TRICLINIUM
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STATISTICAL ANALYSIS PLAN

Protocol title: A phase Ib, randomized, double-blind, dose-escalation clinical trial of the safety, reactogenicity and immunogenicity of MTBVAC compared to BCG Vaccine SSI, in newborns living in a tuberculosis endemic region with a safety arm in adults.	
Protocol number: MTBVAC-201	**Applicable Protocol Version:** 06
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The layout of this document is based on the Guideline on the International Conference of Harmonization (ICH E9).

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Glossary of abbreviations

ABBREVIATION	DESCRIPTION
AE	Adverse event
CI	Confidence interval
CV	Coefficient of variation
DBL	Database lock
eCRF	Electronic case report form
ICH	International Conference on Harmonisation
IMP	Investigational product
MedDRA	Medical dictionary for regulatory activities
MIMS	Monthly Index of Medical Specialities
N	Sample size
ODS	Output delivery system
PT	Preferred term
RTF	Rich text format
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard deviation
SOC	System organ class
TEAEs	Treatment-emergent adverse events
TLFs	Tables, data listings and figures

1. Overview

1.1 Introduction

This document describes the rules and conventions to be used in the presentation and analysis of a phase Ib, randomized, double-blind, dose-escalation clinical trial of the safety, reactogenicity and immunogenicity of MTBVAC compared to BCG Vaccine SSI, in newborns living in a tuberculosis endemic region with a safety arm in adults.

This statistical analysis plan (SAP), is based on protocol MTBVAC-201, version 06, dated 23-Dec-2016.

2. Trial objectives

The following objectives are those stated in the protocol.

2.1 Primary objectives

The primary objectives of this study are to evaluate:

- safety of MTBVAC, compared to BCG Vaccine SSI, in healthy, BCG naïve, HIV unexposed, South African newborn infants; and
- reactogenicity of MTBVAC, compared to BCG Vaccine SSI, in healthy, BCG naïve, HIV unexposed, South African newborn infants; and
- immunogenicity of MTBVAC, compared to BCG Vaccine SSI, in healthy, BCG naïve, HIV unexposed, South African newborn infants.

2.2 Secondary objectives

The secondary objectives of this study are to evaluate:

- safety of MTBVAC, compared to BCG Vaccine SSI, in healthy, BCG vaccinated, HIV negative, QFT negative, South African adults; and
- reactogenicity of MTBVAC, compared to BCG Vaccine SSI, in healthy, BCG vaccinated, HIV negative, QFT negative, South African adults.

3. Endpoints

3.1 Safety and reactogenicity endpoints

The following endpoints are assessed for both adult and infant groups:

- The number of injection site reactions, including redness, swelling, induration, tenderness, ulceration, fluctuation, drainage, crusting and scarring.
- The number of adverse events, solicited and unsolicited.

3.2 Immunogenicity endpoints

Immunogenicity endpoints are assessed for the infant group only.

3.2.1 Primary immunogenicity endpoints

Frequencies and co-expression patterns of CD4 and CD8 T cells expressing IFN-γ, TNF-α, IL-2 and/or IL-17 induced by MTBVAC or BCG, and suitable antigens in healthy, BCG naïve, HIV-unexposed, South African newborn infants.

3.2.2 Exploratory immunogenicity endpoints

Whole blood supernatants samples for further immunogenicity tests will be collected and stored frozen. Exploratory assays will be planned, based on data from the primary immunogenicity analyses.

4. Trial design

4.1 Design overview

Randomized, controlled, double blind clinical trial in 2 stages (adult stage, infant stage).

The first stage will include 18 HIV-uninfected, QFT-negative, BCG-vaccinated, adult participants, randomized 1:1 to receive BCG Vaccine SSI or MTBVAC at equivalent doses ($5x10^5$ CFU/0.1mL) (n=9 in each group). A Data Safety Monitoring Board (DSMB) will evaluate the reactogenicity and safety data for all 18 adults up to day 28 after study vaccination.

