STATISTICAL ANALYSIS PLAN

FINAL ANALYSIS

C-040-404

A RANDOMIZED, PLACEBO CONTROLLED, PARTIALLY BLINDED PHASE II STUDY TO EVALUATE SAFETY, IMMUNOGENICITY, AND PREVENTION OF INFECTION WITH MYCOBACTERIUM TUBERCULOSIS OF AERAS-404 AND BCG REVACCINATION IN HEALTHY ADOLESCENTS

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VERSION NUMBER AND DATE: V2.0, 29SEP2017

STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Statistical Analysis Plan Version 2.0 (Dated 29SEP2017) for Protocol C-040-404.

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MODIFICATION **HISTORY**

Unique Identifier for this Version	**Date of the Document Version**	**Author**	**Significant Changes from Previous Authorized Version**
1.0	26JUL2017	Louise van Aswegen	Not Applicable. First Version.
2.0	29SEP2017	Louise van Aswegen	Update alternative threshold text from '<0.2 at Baseline and > 0.70 post-Day 84' to '<0.20 at any time point prior to conversion and > 0.70 at any time point post-Day 84' Repeat the secondary analyses for this threshold. Add analyses of whole blood ICS to be performed by Aeras

TABLE OF CONTENTS

1. INTRODUCTION

This document describes the rules and conventions that will be used in the planned presentation and analysis of data of the final clinical study report (CSR) for Protocol C-040-404 as set out in the relevant version of the table, listing and figure (TLF) shells. It describes the data to be summarized and analyzed, including specifics of the statistical analyses to be performed on the data.

This SAP is based on protocol Final Version 5.0, dated 25JUL2016.

2. STUDY OBJECTIVES

The following relates to the overall study objectives as described in Section 2.0: Study Objectives and Design of the protocol.

2.1. PRIMARY OBJECTIVES

The primary objectives are:

- To evaluate the safety profile in human immunodeficiency virus (HIV)-uninfected, remotely Bacillus Calmette-Guérin (BCG) vaccinated adolescents of:
  - H4:IC31 (also known as AERAS-404).
  - BCG revaccination.
- To evaluate prevention of *Mycobacterium tuberculosis* (*Mtb*) infection, as measured by rates of conversion using a QuantiFERON Tuberculosis (TB) gold-in-tube (QFT-GIT) assay of:
  - H4:IC31 compared to Placebo.
  - BCG revaccination compared to Placebo.

2.2. SECONDARY OBJECTIVES

The secondary objectives are:

- To evaluate prevention of *Mtb* infection, as measured by rates of sustained conversion using a QFT-GIT assay of:
  - H4:IC31 compared to Placebo.
  - BCG revaccination compared to Placebo.
- To investigate the immunogenicity in HIV-uninfected, remotely BCG vaccinated adolescents of:
  - H4:IC31.
  - BCG revaccination.

2.3. EXPLORATORY OBJECTIVES

The exploratory objectives are:

- To evaluate prevention of *Mtb* infection, as measured by rates of reversion to a negative from a positive QFT-GIT assay of:
  - H4:IC31 compared to Placebo.
  - BCG revaccination compared to Placebo.
- To explore the effect of alternative QFT-GIT test threshold values on rates of QFT-GIT conversion, QFT-GIT reversion and prevention of *Mtb* infection.
- To identify immune correlates of risk for *Mtb* infection.

- To identify immune correlates of vaccine-induced protection against *Mtb* infection induced by H4:IC31 or BCG revaccination.
- To evaluate alternative interferon gamma release assays (IGRAs) or immune markers for diagnosis of *Mtb* infection or as markers of exposure to nontuberculous mycobacteria (NTM).
- To explore trends in TB disease incidence after H4:IC31 vaccination or BCG revaccination.
- To explore trends in QFT-GIT prolonged/sustained conversions and late reversions (i.e., more than 6 months post initial conversion) in early QFT-GIT converters (i.e., among those who converted at Month 6 or Month 12 of follow-up).

3. STUDY DESIGN

3.1. GENERAL DESCRIPTION

A Phase II, randomized, 3-arm, placebo-controlled, partially blinded clinical trial that was conducted in 990 healthy HIV-uninfected, QFT-GIT negative, previously BCG vaccinated adolescents. Participants were recruited from high schools or directly from the community.

