if the pregnancy is already known to have resulted in a spontaneous or elective abortion. At a minimum, the estimated date of conception, the estimated due date, and the dates that the participant received the investigational product should be provided.

Pregnancy will not be recorded as an adverse event. However, pregnancy outcomes will be recorded in the safety database. If the pregnancy results in a miscarriage or a planned termination, the event (spontaneous abortion or elective abortion) will be reported as an adverse event or serious adverse event as per the investigator's judgment and in accordance with the criteria for reporting a serious adverse event. A congenital anomaly or birth defect (i.e. an adverse finding in a child or foetus of a participant exposed to the investigational product before conception or during pregnancy) must be reported as a serious adverse event.

9 STATISTICAL CONSIDERATIONS

9.1 OVERVIEW

This study is a multi-center, randomized, partially blinded trial evaluating the performance of a TB disease biomarker and the efficacy of a TB preventive treatment regimen. The data analysis will evaluate biomarker performance, treatment efficacy and screen-and-treat strategy efficacy.

9.2 STUDY DESIGN

Eligible participants will provide a serum sample for measuring the COR biomarker. Participants that are above a pre-specified biomarker threshold (i.e. COR+) will be enrolled into a preventive treatment group (Analysis Group A) and an observation group

Figure 4: Analysis of Primary Aims by Analysis Group

(Analysis Group B). The enrolment will be randomized using a 1:2 treatment ratio. Since we expect COR positivity to be up to 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). All participants will be followed, with identical scheduled endpoint evaluation in each group.

The performance of the biomarker will be evaluated by comparing the incidence of endpoint-defined TB disease over up to 15 months in Group B versus Group C (RR_{COR}). The screening and enrolment process will ensure that the COR+ and COR- participants in these groups are enrolled contemporarily, 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 up to 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 of treatment efficacy. 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 over up to 15 months 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.

9.3 ENDPOINT DEFINITIONS

Two-sample endpoint definition (primary endpoint):

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 primary and secondary aims will be evaluated using this endpoint definition.
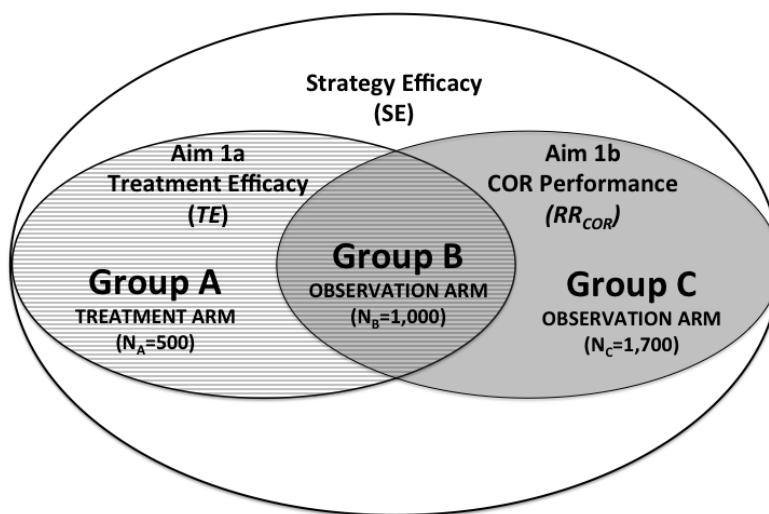
Confidential

One-sample endpoint definition (secondary endpoint):

TB disease confirmed by positive Xpert MTB/RIF and/or MGIT culture on a single sputum sample, or sample from another site if extrapulmonary disease. Exploratory analyses will evaluate the performance of the COR biomarker (RR) and TE (15) using this endpoint definition.

9.4 TRIAL AIMS

9.4.1 PRIMARY AIMS

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

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

9.4.2 SECONDARY AIMS

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

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

Secondary Aim 3: Compare prognostic performance of the COR for incident TB disease with Interferon-gamma release assay (IGRA).

9.5 SAMPLE SIZE

The primary analyses will evaluate TE(15), treatment efficacy, and $RR_{COR}(15)$, relative-risk for TB disease over up to 15 months of follow-up. The study is designed to have 80% power to reject the null-hypothesis, H_0: TE(15) <= 20% under the alternative design hypothesis that TE(15) = 80%, with one-sided alpha of 0.05. The study will also have 90% power to reject the null-hypothesis, H_0: $RR_{COR}(15)$ <= 2, with one-sided alpha of 0.025 based on the alternative design hypothesis that is specified in a trial simulation.

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[5,17-20]. 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 15% 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 2**).

To compute statistical power for the primary aims, a stochastic simulation of the trial was constructed that incorporated the time-varying properties of the biomarker along with a host of epidemiological and operational parameters listed in Table 2. The simulation modelled the incidence of TB disease in each participant using an exponential stochastic process. The COR- participants developed TB disease at a constant baseline rate estimated from similar patient populations. TB disease was simulated in COR+ participants using a time-varying rate function whose exponential rate of decay was derived from the ACS analysis. Treatment efficacy was simulated as a multiplicative decrease in time-varying relative risk equivalent to TE = 80%.

Table 2. Simulation parameters

10000	Total screened
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)
20%	Fraction of COR- followed to the endpoint
42	Enrollment rate (ppts screened per site per wk)
5	Number of sites
80%	Treatment efficacy (TE) among COR+
$RR_{COR}(t = 0)$	15
$RR\text{-decay}_{COR}$	12 months

Initially, the simulation was parameterized with reasonable values for sample size (N), treatment randomization ratio (K) and the fraction of COR- enrolled in Group C (F). Through iteration these parameters were optimized to provide high statistical power. The trial was iteratively simulated 1000 times and the primary objectives were evaluated. For each objective power was computed as the percentage of iterations in which the (1 - alpha)% confidence limit excluded the null-hypothesis (**Figure 5**).