Upon favorable safety review of Day 28 safety data by the DSMB, the second stage will commence in thirty-six (36) HIV unexposed, BCG naïve, newborn infants, randomized 1:3 to receive BCG Vaccine SSI or MTBVAC at one of three different dose levels (n=9 in each group).

After unblinding at Day 180, BCG Vaccine SSI will be given to all MTBVAC vaccinated infants.

4.2 Study duration

Adults

Remain active on the study for a period of 6 months after enrolment and vaccination.

Infants

Infants will be followed up for a period of 12 months after enrolment and study vaccination.

4.3 Schedule of events

Schedule of events in study stage 1 (adults)

Phase		Screen	Post-vaccination safety follow-up						
Month		-2 to -1	0	1	1	1	2	3	6
Day		-30 to -0	0	7	14	28	56	90	180
Visit		1	2	3	4	5	6	7	8
Dose			1						
Informed consent		•							
Confirmation of eligibility		•	•						
Medical history		•							
Physical examination and all other screening tests									
Pregnancy test: β-HCG-serum (3 ml)		•							
β-HCG –urine			•						
Safety blood samples (Biochemical and haematological analysis)		•		•		•			
HIV test		•							
Quantiferon (3 ml)		•							•
Focused Physical examination		•	•	•	•	[a]	[a]	[a]	[a]
Resting vital signs incl. temperature measurement		•	•	•	•	•	•	•	•
Recording of concomitant medication		•	•	•	•	•	•	•	•
Vaccination			•						
Injection site assessment		•	•	•	•	•	•	•	•
Diary cards	Distribution by study team		•	•					
	Return			•	•				
AE and medication form	Distribution by study team		•	•	•	•	•	•	
	Return				•	[a]	[a]		
Recording of solicited symptoms			•	•					
Non-serious AEs post vaccination			•	•	•	•	•	•	
Reporting of SAEs, SUSARS			•	•	•	•	•	•	

• is used to indicate a study procedure that requires documentation in the individual CRF

[a] Only examine if abnormalities.

Table 4.3.1 Schedule of events for stage 1

Schedule of events in study stage 2 (infants)

Phase		Screen Mother	Post-vaccination follow-up								
Month		-2 to -1	0	1	1	1	3	3	6	6.5	12
Day		-60 to -0	0	7	14	28	70	91	180	+/-194	360
Visit		-1	0	1	2	3	4	5	6	7	8
Dose			1								
Informed consent (mother and legal guardian)		•									
Confirmation of eligibility criteria		•	•								
Medical history		•									
HIV test		•									
Physical examination			•	•	•	•	[a]	[a]	[a]		•
Resting vital signs			•	•	•	•	•	•	•		•
Recording of concomitant medication pre-/post-vaccination			•	•	•	•	•	•	•		
Pre- and post-vaccination assessment incl. temperature measurement			•	•	•	•	•	•	•		
Vaccination			•								
Diary cards	Distribution		•	•							
	Return			•	•						
AE and medication form	Distribution		•	•	•	•	•	•	•		
	Return			•	•	•	[a]	[a]			
Recording of solicited symptoms			•	•	•	•	•	•	•		•
Recording of non-serious AEs			•	•	•	•	•	•	•		•
Reporting of SAEs and SUSARS			•	•	•	•	•	•	•		•
Microbiological analyses											
Swabs at injections site[b]				•	•	•	•	•	•		
Biochemical and haematological analysis											
Safety blood samples (2 ml)				•		•					
Primary Immunogenicity endpoints											
Whole Blood ICS (WB-ICS) Assay *(0.75 ml at D7 and 2.5 ml for the rest)*[c]				•		•	•		•		
QuantiFERON (QFT) (3 ml)									•		•
Blood volume per visit in ml:				2.75	0	4.5	2.5	0	5.5		
Cumulative blood volume (ml):				2.75	2.75	7.25	9.75	9.75	15.26		
BCG rescue dose given to all MTBVAC vaccinated infants[d]										•	

• is used to indicate a study procedure that requires documentation in the individual CRF

[a] Only examine if abnormalities.