Participants were enrolled in two sequential cohorts:

- Safety and Immunogenicity Cohort:
  - First 90 participants (30 from each arm).
  - More intensive collection of safety data.
  - Selected immunogenicity assays (including whole blood intracellular cytokine staining [ICS]).
  - Data reviewed by the data monitoring committee (DMC), principal investigator and local medical monitor.
- Correlates Cohort:
  - Remaining 900 participants.

All 990 participants in the study were evaluated for:

- Safety outcomes.
- Biomarker outcomes.
- Prevention of *Mtb* infection.

Within each cohort, participants were randomized in a 1:1:1 ratio to one of the following treatment groups:

- H4:IC31:
  - 15 mcg H4/500 nmol IC31.
  - Two doses (administered on Day 0 and Day 56).
  - Intramuscular injection.
- Placebo:
  - Saline volume equivalent to the H4:IC31 injection.
  - Two doses (administered on Day 0 and Day 56).
  - Intramuscular injection.

- BCG:
  - 2-8 x 10^5 CFU.
  - One dose (administered on Day 0).
  - Intradermal injection.

Randomization to the H4:IC31 and Placebo treatment groups was double-blinded. Since BCG causes a recognizable local injection site reaction, the BCG revaccination treatment group was not blind. Laboratory staff performing QFT-GIT, immunogenicity and correlates assays were blinded to all three treatment groups. Planned randomization of participants is specified in Table 1: Planned Enrollment by Treatment Group and Cohort, below:

Table 1: Planned Enrollment by Treatment Group and Cohort

	Planned Number of Participants			
	Treatment Group			
Cohort	Placebo	BCG	H4:IC31	Total
Safety and Immunogenicity	30	30	30	90
Correlates	300	300	300	900
Total	330	330	330	990

BCG: Bacillus Calmette-Guerin.

Safety outcomes included solicited and unsolicited adverse events (AEs), injection site assessment, adverse events of special interest (AESIs) and serious adverse events (SAEs).

Each participant was followed for safety for a minimum of 6 months after the last vaccination.

The primary endpoint is:

- QFT-GIT conversion from negative to positive at any time point after Day 84 through end of follow-up in participants who were QFT-GIT negative at Study Day 84.

The secondary endpoint is:

- The primary endpoint occurrence (see aforementioned), persisting without QFT-GIT reversion from positive to negative through 6 months after QFT-GIT conversion.

The duration of the trial to primary analysis was endpoint-driven. The primary analysis was triggered when all of the following conditions were met:

- At least 64 primary endpoints were accrued in the study (regardless from which cohort).
- The median follow-up time was at least 15 months:
  - Maximum individual follow-up time to detect QFT-GIT conversion of 24 months.

The protocol stated that if an initial reduction in infection rate in the BCG or H4:IC31 treatment group was seen in the primary analysis, follow-up for the entire study may be extended to examine the duration of prevention of *Mtb* infection. Following the primary analysis, there were no safety concerns of note. The DMC recommended that follow-up be continued as per protocol with a further DMC review close to the end of follow-up. Aeras confirmed that this second review by the DMC will only be completed following database (DB) lock. They also recommended that all participants have a QuantiFERON test performed at 24 months, including

all converters. The Sanofi Pasteur-Aeras Joint Steering Committee convened on June 14, 2016 and agreed to follow the DMC recommendations and to maintain study blind until study completion.

All participants with a primary endpoint (QFT-GIT conversion) were followed for an additional 6 months post-conversion to confirm whether they met the secondary or exploratory endpoints of sustained conversion or QFT reversion.

Participants who converted to a positive QFT-GIT at Month 6 or Month 12 were approached for a final QFT-GIT test and assessment for TB signs and symptoms at least 24 months after their initial vaccination.

The schedule for follow-up for individual participants was contingent on results of the QFT-GIT tests conducted at Month 3 (Day 84) and Months 6, 12, 18 and 24 study visits. A schematic of follow-up and QFT-GIT testing is presented in Figure 1: Schematic of Follow-up and QFT-GIT Testing, below.