Figure 5. Power for primary aims.
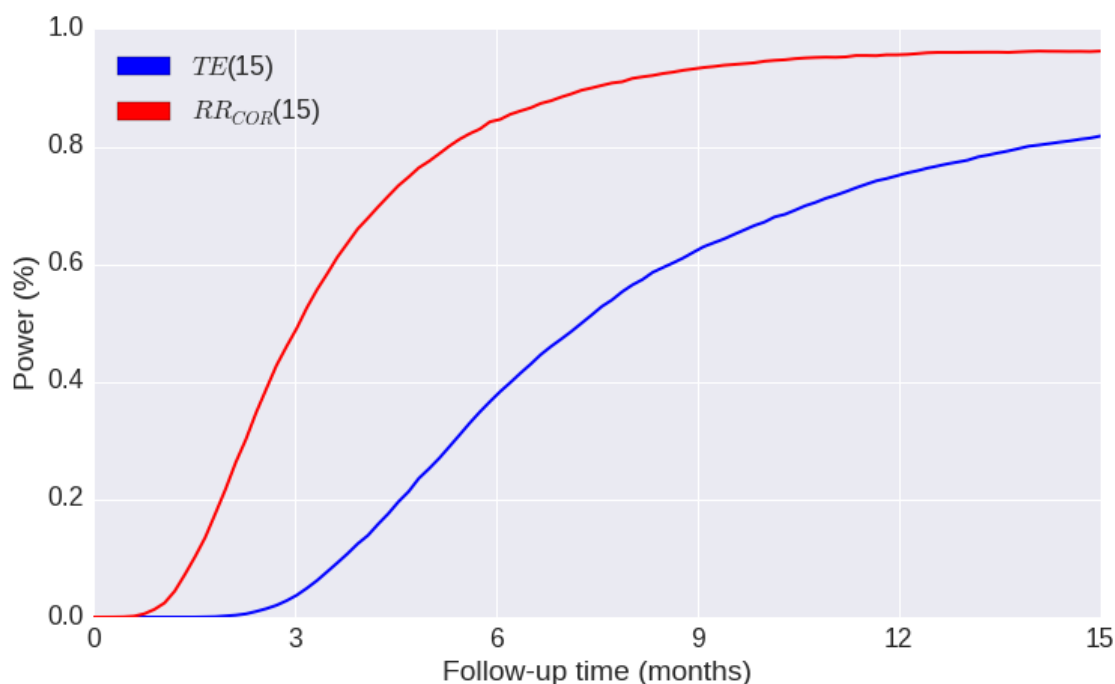
Based on these simulations the trial will require up to 1500 COR+ and 1700 COR- participants. The study is expected to have 80% power to reject the null-hypothesis, H_0: TE(15) <= 20% under the simulated design hypothesis, TE(15) = 80%, with a one-sided alpha of 0.05. The study will have 90% power to reject the null-hypothesis, H_0: RR_{COR}(15) <= 2, with a one-sided alpha of 0.025. Of the COR+ participants, 500 will be randomized to preventive therapy (Group A), while the remaining 1000 will be enrolled for standard of care (Group B). Only a fraction of the COR- participants that are screened will be enrolled in Group C. Based on the simulations we expect to observe 33 TB disease endpoints among COR+ and 7 TB disease endpoints among COR- participants.

In the event that accrual of TB cases is faster than expected and follow-up is reduced from 15 to a minimum of 3 months, with mean follow-up of 12 months, the study is expected to have 70% power to reject the null-hypothesis, H_0: TE(12) <= 20% under the simulated design hypothesis, TE(12) = 80%, with a one-sided alpha of 0.05; and 90% power to reject the null-hypothesis, H_0: RR_{COR}(15) <= 2, with a one-sided alpha of 0.025.

9.6 METHOD OF RANDOMISATION

Assignment to study arm will be based on COR status at screening. COR+ participants will be randomly assigned to study arm (Treatment or Observation Arm) in accordance with a randomisation 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.

In order to maintain the partial blind of the trial personnel (blind to COR status in the Observation Arm), the randomisation 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 randomisation process will be managed by a dedicated, unblinded randomisation 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. The list will indicate the study arm to which each participant has been allocated. Participants who satisfy the eligibility criteria at Visit 2 will then

be enrolled. Participants who are ineligible for inclusion at Visit 2 or who fail to present for this visit, will be replaced by participants from a subsequent batch of COR assay results as determined by the Data Centre.

Participants who are withdrawn or lost to follow-up after enrolment will not be replaced.

9.7 ANALYSIS DATASETS

The following specific analysis populations will be defined:

Intention-to-treat (ITT)
The intention-to-treat cohort will include all enrolled participants who complete the first endpoint evaluation (Visit 2), regardless of COR status or treatment adherence.

Modified intention-to-treat (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 endpoint-defined TB disease cases identified at the first endpoint evaluation visit (Visit 2).

Per-protocol (PP)
The per-protocol cohort will include all participants in the mITT population who completed all eight endpoint evaluation visits (Visit 2-9), were TB negative at Visit 2, and who completed the full treatment regimen (if assigned to Group A).

Primary Aim 1 (*TE (15))* will be evaluated in the mITT population. Primary Aim 2 (*RR$_{cor}$*) will be evaluated in the ITT population; an exploratory analysis will include re-evaluation in the per-protocol population.