[b] Swabs at injection site for microbiology analysis will be conducted in all infants that show site-opening event and will be repeated until 2 negative cultures are obtained.

[c] Stimulation of blood cells (whole blood) with live mycobacteria BCG, MTBVAC, or "mega pool" of mycobacteria peptides, or phytahemagglutinin (PHA), or left unstimulated. D7 stimulation conditions include half the blood volume [250 µL (0.25 mL)] and only Nil, MTBVAC and BCG. Evaluation of the frequency of specific CD4+ and CD8+ T cells that secrete cytokines in response to the stimulation.

[d] visit at 2 weeks post BCG for recording BCG receipt to all infants

Table 4.3.2 Schedule of events for stage 2

5. Changes/deviations from the planned analysis

Not applicable.

6. Analysis populations

Agreement and authorization of participants included/excluded from each analysis population will be reached prior to final database hard lock. TCD will supply a list of all participants to be excluded from the relevant analysis populations, including the reason(s) for exclusion from the analysis populations. All analysis sets will be split into stage 1 and 2.

6.1 Full Analysis Set (Adult FAS/ Infant FAS)

This population will include all participants that were randomized to receive IMP. The treatment groups will reflect the IMP per the randomization list, regardless of the actual IMP they may have received.

6.2 Safety Analysis Set (Adult SAF/Infant SAF)

This analysis population will include all randomized participants who received IMP. Analyses based on the SAF population will reflect the actual IMP administered to participants, regardless of the randomization list.

7. General considerations

7.1 Visit and date conventions

Visit day will be calculated from the reference start date which will be used to present start/stop day of assessments and events. The *reference start date* is defined as the date of first IMP administration. The following conventions will be used for visit references:

- $Visit\ day = date\ of\ event - reference\ start\ date$
- $Visit\ week = \frac{visit\ day}{7},\ rounding\ up\ to\ next\ whole\ number$
- $Visit\ month = \frac{visit\ day}{30},\ rounding\ up\ to\ next\ whole\ number$

No visit windowing (i.e. remapping of visits based on visit windows) will be performed for this trial. The assigned nominal visit will be used for by-visit summaries. In the situation where the assessment/event date is partial or missing, visit day/week/month, and any corresponding durations will appear missing in the data listings. Unscheduled measurements will not be included in by-visit summaries. In the case of a retest (same visit number assigned), the last available measurement for that visit will be presented for by-visit summaries. Data listings will include scheduled, unscheduled, retest and early discontinuation data. Trial visit will be assigned as delineated in Table 7.1.1:

	Screen	**Post-vaccination follow-up visit**						
Visit Day	-21 to -1	0	7 ±3 days	14 ±3 days	28 ±3 days	56 ±7 days	90 ±7 days	180 ±7 days
Visit Week	-3 to -1	0	1	2	4	8	13	26
Visit Month	-1 to -1	0	1	1	1	2	3	6
Visit No.	1	2	3	4	5	6	7	8

Table 7.1.1: Trial visit assignment schedule (adult stage).

	Screen (mother)	Post-vaccination follow-up visit								
Visit Day	-60 to 0	0	7 ±3 days	14 ±3 days	28 ±3 days	70 ±14 days	90 ±14 days	180 ±14 days	~194	360 ±14 days
Visit Week	-9 to -1	0	1	2	4	10	13	26	28	52
Visit Month	-2 to -1	0	1	1	1	3	3	6	6.5	12
Visit No.	-1	0	1	2	3	4	5	6	7	8

Table 7.1.2: Trial visit assignment schedule (infant stage).

7.2 Baseline

Unless stated otherwise, baseline is defined as the last non-missing observation made prior to the first administration of IMP.