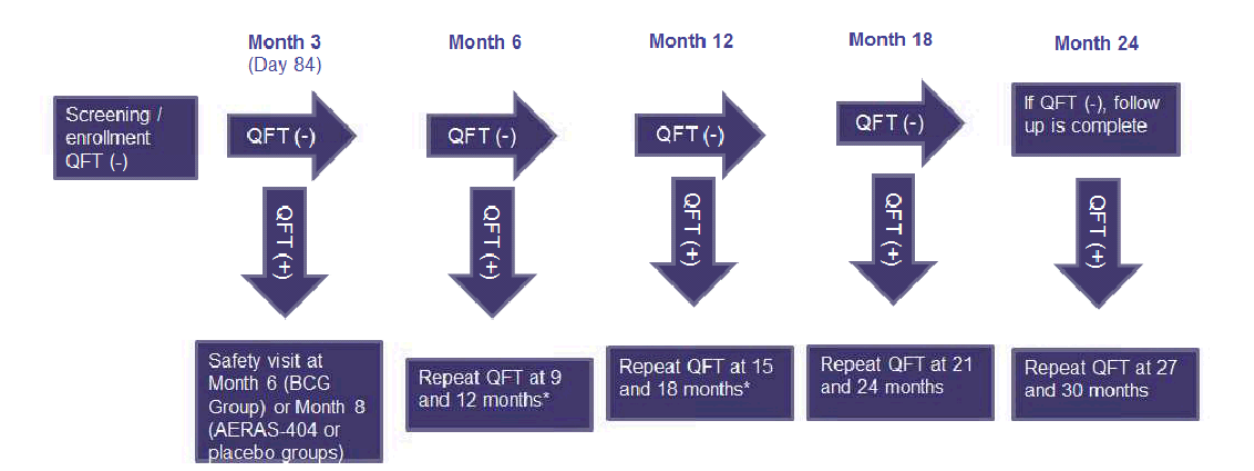

Figure 1: Schematic of Follow-up and QFT-GIT Testing

***Participants who converted at Month 6 or Month 12 were asked to return for a repeated QFT-GIT test done at least 24 months after their initial vaccination.**

3.2. SCHEDULE OF EVENTS

The schedules of events for the BCG participants as well as the H4:IC31/Placebo participants are presented in Table 2: Schedule of Participant Evaluations (Participants Receiving BCG, N = 330) and Table 3: Schedule of Participant Evaluations (Participants Receiving H4:IC31 [N=330] or Placebo [N=330]), below.

Table 2: Schedule of Participant Evaluations (Participants Receiving BCG, N = 330)

Study Visit Day (D) or Month (M) →	Screen	0	D7	D28	D70	D84[c]	M6 (D168)[d,e] M12 (D336) M18 (D504) M24 (D672)
Eligibility criteria verification	X	X					
Medical history	X						
Physical examination	X						
Urine βHCG (all females)	X	X					
QuantiFERON®-TB Gold in-tube (mL)	3					3	3
HIV-1 (mL) with HIV counselling	3						
Urinalysis	X		X[b]				
Serum chemistry (mL)[g]	5		5[b]				
CBC, differential, platelets (mL)	5		5[b]				
Vital signs	X	X					
Interval history		X	X	X	X	X	X
Focused physical examination[a]		X	X	X	X	X	X
Distribute/review diary cards		X[b]	X[b]				
Solicited adverse events (incl. con. meds.)		X	X				
Unsolicited adverse events (incl. con. meds.)		X	X	X			
SAEs, AESIs, and SUSARs (incl. con. meds.)		X	X	X	X	X	X
Solicited and unsolicited injection site reaction adverse events (incl. con. meds.)		X	X	X	X	X	
Site of injection examination		X	X	X	X	X	
TB symptom screen	X			X	X	X	X
BCG administration		X					
Whole blood assay (mL)		6[b]			6[b]		
Absolute blood count (mL)		0.5	0.5				0.5
RNA (mL)		2.5	2.5				2.5
PBMC for ICS (mL)		8[b]			8[b]		
Serum for multiplex ELISA (mL)		3[b]	3[b]				
PBMC, plasma, and serum for correlates of risk/protection (mL)		16			16		40[i]
Whole blood for evaluation of novel IGRA (mL)[f]	7	7				7	7
PBMC for evaluation of NTM exposure (mL)		10					
Per visit phlebotomy volume (mL)[h]	23	53	16	0	32.5	10	53 (M6,M12)/ 13 (M18,M24)
Cumulative phlebotomy volume (mL)[h]	23	76	92	92	124.5	134.5	266.5