9.8 MISSING DATA METHODS

In spite of the best efforts to obtain complete data and follow-up 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. Potential methods, which will be detailed in a statistical analysis plan, may include complete-case analysis under a missing-completely-at-random assumption, multiple imputation under a missing-at-random assumption, and/or sensitivity analysis using a missing-not-at-random assumption.

9.9 ANALYSIS AND PRESENTATION OF DATA

The participant disposition will be summarised. Trial completion, trial withdrawals, exclusions and protocol non-compliances will be summarised.

Data for background and demographic variables will be listed by study arm, COR status and participant. Descriptive statistics will be provided.

COR status and any other relevant baseline TB risk factors, such as smoking and TB contact history will be listed by study arm and participant.

Fisher's Exact test (categorical data) or ANOVA (continuous data) will be used to test for any statistically noticeable differences ($p<0.100$) in categorical demographic or baseline data between the treatment groups.

Concomitant medication taken from Day 0 to end of study will be listed by study arm.

9.9.1. SAFETY ANALYSIS

The analysis of adverse events will include all treatment-emergent adverse events. Adverse events will be coded using MedDRA and will be presented by system organ class and preferred term for each treatment group.

No formal statistical testing will be performed on the safety data.

9.9.2. EFFICACY ANALYSIS

Primary Aim 1: Treatment efficacy
We will evaluate treatment efficacy based on the cumulative incidence of endpoint-defined TB among COR+ participants randomized to Groups A (preventive therapy) and B (observation). The primary analysis will evaluate TE(15), treatment efficacy over 15 months of follow-up (**Figure 6**), on endpoints in the mITT cohort using the two-sample endpoint definition and according to the formula:

$$TE(15) = 1 - \frac{H_A}{H_B}$$

where H_X is the cumulative incidence estimated for each group using the Product-Limit estimator of Nelson-Aalen (Aalen, O.O., "Non-parametric inference for a family of counting processes", Annals of Statistics, 1978).

Figure 6. Treatment efficacy over 15 months based on cumulative incidence.
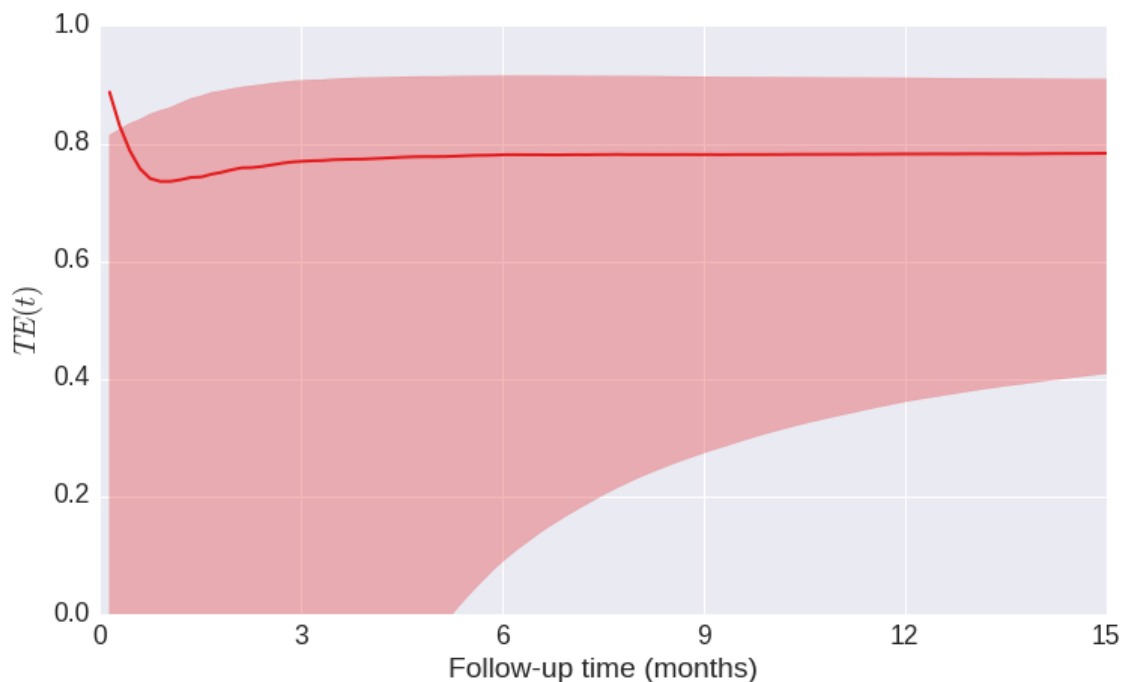
A point-estimate for TE(15) will be presented with 90% confidence intervals and a p-value for the null-hypothesis H_0: TE(15) <= 20%. Descriptive plots will include Kaplan-Meier estimators with 95% confidence intervals for each group (**Figure 7**).

Figure 7. Kaplan-Meier survival curves.