7.3 Stratifications

For analysis purposes, stage 1 participants (adults) may be sub-classified into the following stratification levels, where applicable:

- Treatment
  - BCG SSI (reference)
  - MTBVAC
- Gender
  - Male (reference)
  - Female

For analysis purposes, stage 2 participants (infants) may be sub-classified into the following stratification levels, where applicable:

- Treatment

- BCG SSI (reference)
- MTBVAC

- Dose
  - 2.5×10^5 CFU/0.05 mL (reference)
  - 2.5×10^4 CFU/0.05 mL
  - 2.5×10^3 CFU/0.05 mL
- Gender
  - Male (reference)
  - Female

7.4 Statistical tests

The default significance level for this trial is set at 5%. All 95% confidence intervals (CIs) and statistical tests will be two-sided, unless otherwise specified.

7.5 Common calculations

For quantitative measurements, change from baseline will be calculated as: (Test value at Visit Day X – Baseline value).

7.6 Software

All analyses will be conducted using SAS® Version 9.4.

8. Statistical considerations

8.1 Sample size

The sample size for the study was selected as adequate for an initial review of the safety profile, rather than for statistical reasons. This is accepted practice for early phase trials designed to detect only relatively common safety events, major safety signals, or important trends.

8.2 Multicentre studies

This trial was only conducted at one site.

8.3 Missing data

Missing safety data will not be imputed for this trial.

9. Output presentations

Summary tables will be stratified by treatment group, unless otherwise specified.

The templates provided in the separate output templates document describe the format and content for presentation of tables, listings and figures (TLFs).

All percentages (%) for a specific summary are calculated using the total number of participants included in the relevant analysis population as the denominator, unless otherwise specified.

Data listings will be based on all participants randomized to IMP, unless otherwise specified.

By default, descriptive statistics for quantitative measurements will include the number of participants (n), mean, standard deviation (SD), minimum, median and maximum.

10. Participant disposition and withdrawal

10.1 Variables and derivations

End of trial classifications are defined as follows:

- Early withdrawal: Participants who exited the trial prior to completion for any reason other than being lost to follow-up.
- Completed trial: Participants that completed all trial visits, as indicated in the 'End of Study Status' CRF page.
- Lost to follow-up: Participants that completed all trial visits but withdrew during follow-up period.

Participants who completed the trial, as indicated on the 'Study Conclusion' page of the eCRF, will be assumed to have completed treatment (i.e. participants who completed the trial will be counted under both the "completed treatment" and "completed trial" category).

10.2 Analysis

Participant disposition and reason for withdrawal (obtained from 'Study Conclusion' on eCRF) will be summarized and presented in data listings for the FAS populations.

The number of participants included in the relevant analysis populations, as well as the number of participants excluded with reasons for exclusion from the relevant analysis populations (Section 6) and protocol violations/deviations will be summarized for the SAF populations and listed in data listings for the FAS populations.

11. Participant demographics and baseline characteristics

11.1 Variables and derivations

The following demographic and baseline characteristics will be reported for stage 1:

- Age (years), height (cm), weight (kg), BMI (kg/m^2)
- Date of birth, date of informed consent, date of HIV test informed consent
- Race, gender, HIV status, smoking (status, years of smoking, number of cigarettes), current alcohol use, BCG experience

The following demographic and baseline characteristics will be reported for stage 2:

- Mother's age (years), date of birth, race, HIV status, TB history, household exposure to TB, date of written informed consent; and
- Infant's age (days), date of birth, gender, race, recumbent length (cm), weight (kg), eligibility, Apgar score, head circumference.