a. If indicated by interval history
b. Subjects in the Safety & Immunogenicity Cohort only
c. Subjects who convert from QFT-GIT(-) to (+) at Day 84 will have a final visit at 168 days ±14 days after vaccination for assessment of SAEs, AESIs, SUSARs, and TB symptom screen
d. Month 6, 12, 18, and 24 study visits will be completed by subjects who did not convert from QFT-GIT (-) to (+) at the previous visit; the Month 24 visit will be the final visit for subjects who remain QFT-GIT(-) throughout the study.
e. Subjects who convert from QFT-GIT (-) to (+) at Month 6-24 visits will have two additional visits with repeat QFT-GIT testing, assessment of SAEs, AESIs, SUSARs, and TB symptom screen 84 days ±14 days and 168 days ±14 days after conversion. Up to 10 mL of blood will be collected at each of those visits, including blood for absolute blood count and RNA. Subjects who initially convert to QFT-GIT(+) at Month 6 or 12 will be asked to have a final QFT-GIT test, blood collection for absolute blood count and RNA, and TB symptom screen done at least 24 months after their initial vaccination.
f. May not be collected at all time points shown.
g. Serum chemistry includes AST, ALT, alkaline phosphatase, total bilirubin, creatinine, and BUN.
h. Blood volumes are approximate.
i. Study Months 6 and 12 only.

Table 3: Schedule of Participant Evaluations (Participants Receiving H4:IC31 [N=330] or Placebo [N=330])

Study Visit Day (D) or Month (M) →	Screen	0	D3	D7	D28	D56	D63	D70	D84[c]	M6 (D168)[d,e] M12 (D336) M18 (D504) M24 (D672)
Eligibility criteria verification	X	X				X				
Medical history	X									
Physical examination	X									
Urine βHCG (all females)	X	X				X				
QuantiFERON®-TB Gold in-tube (mL)	3								3	3
HIV-1 (mL) with HIV counselling	3									
Urinalysis	X			X[b]			X[b]			
Serum chemistry (mL)[g]	5			5[b]			5[b]			
CBC, differential, platelets (mL)	5			5[b]			5[b]			
Vital signs	X	X				X				

Study Visit Day (D) or Month (M) →	Screen	0	D3	D7	D28	D56	D63	D70	D84[c]	M6 (D168)[d,e] M12 (D336) M18 (D504) M24 (D672)
Interval history		X	X	X	X	X	X	X	X	X
Focused physical examination[a]		X	X	X	X	X	X	X	X	X
Distribute/review diary cards		X[b]		X[b]		X[b]	X[b]			
Solicited adverse events (incl. con. meds.)		X	X	X		X	X			
Unsolicited adverse events (incl. con. meds.)		X	X	X	X	X	X	X	X	
SAEs, AESIs, and SUSARs (incl. con. meds.)		X	X	X	X	X	X	X	X	X
Solicited injection site reaction adverse events (incl. con. meds.)		X	X	X	X	X	X	X	X	
Site of injection examination		X	X	X	X	X	X	X	X	
TB symptom screen	X				X	X			X	X
Study vaccine administration		X				X				
Whole blood assay (mL)		6[b]						6[b]		
Absolute blood count (mL)		0.5	0.5							0.5
RNA (mL)		2.5	2.5							2.5
PBMC for ICS (mL)		8[b]						8[b]		
Serum for multiplex ELISA (mL)		3[b]	3[b]							
PBMC, plasma, and serum for correlates of risk/protection (mL)		16						16		40[i]
Whole blood for evaluation of novel IGRA (mL)[f]	7	7							7	7
PBMC for evaluation of NTM exposure (mL)		10								
Per visit phlebotomy volume (mL)[h]	23	53	6	10	0	0	10	32.5	10	53 (M6,M12)/ 13 (M18,M24)
Cumulative phlebotomy volume (mL)[h]	23	76	82	92	92	92	102	134.5	144.5	276.5

a. If indicated by interval history
b. Subjects in the Safety & Immunogenicity Cohort only
c. Subjects who convert from QFT-GIT(-) to (+) at Day 84 will have a final visit at 168 days ±14 days after second vaccination (Month 8, Study Day 224) for evaluation of SAEs, AESIs, SUSARs, and TB symptom screen
d. The Month 6, 12, 18, and 24 study visits will be completed by subjects who did not convert from QFT-GIT (-) to (+) at the previous visit; the Month 24 visit will be the final visit for subjects who remain QFT-GIT(-) throughout the study
e. Subjects who convert from QFT-GIT (-) to (+) at Month 6-24 visits will have two additional visits with repeat QFT-GIT testing, assessment of SAEs, AESIs, SUSARs, and TB symptom screen 84 days ±14 days and 168 days ±14 days after conversion. Up to 10 mL of blood will be collected at each of those visits, including blood for absolute blood count and RNA. Subjects who initially convert to QFT-GIT(+) at Month 6 or 12 will be asked to have a final QFT-GIT test, blood collection for absolute blood count and RNA, and TB symptom screen done at least 24 months after initial vaccination.
f. May not be collected at all time points shown.
g. Serum chemistry includes AST, ALT, alkaline phosphatase, total bilirubin, creatinine, and BUN.
h. Blood volumes are approximate.
i. Study Months 6 and 12 only.