Primary Aim 2: COR performance

We will evaluate the relative-risk of endpoint-defined TB over 15 months, $RR_{COR}(15)$, in COR+ (Group B) versus COR- (Group C) participants under active-surveillance using a cumulative incidence based approach (**Figure 7**). The primary analysis will evaluate $RR_{COR}(15)$ on endpoints in the ITT cohort using the two-sample endpoint definition and according to the formula:
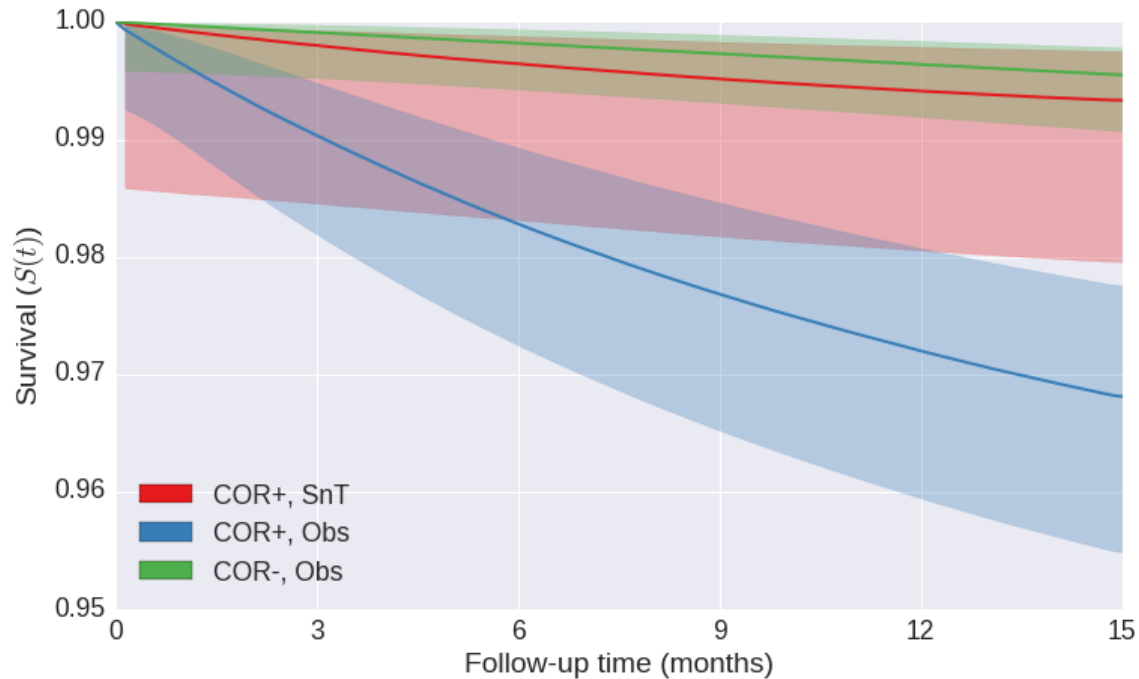
$$RR_{COR}(15) = \frac{H_A}{H_B}$$

where H_X is the cumulative incidence estimated for each group using the Product-Limit estimator of Nelson-Aalen (Aalen, O.O., "Non-parametric inference for a family of counting processes", Annals of Statistics, 1978). A point-estimate for $RR_{COR}(15)$ will be presented with 90% confidence intervals and a p-value for the null-hypothesis H_0: $RR_{COR}(15) <= 1$. Descriptive plots will include Kaplan-Meier estimators with 95% confidence intervals for each group. In addition we will present time-dependent estimates of sensitivity, specificity, positive predictive value (PPV) and number needed to treat (NNT) using the methods of Heagerty et al. (2000, Biometrics, "Time-dependent ROC Curves for Censored Survival Data and a Diagnostic Marker") as these will offer important insights into the performance and application of the COR in future strategies.

Figure 8. Relative-risk for COR positivity based on cumulative incidence.
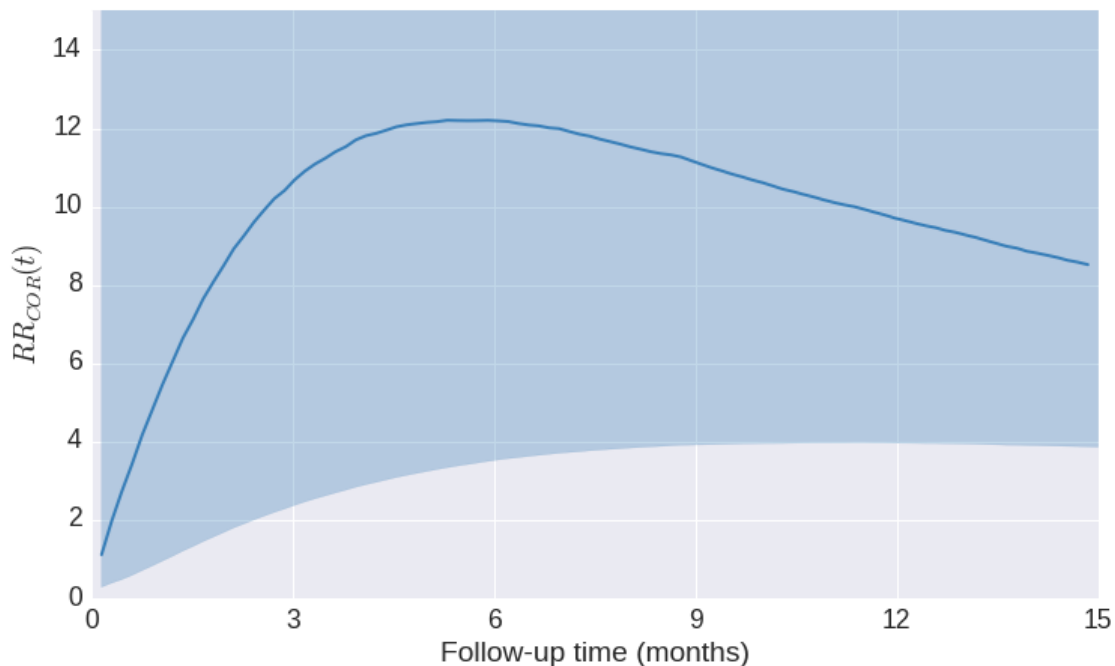
Secondary Aim 1:
We will evaluate the relative-risk of endpoint-defined TB, RR_{COR}, in COR+ (Groups A and B) versus COR- (Group C) participants, based on the prevalence of endpoint-defined TB in the ITT cohort using the two-sample endpoint definition. Descriptive plots will be analogous to those presented for Primary Aim 2.