Age and will be calculated as follows:

- $Age\ (days) = \ treatment\ start\ date\ (TRTSDT) - \ date\ of\ birth\ (BRTHDT)$
- $Age\ (years) = \ floor((informed\ consent\ date\ (RFICDT) - date\ of\ birth\ (BRTHDT))/365.25)$
- $BMI\ \left(\frac{kg}{m^2}\right) = \ weight\ (BLWEIGHT)/\ height\ (BLHEIGHT)^2$

11.2 Analysis

Demographic data and baseline characteristics will be summarized for each treatment group for the SAF populations and presented in data listings for the FAS populations by treatment group, participant number and visit.

12. IMP administration

12.1 Variables and derivations

None.

12.2 Analysis

IMP administration data will be presented in data listings for the SAF population.

13. Medical and treatment history

13.1 Variables and derivations

Medical history will be coded using the MedDRA central coding dictionary, Version 19.0.

13.2 Analysis

Medical history will be summarized for each stage as well as treatment group, by system organ class (SOC) and preferred term (PT), only for the SAF populations. Medical history will be presented as data listings for the FAS populations.

14. Prior and concomitant medications

14.1 Variables and derivations

'Prior medications' are defined as any TB medication (i.e. BCG vaccination) or other medication received prior to first administration of the IMP.

'Concomitant medications' are defined as any medication taken after first administration of the IMP, during the trial until after the follow-up period (up until D180 ± 14 days).

Where necessary, start and end dates for concomitant medications will be imputed as for AEs (see section 15 of this SAP for details).

All medications will be coded using the MIMS.

14.2 Analysis

Prior- and concomitant medications will be presented in data listings for the SAF populations. All medications captured on the 'Prior and Concomitant Medication' page of the eCRF will be categorised (prior/concomitant) and listed.

15. Adverse events

15.1 Variables and derivations

Adverse Events (AEs) will be coded using MedDRA central coding dictionary, Version 19.0.

Treatment-emergent adverse events (TEAEs) are defined as AEs that started at the time of, or after the, first IMP administration as well as those events that started prior to the first study drug administration, but which worsened after the first study drug administration. Appendix 2 contains conventions for the calculation of TEAEs.

Imputations will only be performed where at least the year is provided. The imputations derived for partial dates will be as follows:

- Imputation on the AE start date:
  - if completely missing then the treatment start date is used;
  - if only the day-part is missing, and the month and year are equal to treatment start month OR if both the day- and month-part are missing, and the year is equal to treatment start year, then the minimum of treatment start date and AE end date is used;
  - otherwise the missing day-part becomes the 1st day of the month, and the missing month-part becomes the 1st month of the year.
- Imputation on the AE end date:
  - if only the day part is missing then the last day of the month is used if this does not result in a date after the subject's death in which case the death date will be used;
  - in all other cases the AE end date will not be imputed.
- There will be no default for a missing year field.

In the case where it is impossible to define an AE as treatment-emergent or not, the AE will be classified by the worst case assigned, i.e. a TEAE.

15.2 Analysis

All tables and listings for AEs will be performed on the SAF populations for the respective 2 stages (adult and infant). An overall summary will be presented as the number of participants within each of the event type categories described in the sub-sections below, including the incidence of TEAEs by SOC (system organ class) and PT (preferred term), unless otherwise specified. Both number of participants, number of mentions and percentage will be provided.

A data listing with all AEs (including coding details [SOC and PT only]) will be presented for each stage, respectively.

15.2.1 Incidence of TEAEs

The incidence of all TEAEs by SOC and PT will be presented by stage and treatment group. A separate summary of unexpected TEAEs will be presented by SOC and PT, by stage and treatment group. In addition, an overall summary will be presented indicating the following counts:

- Participants with at least one TEAE
- Participants with at least one serious TEAE
- Participants with at least one grade 3+ TEAE
- Participants with at least one unexpected TEAE
- Participants with at least one drug-related TEAE
- Participants with at least one drug-related grade 3+ TEAE
- Participants with at least one drug-related, unexpected TEAE

15.2.2 TEAEs by severity

TEAEs will be graded on a scale of 1-4, per Appendix 2 in the protocol. The incidence of all TEAEs will be presented by SOC, PT and severity for each treatment group.