3.3. CHANGES TO ANALYSIS FROM PROTOCOL

- On page 23 of the protocol, the following is stated: "The secondary analysis will be triggered after 6 months of additional post-conversion follow-up for individuals who convert, regardless of the rate of QFT-GIT reversion."

Following discussions with Aeras, it was clarified that there will not be any formal secondary analysis. Following the primary analysis there will only be one additional analysis, the final analysis. The final analysis will occur once all planned follow-up visits have been completed, or following the termination of the trial (if terminated before the required follow-up visits occurred).

- On page 52 of the protocol the Intent-to-treat analysis set is defined as: "The intent-to-treat population for efficacy and immunogenicity analyses will consist of all randomized subjects."

Following discussions with Aeras, it was decided that since the Intent-to-treat analysis set is the same as the Randomized analysis set, a Modified Intent-to-treat analysis set will be defined and used for analysis purposes.

The Modified Intent-to-treat analysis set is defined as described in Section 5.3: Modified Intent-to-treat Analysis Set.

- The following exploratory analyses will not be performed as part of this SAP, as agreed by Aeras:
  - Identifying immune correlates of risk for *Mtb* infection.
  - Evaluating alternative IGRAs or immune markers for diagnosis of *Mtb* infection or as markers of exposure to nontuberculous mycobacteria (NTM).
  - Identifying immune correlates of vaccine-induced protection against *Mtb* infection induced by H4:IC31 or BCG revaccination.
  - Exploring trends in TB disease incidence after vaccination.

Aeras and some of its external partners will prepare a separate correlates SAP once the trial's efficacy results become available.

- On 5 April 2016, Aeras Biostatistics and Data Management were notified of a manufacturer's recall of a portion of the QuantiFERON (QFT) tubes that were used in determination of endpoints. The recall primarily stemmed from changes in Qiagen's quality control (QC) process, which resulted in their recalling all unexpired partial lots that had been previously circulated for use. Although Qiagen's ongoing QC processes did not detect a spike in false positive results within this partial lot, they were unable to rule out the possibility of false positive results coming from the tubes in question, thereby resulting in the recall.
  - Sixteen (16) positive QFT results came from these recalled tubes, affecting 14 unique participants. Nine (9) of the tubes contributed toward the trial's primary efficacy endpoint. Even though the information provided by Qiagen does not suggest that these results are false positives, the tubes were recalled nonetheless. Therefore, in an abundance of caution, Aeras considered an additional analysis set that would remove these results from the primary endpoint and final endpoint analysis.

Aeras requested the following approach to handle this:

- Create an additional analysis set (refer to Section 5.4: Adjusted Modified Intent-to-treat (first recall positive omit Analysis Set)).
- Perform the following additional analysis:
  - Modified Intent-to-treat (mITT) with adjudication: This analysis will retain QFT data from all visits for participants who received positive QFT results from recalled tubes provided they also received positive results from non-recalled tubes. In other words, if a participant has positive QFT results from both non-recalled and recalled tubes, then all of these results will be treated as true positives.

- Whilst setting up the programming for the medical review listings, Data Management (DM) was requested to use the following toxicity criteria for Urine Erythrocytes since this is recorded as a qualitative value and the protocol provides the toxicity criteria for quantitative values. These criteria will be used to determine the toxicity grading. ++/+++ values will therefore be regarded as 'Grade 2/3/4'.

Laboratory Test	Grade 1	Grade 2	Grade 3	Grade 4
Urine Erythrocytes	+	++/+++	++/+++	++/+++

4. PLANNED ANALYSES

The following formal analyses will be performed for this study:

- Day 7 DMC.
- Day 84 DMC.
- Primary analysis.
- Final analysis.