Secondary Aim 2:
We will evaluate the relative-risk of endpoint-defined TB over 15 months, $RR_{COR}(15)$, in COR+ (Group B) versus COR- (Group C) participants under active-surveillance, based on the cumulative incidence of endpoint-defined TB in the mITT cohort using the two-sample endpoint definition. Descriptive plots will be analogous to those presented for Primary Aim 2.

Secondary Aim 3:
We will evaluate the relative-risk of endpoint-defined TB over 15 months, $RR_{QFT}(15)$, in IGRA+ versus IGRA- participants in under active surveillance pooling across Groups B and C. 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 described in Primary Aim 2.

9.9.3. INTERIM ANALYSIS

Operational monitoring
During the trial we will periodically perform a group-blinded analysis based on the rate of screening and enrolment, COR+ prevalence and the number of accrued TB disease endpoints. The first analysis will occur at 6 months and will be repeated every 3 months thereafter. Based on simulations of the trial we expect to accrue a total of 40 endpoints (IQR [33, 47]) over 27 months from the date of the first screening. At each analysis we will conduct simulations of the remaining duration of the trial.

Based on these cumulative 3-monthly operational analyses of recruitment rate, observed COR+ prevalence and rate of accrual of TB disease endpoints, if it is determined that the primary and

secondary aims may be achieved with shorter duration of follow-up than the maximum 15 months, follow-up of subsequent participants may be incrementally reduced to a minimum of 3 months; with mean follow-up of 12 months. Achievement of the primary aims will be prioritised over the secondary aims in determining whether to reduce individual follow-up.

By contrast, if it is determined that the enrolment rate is slower than expected, possibly due to low COR prevalence or operational challenges, and that >90% of the simulated trials are predicted to have a total duration of >36 months then we will halt the trial for operational futility. Additionally, if the overall rate of endpoint-defined TB is lower than expected, possibly due to low TB incidence, and that >90% of simulated trials are predicted to accrue <20 endpoint-defined TB cases at the conclusion of the trial, then the trial may be halted for operational futility. Similarly, enrolment into one study arm may be halted prior to the other arm, in which case all remaining participants would be enrolled into the remaining arm. No adjustment for operational futility monitoring will be made in the primary analyses as the operational monitoring will be performed on blinded data.

Unblinded interim prognostic analysis
An unblinded interim analysis of the primary objectives will be performed after identification of 40 endpoint-defined cases of incident TB in the mITT cohort. The analysis has two objectives: (Scenario A) To detect the possibility of high prognostic biomarker performance in the presence of high treatment efficacy, (Scenario B) To detect the possibility of high prognostic biomarker performance in the presence of low treatment efficacy (**Table 3**). To test these objectives the primary treatment efficacy and prognostic biomarker performance analyses will be conducted on the mITT cohort (i.e. excluding prevalent cases). 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 3. Criteria and power for interim efficacy analysis.

	Scenario A	**Scenario B**
Simulated design hyp.	$RR_{COR}(15) = 45$ & $TE(15) = 95\%$	$RR_{COR}(15) = 45$ & $TE(15) = 5\%$
Null-hyp. (H_0)	$RR_{COR}(15) \leq 5$ & $TE(15) \leq 60\%$	$RR_{COR}(15) \leq 5$ & $TE(15) \geq 60\%$
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 incident TB 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 incident TB 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.

Unblinded interim diagnostic analysis
Depending on observed rates of TB disease accrual during the course of the trial, the final number of participants enrolled into the Treatment and Observation Arms, the final balance of COR+ and COR- participants and duration of follow-up will be adapted based on 3-monthly operational monitoring reports. To inform these decisions, a group-unblinded interim analysis of COR diagnostic performance will be performed after identification of 40 endpoint-defined cases of prevalent TB in the

ITT cohort. The diagnostic analysis will be based solely on prevalent TB endpoints detected at Visit 2 up until the date of data transfer.

The analyses 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.

9.10. MODELLING

Data generated during the trial will be used to refine preliminary models of the population level impact of a COR screen and treat strategy accounting for both direct effects (prevention of incident cases) and indirect effects (reduction in MTB transmission). These models will be used to predict the impact of the strategy on TB incidence and mortality in South Africa under programmatic conditions and explore alternative scenarios of implementation (coverage of screening, frequency of screening, extension to HIV infected individuals).

Models will make use of baseline data (including age of trial participants, prevalence of undiagnosed TB), diagnostic performance of COR (for prevalent and incident TB), treatment efficacy of 3HP (for preventing incident disease), data on adherence/retention on 3HP and rates of adverse events.

10 DATA HANDLING AND QUALITY ASSURANCE

10.1 SOURCE DOCUMENTS AND CASE REPORT FORMS

As part of the responsibilities assumed by participating in the trial, the investigator agrees to maintain adequate case histories for all participants treated as part of the research under this protocol. This includes the maintenance of both source documentation and accurate electronic CRFs (eCRFs) for all participants who consent to participation in the trial.

Information recorded in the eCRFs will be supported by corresponding source documentation. All paper and electronic source documents pertaining to this trial will be maintained by the investigators.

eCRFs are considered confidential documents and will be handled and accessed accordingly. The Data Centre will provide the necessary training on the use of the specific eCRF system utilised during the trial to ensure that data are captured accurately and appropriately. Each completed eCRF will be reviewed, signed, and dated by the investigator in a timely manner.