Additional grading summary tables (separate tables for each cohort) will be prepared that make use of conditional formatting ('traffic-lighting') to colour-code the worst grade AE experienced by a participant. Table columns will present the participants in the particular

cohort, as well as sums of Grade 1, 2, 3+ and total number of AEs recorded. Rows will present the various AEs (preferred term) that were recoded in the cohort. Conditional formatting will be implemented as follows:

- Grade 1 AE: Green
- Grade 2 AE: Yellow
- Grade 3+ AE: Red

The numeric grade value will be presented in the cell where conditional formatting is applied.

15.2.3 Drug-related TEAEs

TEAE relatedness to IMP (determined by the principal investigator) will be summarized per the following categories:

- Related ("Definitely related", "Probably related", "Possibly related")
- Not related ("Unlikely related", "Not related")

If relatedness is missing, the worst case will be assumed, i.e. related. The incidence of all drug-related TEAEs will be presented by SOC and PT for each treatment group.

15.2.4 Serious TEAEs

Serious TEAEs are defined as TEAEs for which seriousness is indicated as "yes". In cases where seriousness criteria are missing, the worst-case scenario will be assumed, i.e. serious AE.

The incidence of all serious TEAEs will be presented by SOC and PT for each treatment group. A data listing of serious adverse events (SAEs) will also be presented.

15.2.5 TEAEs leading to early withdrawal from study

The incidence of all serious TEAEs leading to early withdrawal will be presented by SOC and PT for each treatment group. A data listing of AEs leading to early withdrawal from study will be presented.

15.2.6 TEAEs leading to death

The incidence of all TEAEs leading to death will be presented by SOC and PT for each treatment group. A data listing of all AEs for deceased participants will be presented.

16. Safety laboratory tests

All summaries for safety laboratory data will be based on the SAF population.

16.1 Variables and derivations

For safety laboratory data, baseline will be defined as the last observation made prior to the first administration of IMP.

The following laboratory tests (haematology, clinical chemistry and urinalysis) will be included in the stage 1 (adult group) analysis; urinalysis only if clinically indicated and documented as part of the applicable adverse event:

- Haematology: haemoglobin, haematocrit, mean corpuscular volume, mean corpuscular haemoglobin, mean corpuscular haemoglobin concentration, percent and absolute differential counts (leucocytes, neutrophils, eosinophils, lymphocytes, monocytes, basophils), red cell distribution width, red and white blood cell and platelet count, immature cell count.
- Clinical Chemistry: alanine transaminase, aspartate transaminase, alkaline phosphatase, creatinine, total and conjugated bilirubin, urea, eGFR (MDRD formula).
- HIV serology: HIV-1
- Pregnancy: serum pregnancy
- QuantiFERON®: QuantiFERON®-TB Gold (Cellestis)

The following laboratory tests (haematology and clinical chemistry) will be included in the stage 2 (infant group) analysis:

- Haematology: haemoglobin, haematocrit, mean corpuscular volume, mean corpuscular haemoglobin, mean corpuscular haemoglobin concentration, percent and absolute differential counts (leucocytes, neutrophils, eosinophils, lymphocytes, monocytes, basophils), red cell distribution width, red and white blood cell and platelet count, immature cell count.

- Clinical Chemistry: alanine transaminase, aspartate transaminase, alkaline phosphatase, creatinine, total and conjugated bilirubin, urea, eGFR (MDRD formula).
- QuantiFERON®: QuantiFERON®-TB Gold (Cellestis)

Quantitative laboratory measurements reported as "< X", i.e. below limit of quantitation, or "> X", i.e. above the upper limit of quantification, will be converted to X for quantitative summaries, but will be presented as recorded, i.e. as "< X" or "> X" in the data listings.