4.1. DATA MONITORING COMMITTEE (DMC)

The DMC safety reviews, based on a separate statistical analysis plan (SAP) and set of TLF shells (as provided by Aeras), have been completed at two time points:

- Day 7 DMC:
  - For the Safety and Immunogenicity Cohort once the last participant reached Day 7, the DMC reviewed unblinded safety data.
- Day 84 DMC:
  - For the Safety and Immunogenicity Cohort once the last participant reached Day 84, the DMC reviewed unblinded safety data.

The DMC made a formal recommendation about the continued conduct of the trial after each safety review. Enrollment continued while the reviews were being conducted.

4.2. PRIMARY ANALYSIS

The primary analysis, based on a separate SAP and set of TLF shells was completed once the following two conditions were met:

- At least 64 primary endpoints had accrued (refer to Section 14.1.1: Primary Efficacy Endpoint for a description of the primary endpoints).
- The median follow-up time (for all participants in the Modified Intent-to-treat [mITT] analysis set) from Day 0 was at least 15 months.

The DMC received the primary analysis report and provided a recommendation to the study sponsor regarding whether to continue, stop or modify the trial as currently planned.

4.3. FINAL ANALYSIS

The final analysis identified in this SAP and relevant set of TLF shells will be performed by QuintilesIMS Bloemfontein, South Africa (QBLM) Biostatistics. The final analysis is planned following:

- Aeras's authorization of the final version of the SAP and relevant set of TLF shells.
- Aeras's authorization of the final analysis sets.
- Final database lock and unblinding.

The final analysis will be performed on a clean locked database:

- All outstanding data issues and queries resolved.
- All unresolvable data issues documented in a separate data handling report (DHR) document from Data Management.
- All coding of medications, medical conditions, physical examination abnormalities and adverse events (AEs) completed.
- All reconciliation of vendor data with electronic case report form (eCRF) data completed successfully.

5. ANALYSIS SETS

Aeras authorization of assigned analysis sets is required for the final analysis. Agreement and authorization of participants included/excluded from each analysis set will be obtained prior to the unblinding activities of the study.

In view of the final analysis, the following analysis sets will be defined:

5.1. RANDOMIZED ANALYSIS SET

The Randomized analysis set is defined as all participants who were randomized to either H4:IC31, Placebo or BCG regardless of whether they received a study vaccination.

A participant will be programmatically included in the Randomized analysis set if the participant has a randomization number in the clinical study database, as recorded on the System Enrollment eCRF.

For analyses and presentations based on Randomized analysis set, participants will be analyzed according to the treatment assigned regardless of the treatment received.

5.2. SAFETY ANALYSIS SET

The Safety analysis set is defined as all participants included in the Randomized analysis set who received at least one dose of study vaccination (H4:IC31, Placebo or BCG).

A participant will be included in the Safety analysis set if the participant:

- Is included in the Randomized analysis set.

  AND

- Has at least one date of study vaccination in the database as recorded on the Exposure (Day 0) or Exposure (Day 56) eCRF.

For analyses and presentations based on the Safety analysis set, participants will be analyzed according to the treatment received regardless of the treatment allocated (that is 'as treated'):

- For all presentations, including by dose at onset presentations, participants who received a different treatment to that allocated, but the same consistent treatment for all relevant doses, analyze and present participants according to the treatment received (both overall and per dose at onset).
- Participants who received a different treatment to that allocated, but not the same consistent treatment for all relevant doses (mixed treatment regimen), will be analyzed as described below:
  - For all presentations, with the exception of by dose at onset presentations, analyze and present participants according to the following vaccine hierarchy: H4:IC31 followed by BCG and then placebo.
  - For all by dose at onset presentations, analyze participants according to the treatment received for each dose at onset; therefore, participants are analyzed and presented according to different treatments per the relevant doses.

The Safety analysis set will be used as the primary analysis set for all safety and immunogenicity analyses.

5.3. MODIFIED INTENT-TO-TREAT ANALYSIS SET

The Modified Intent-to-treat analysis set is defined as all participants included in the Safety analysis set who had a negative QFT-GIT test result at Day 84.

A participant will be programmatically included in the Modified Intent-to-treat analysis set if the participant:

- Is included in the Safety analysis set.

  AND

- Has a negative QFT-GIT test result at the Day 84 visit.

For analyses and presentations based on the Modified Intent-to-treat analysis set, participants will be analyzed according to the treatment assigned regardless of the treatment received.

The Modified Intent-to-treat analysis set will be used for efficacy analyses.