10.2 MONITORING THE TRIAL

The clinical site will be monitored by a clinical research associate (CRA) to ensure compliance with the protocol, GCP and applicable regulations and guidelines. The CRA(s) will conduct site visits to the trial facilities and will be responsible for ensuring that the clinical trial protocol is adhered to. The assigned CRA(s) will visit the investigator and clinical site at periodic intervals and maintain periodic communication. The CRA(s) will maintain current personal knowledge of the trial through observation, review of trial records and source documentation, and discussion of the conduct of the trial with the investigator and staff. While on site, the CRA(s) will review regulatory documents, compare entries in the CRF system with the source documents, and review investigational drug accountability records. The CRA(s) will ask for clarification and/or correction of any noted inconsistencies. Any necessary corrections will be made in such a way that the original entry, the date of the correction and the identity of the person making the correction is accessible.

By signing the protocol, the Investigator agrees to meet with the CRA(s) during clinical site visits, to ensure that site staff are available to the CRA(s) as needed, to provide the CRA(s) access to all trial documentation, to the clinical supplies dispensing and storage area, and agrees to assist the monitors in their activities, if requested.

10.3 DATABASE MANAGEMENT AND QUALITY CONTROL

Data management, including the development and management of a database, will be performed in accordance with regulatory requirements by the Triclinium Data Centre. Triclinium will review the eCRF data for completeness and accuracy. A formal querying process will be followed whereby the data management group will request the site personnel to clarify any apparent erroneous entries or inconsistencies and will request additional information from the site as required.

Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA, version 18.1 or higher) terminology. Concomitant medications will be coded using the MIMS classification.

After all data have been captured and reviewed in the eCRF, all queries have been resolved with the site and any protocol non-compliances that were identified during the data management processes have been confirmed by the site, the database will be declared to be complete and accurate. It will then be locked and the COR status of participants in the Observation Arm will be unblinded and made available for data analysis. Any changes to the database after that time may only be made by the data manager, in consultation with the sponsor and in accordance with documented database unlock and relock procedures.

Data management procedures will be described in detail in the Data Management Plan which will be documented and approved prior to study start.

10.4 INSPECTION OF RECORDS

Investigators and institutions involved in the trial will permit trial-related monitoring, audits, IEC review, and regulatory inspection(s) by providing direct access to all trial records. In the event of an audit, the investigator agrees to allow the sponsor, representatives of SANOFI, and applicable regulatory authorities access to all trial records. The confidentiality of records that can identify participants will be protected, respecting the privacy and confidentiality rules in accordance with regulatory requirements.

The investigator must promptly notify the sponsor of any audits scheduled by any regulatory authorities and promptly forward copies of any audit reports received to the sponsor.

10.5 RETENTION OF RECORDS

Essential documents should be retained for the longest of the following three periods:
until at least two years after the last approval of a marketing application in the ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least two years have elapsed since the formal discontinuation of clinical development of the investigational product, or for not less than 10 years after trial completion.

These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

11   DATA SAFETY MONITORING BOARD

During the trial, an external and independent DSMB appointed by the sponsor will meet periodically to review blinded safety data. The timing and scope of the DSMB review will be detailed in the DSMB Charter. An independent statistician will conduct an unblinded analysis of COR prognostic performance and efficacy of 3HP after 40 primary endpoint incident TB cases have accrued. In the event that the lower bound of the 95% CI for Relative Risk for TB disease exceeds 2, for either COR+ vs. COR- participants, and/or for COR+ participants in the Observation vs. Treatment Arm, the DSMB might recommend that the study be halted or that the protocol be revised, for example, to provide a preventive (or curative) therapy regimen to all COR+ participants.

All procedures associated with DSMB reviews, including objectives, data handling, and elements included for review will be documented in the DSMB minutes. The DSMB will also review any SAEs and Grade 3 or 4 laboratory adverse events considered related to the investigational product (relationship assessed as possible, probable or certain). Based on its review the DSMB will make recommendations to the sponsor regarding the further conduct of the trial and if considered necessary, may recommend pausing or stopping further administration of the investigational product. The conclusions of the DSMB will be communicated to the investigator, the IEC and the national regulatory authority as required. The sponsor agrees to abide by the decision of its DSMB.

12   ETHICAL CONSIDERATIONS

12.1 REGULATORY AND ETHICAL COMPLIANCE

This trial will be conducted according to the ethical principles set forth in the Declaration of Helsinki (Fortaleza, Brazil 2013),[21] ICH-GCP,[22] European Directive 2001/20/EC,[23] US Code of Federal Regulations Title 21,[24] South African Good Clinical Practice Guidelines,[25] and other local regulatory requirements.

12.2 INFORMED CONSENT PROCEDURES

Eligible participants may only be included in the trial after providing written, IEC-approved informed consent in the language of their choice. Illiterate participants require an impartial witness to be present for the informed consent process, and to sign and date that all information in the informed consent form was shared with participant, and the participant must sign by means of a thumbprint. Informed consent must be obtained before conducting any trial-specific procedures (i.e. any of the procedures described in the protocol). The timing and process of obtaining informed consent must be documented in the participant source documents. The investigator must provide a copy of the signed informed consent document to the participant. The original form must be maintained in the designated section in the Investigator Site File and a copy with the participant's source documents at the site.

12.3 RESPONSIBILITIES OF THE INVESTIGATOR AND IEC

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted IEC before commencement of the clinical trial. A signed and dated statement that the protocol and informed consent have been approved by the IEC must be provided to the sponsor before trial initiation at the site.

By signing this clinical trial protocol, the principal investigator agrees to conduct this trial in accordance with all laws, regulations and guidelines of the pertinent regulatory authorities, including and in accordance with the April 1996 ICH Guidance for Industry E6 GCP and in agreement with the 2013 Version of the Declaration of Helsinki. While delegation of certain aspects of the trial to sub-investigators and trial coordinators is appropriate, the principal investigator will remain personally accountable for overseeing the trial and for ensuring compliance with the protocol and all applicable regulations and guidelines.