16.2 Analysis

Grading for Safety laboratory results will be performed per Appendix 3. Table of toxicity reference ranges for grading SAFETY LABORATORY EVENTS of the protocol. Summaries of laboratory tests for each treatment group, by visit and by time point, will include descriptive statistics of the following:

- Actual and change from baseline (for quantitative measurements)
- Frequencies and percentages (n and %) (for qualitative measurements)

Data for specific safety laboratory test of interest (white cell count, neutrophil count and platelets) will also be presented graphically as a function of time. These will include line plots of mean ± standard deviation and median ± range for each treatment group, as well as separate line plots of individual participant's data over time, presented per treatment group.

Quantitative laboratory measurements will be compared with the relevant laboratory reference ranges and categorised as:

- Low: Below the lower limit of the laboratory reference range
- Normal: Within the laboratory reference range (upper and lower limit included)
- High: Above the upper limit of the laboratory reference range

These categorizations will only be presented in data listings. Other laboratory results (apart from haematology, clinical chemistry and urinalysis laboratory tests), e.g. urine microscopy, will be listed. A separate listing containing clinically significant laboratory results will be presented.

17. Vital signs

All summaries for vital signs will be based on the SAF population.

17.1 Variables and derivations

For vital signs, baseline is defined as the last observation made prior to the first administration of IMP.

The following vital signs will be reported for stage 1 (adults):

- Height (cm)
- Weight (kg)
- BMI (kg/m^2)
- Systolic blood pressure (mmHg)
- Diastolic blood pressure (mmHg)
- Heart rate (beats/min)
- Body temperature (°C)

The following vital signs will be reported for stage 2 (infants):

- Recumbent length (cm)
- Weight (kg)
- Pulse rate (beats/min)
- Respiratory rate (beats/min)
- Body temperature (°C)

17.2 Analysis

All summaries for vital signs will be based on the SAF population. Summaries of actual and change from baseline will be provided for each treatment group, by visit and protocol time point.

Abnormal quantitative vital signs will be identified in accordance with the grading scale given in Appendix 2 of the protocol.

18. Reactogenicity assessments

Reactogenicity will be assessed for both adult and infant groups.

18.1 Variables and derivations

The following variables will be reported for this study:

- Injection site reactions: erythema, swelling, induration, lymphadenopathy, pain, tenderness, severity of tenderness, ulceration, fluctuation, drainage, subcutaneous abscess, crusting and scarring.
- Systemic and regional adverse events: irritability, lethargy, malaise, myalgia, fever, skin rash, lymphadenopathy, lymphadenitis, and abscess formation.

18.2 Analyses

Reactogenicity data will be summarized with a frequency table and summary statistics for reaction diameter, based on SAF populations, by treatment and visit.

Between-group comparisons will be performed on the SAF populations using the Wilcoxon Rank Sum test for continuous variables. Any potential dose-response effects will be evaluated graphically, i.e. response variable *vs.* dose.

For categorical variables the Chi-square test will be used for between-group comparisons, and the Cochran-Mantel-Haenzel test will be performed to assess the effect of dose on reactogenicity.

Additional injection site reaction summary tables (separate tables for each cohort) will be prepared that make use of conditional formatting, as described in section 15.2.2 of this SAP.

19. Immunogenicity assessments

Immunogenicity data will be analysed and reported separately by the South African Tuberculosis Vaccine Initiative (SATVI) laboratory.

20. Physical examination

20.1 Variables and derivations

The following physical examinations will be reported for both stages of the study:

- General appearance
- Head and neck
- Eyes, ears, nose, throat and mouth
- Cardiovascular system
- Chest and lungs
- Abdomen
- Urogenital
- Musculoskeletal
- Neurological
- Skin
- Lymph nodes

20.2 Analysis

Physical examination data will be presented as normal/abnormal by treatment and visit and will be based on the SAF populations.

21. Revision history

Version	Date	Change
1.0	11-Mar-2018	Original document