The PI must ensure that all persons who have been delegated trial-related responsibilities are adequately qualified and informed about the protocol, investigational drugs, and their specific duties within the context of the trial. The principal investigator is responsible for providing the sponsor with documentation of the qualifications, GCP training, and research experience of site staff as required by the sponsor and the relevant governing authorities. In addition to this, the principal investigator is responsible for maintaining a list of all personnel who have been trained and to whom trial-related responsibilities have been delegated, including the specific trial-related duties concerned. Proof of training on the protocol and protocol-specific procedures must be kept on file to allow verification of training for delegated duties.

13 GENERAL CONSIDERATIONS

13.1 PROTOCOL ADHERENCE

A protocol non-conformance is an unintended and/or unanticipated departure from the procedures and/or processes approved by the sponsor, the IEC, the MCC and agreed to by the investigator. Investigators must agree to apply due diligence to avoid protocol non-conformances and must document and explain any such events. Protocol non-conformances will also be documented by the CRA throughout the course of monitoring visits. The investigator will be notified of non-conformances in writing by the CRA. The IEC must be notified of major protocol non-conformances in accordance with the IEC standard operating procedures.

13.2 AMENDMENTS TO THE PROTOCOL

Any change or addition to the protocol can only be made by means of a written protocol amendment that is approved by the sponsor, the MCC and the IEC. Amendments that are deemed necessary to ensure participant safety may be implemented prior to MCC and IEC approval. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any participant included in this trial, even if this action represents a deviation from the protocol. In such cases, the sponsor should be notified of this action immediately and the IEC at the clinical trial site should be informed within 10 working days of the action.

13.3 PARTICIPANT INJURY

The sponsor will ensure that provisions are made for insurance or indemnity by a third party to cover the liability of the investigator and sponsor in relation to the trial. In the event of any injury, suffering, deterioration in health or well-being or any harmful susceptibility or toxicity resulting from a participant's participation in the trial, the participant will receive appropriate compensation irrespective of their ability to prove fault on the part of the sponsor or anyone else connected with the trial.

13.4 SAMPLE RETENTION

Biological samples may only be used for purposes related to this research. The samples will be stored until the clinical trial team has determined that specimens are no longer needed and the decision has been made that there are no samples to be re-assayed, up to a maximum period of 10 years. In addition, identifiable samples can be destroyed at any time at the request of the participant.

13.5 TRIAL TERMINATION BY SPONSOR

The trial may be terminated at the sponsor's discretion at any time for any reason. If the sponsor discovers conditions that warrant early termination of the trial, the investigator will be notified by the sponsor or by its designee. An example of a condition that may warrant premature termination of the trial includes, but is not limited to, the discovery of an unexpected, serious, or unacceptable risk to the participants enrolled in the trial.

13.6 CLINICAL SITE CLOSURE

On termination of the trial, all screening and ongoing trial-related procedures conducted at the clinical trial site will be closed. The sponsor may terminate participation of the clinical site at any time. Examples of conditions that may warrant premature termination of a clinical site include, but are not limited to the following:
Noncompliance with the protocol and/or applicable regulations and guidelines
Inadequate participant enrolment.

13.7 PUBLICATION OF THE CLINICAL TRIAL PROTOCOL AND RESULTS

All information concerning the sponsor's operations, patent applications, formulae, and scientific data supplied by the sponsor to the investigator and not previously published, is considered confidential and remains the sole property of the sponsor. The complete participant CRFs also remain the

property of the sponsor. The investigator agrees to use this information for purposes of the clinical trial execution only.

The sponsor will post the key design elements of this protocol in a publicly accessible database such as clinicaltrials.gov. In addition, upon trial completion and finalization of the clinical trial report the results of this trial will be submitted for publication and/or posted in a publicly accessible database of clinical trial results.

Publications or other public presentations of the data resulting from this trial will be planned and prepared by a Writing Committee chaired by the National PI and including the trial investigators.

14   REFERENCES

1.   Guidelines on the Management of Latent Tuberculosis Infection. WHO. Geneva; 2015.

2.   Andrews JR, Hatherill M, Mahomed H, et al. The dynamics of QuantiFERON-TB gold in-tube conversion and reversion in a cohort of South African adolescents. *Am J Respir Crit Care Med* 2015; **191**(5): 584-91.

3.   Andrews JR, Noubary F, Walensky RP, Cerda R, Losina E, Horsburgh CR. Risk of progression to active tuberculosis following reinfection with Mycobacterium tuberculosis. *Clin Infect Dis* 2012; **54**(6): 784-91.

4.   Churchyard GJ, Fielding KL, Lewis JJ, et al. A trial of mass isoniazid preventive therapy for tuberculosis control. *N Engl J Med* 2014; **370**(4): 301-10.

5.   Mahomed H, Hughes EJ, Hawkridge T, et al. Comparison of mantoux skin test with three generations of a whole blood IFN-gamma assay for tuberculosis infection. *Int J Tuberc Lung Dis* 2006; **10**(3): 310-6.

6.   Dye C, Glaziou P, Floyd K, Raviglione M. Prospects for tuberculosis elimination. *Annual review of public health* 2013; **34**: 271-86.

7.   Kaforou M, Wright VJ, Oni T, et al. Detection of tuberculosis in HIV-infected and -uninfected African adults using whole blood RNA expression signatures: a case-control study. *PLoS medicine* 2013; **10**(10): e1001538.

8.   Berry MP, Graham CM, McNab FW, et al. An interferon-inducible neutrophil-driven blood transcriptional signature in human tuberculosis. *Nature* 2010; **466**(7309): 973-7.

9.   Bloom CI, Graham CM, Berry MP, et al. Transcriptional blood signatures distinguish pulmonary tuberculosis, pulmonary sarcoidosis, pneumonias and lung cancers. *PLoS One* 2013; **8**(8): e70630.

10.   Bloom CI, Graham CM, Berry MP, et al. Detectable changes in the blood transcriptome are present after two weeks of antituberculosis therapy. *PLoS One* 2012; **7**(10): e46191.

11.   Sterling TR, Villarino ME, Borisov AS, et al. Three months of rifapentine and isoniazid for latent tuberculosis infection. *N Engl J Med* 2011; **365**(23): 2155-66.

12.   WHO. Global Tuberculosis Control Report. 2015.

13.   Kopanoff DE, Snider DE, Jr., Caras GJ. Isoniazid-related hepatitis: a U.S. Public Health Service cooperative surveillance study. *The American review of respiratory disease* 1978; **117**(6): 991-1001.

14.   Martinson NA, Barnes GL, Moulton LH, et al. New regimens to prevent tuberculosis in adults with HIV infection. *N Engl J Med* 2011; **365**(1): 11-20.

15.   Miyazaki E, Chaisson RE, Bishai WR. Analysis of rifapentine for preventive therapy in the Cornell mouse model of latent tuberculosis. *Antimicrobial agents and chemotherapy* 1999; **43**(9): 2126-30.

16.   Chapuis L, Ji B, Truffot-Pernot C, O'Brien RJ, Raviglione MC, Grosset JH. Preventive therapy of tuberculosis with rifapentine in immunocompetent and nude mice. *Am J Respir Crit Care Med* 1994; **150**(5 Pt 1): 1355-62.

17.   Mahomed H, Hawkridge T, Verver S, et al. Predictive factors for latent tuberculosis infection among adolescents in a high-burden area in South Africa. *Int J Tuberc Lung Dis* 2011; **15**(3): 331-6.

18.   Mahomed H, Hawkridge T, Verver S, et al. The tuberculin skin test versus QuantiFERON TB Gold(R) in predicting tuberculosis disease in an adolescent cohort study in South Africa. *PLoS One* 2011; **6**(3): e17984.

19.   Mahomed H, Ehrlich R, Hawkridge T, et al. Screening for TB in high school adolescents in a high burden setting in South Africa. *Tuberculosis (Edinb)* 2013; **93**(3): 357-62.

20.   Mahomed H, Ehrlich R, Hawkridge T, et al. TB incidence in an adolescent cohort in South Africa. *PLoS One* 2013; **8**(3): e59652.

APPENDIX 1: DAIDS TOXICITY TABLE

Laboratory Values
Chemistries

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Acidosis	NA	pH ≥ 7.3 to < LLN	pH < 7.3 without life-threatening consequences	pH < 7.3 with life-threatening consequences
Albumin, Low (g/dL; *g/L*)	3.0 to < LLN *30 to < LLN*	≥ 2.0 to < 3.0 *≥ 20 to < 30*	< 2.0 *< 20*	NA
Alkaline Phosphatase, High	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Alkalosis	NA	pH > ULN to ≤ 7.5	pH > 7.5 without life-threatening consequences	pH > 7.5 with life-threatening consequences
ALT or SGPT, High *Report only one*	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Amylase (Pancreatic) or Amylase (Total), High *Report only one*	1.1 to < 1.5 x ULN	1.5 to < 3.0 x ULN	3.0 to < 5.0 x ULN	≥ 5.0 x ULN
AST or SGOT, High *Report only one*	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Bicarbonate, Low (mEq/L; *mmol/L*)	16.0 to < LLN *16.0 to < LLN*	11.0 to < 16.0 *11.0 to < 16.0*	8.0 to < 11.0 *8.0 to < 11.0*	< 8.0 *< 8.0*
Bilirubin *Direct Bilirubin[14], High* > *28 days of age*	NA	NA	> ULN	> ULN with life-threatening consequences (e.g., signs and symptoms of liver failure)
≤ *28 days of age*	ULN to ≤ 1 mg/dL	> 1 to ≤ 1.5 mg/dL	> 1.5 to ≤ 2 mg/dL	> 2 mg/dL
Total Bilirubin, High > *28 days of age*	1.1 to < 1.6 x ULN	1.6 to < 2.6 x ULN	2.6 to < 5.0 x ULN	≥ 5.0 x ULN
≤ *28 days of age*	See Appendix A. Total Bilirubin for Term and Preterm Neonates	See Appendix A. Total Bilirubin for Term and Preterm Neonates	See Appendix A. Total Bilirubin for Term and Preterm Neonates	See Appendix A. Total Bilirubin for Term and Preterm Neonates
Calcium, High (mg/dL; *mmol/L*) ≥ *7 days of age*	10.6 to < 11.5 *2.65 to < 2.88*	11.5 to < 12.5 *2.88 to < 3.13*	12.5 to < 13.5 *3.13 to < 3.38*	≥ 13.5 *≥ 3.38*
< *7 days of age*	11.5 to < 12.4 *2.88 to < 3.10*	12.4 to < 12.9 *3.10 to < 3.23*	12.9 to < 13.5 *3.23 to < 3.38*	≥ 13.5 *≥ 3.38*

---

[14] Direct bilirubin > 1.5 mg/dL in a participant < 28 days of age should be graded as grade 2, if < 10% of the total bilirubin.

DAIDS AE Grading Table Version 2.0- November 2014