5.4. ADJUSTED MODIFIED INTENT-TO-TREAT (FIRST RECALL POSITIVE OMIT ANALYSIS SET)

This analysis set will omit all participants whose first positive QFT-GIT result came from a recalled tube (refer to Section 3.3: Changes to Analysis from Protocol). This analysis set will therefore include the same participants who are included within the mITT set except for the following nine participants, all of whom had their first positive QFT-GIT result from a recalled tube:

044002-00288
044002-01409
044002-00433
044002-01438
044002-00587
044002-01506
044002-00883
044002-02063
044002-00923

Some of the primary efficacy analyses will also be performed using the Adjusted Modified Intent-to-Treat analysis set as a sensitivity analysis.

5.5. PER PROTOCOL ANALYSIS SET

The Per Protocol analysis set is defined as all participants in the Modified Intent-to-treat analysis set who received all relevant doses of BCG, H4: IC31 or Placebo and had no major protocol deviations.

A participant will be included in the Per Protocol analysis set if the participant:

- Is included in the Modified Intent-to-treat analysis set.
- Received all relevant doses, based on the date of study vaccination as recorded on Exposure (Day 0) and Exposure (Day 56) eCRFs:
  - BCG: Day 0.
  - H4:IC31 or Placebo: Day 0 and Day 56.
- Did not have any major protocol deviations as recorded on the Protocol Deviation eCRF and agreed with Aeras prior to the relevant unblinding activities of the analysis/study.
- Did not have a treatment deviation as identified in collaboration with the clinical trial manager (CTM) in accordance with the Aeras/QuintilesIMS Process Instruction Treatment Deviation Identification and Authorization document.
- Out-of-window QFT-GIT positive results should not be included in the analysis for the PP analysis set.

Refer to the relevant Blind Data Review (BDR) documentation for additional details.

The Per Protocol analysis set will be based on the participant level flag assigned in Appendix 1 of the BDR report, as authorized by Aeras prior to DB lock.

Efficacy analyses will also be performed using the Per Protocol analysis set as a sensitivity analysis.

6. GENERAL CONSIDERATIONS

6.1. REFERENCE START DATE AND STUDY DAY

Reference start date is defined as the date of first study vaccination and equals Day 0. Study day will be calculated relative to the reference start date and will be used to show start or stop day of an assessment or event. Study day will be calculated as follows:

- If the date of the assessment/event is prior to, on or after the reference start date:
  - Study day = (date of assessment/event – reference start date).

Unless otherwise specified, if the date of the assessment/event is partial or missing, study day and any corresponding durations will not be calculated and will be presented as missing in the listings.

Some presentations include the study day relative to the most recent vaccination (presented as relative day) and will be calculated as follows:

- If the date of the assessment/event is on or after the most recent vaccination:
  - Relative day = (date of assessment/event – date of most recent vaccination).

6.2. BASELINE

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

6.3. RETESTS, UNSCHEDULED VISITS AND PREMATURE DISCONTINUATION DATA

In general, for by-visit summaries, data recorded at the scheduled visit will be presented. Unscheduled assessments will not be included in by-visit summaries, but may contribute to the Baseline value.

In the case of a retest (same visit number assigned), the latest available test result as provided in the data transfer for that visit/time point will be used for by-visit summaries.

Listings will include scheduled, unscheduled and premature discontinuation data. No mapping of premature discontinuation data will be performed.

6.4. STATISTICAL TESTS

Unless otherwise specified:

- The default summary statistics for quantitative variables will be as follows:
  - Number of participants in each category (n).
  - Mean.
  - Standard deviation (SD).
  - Median.
  - Minimum.
  - Maximum.
- The default summary statistics for qualitative variables will be as follows:
  - Number of participants in each category (n).
  - Percentage of participants in each category (%), presented relative to either one of the following:
    - Total number of participants in the relevant analysis set.
    - Total number of participants in the relevant analysis set, with assessments available (observed cases).
- In the event of missing assessments, a 'Missing' category showing the number of participants with missing assessments at each level of summarization will be presented.
- Methods for determining confidence intervals (CIs) will be specified in each relevant section.

6.5. COMMON CALCULATIONS

The following common calculations are defined:

- Change from Baseline = (Result at relevant post-baseline time point – Result at Baseline).
- Most recent vaccination:
  - Calculate the difference in the start date of the assessment/event and all available study vaccination dates:
    - Days since dose x: (AE start date – study vaccination dose x date [where x = 1, 2 {not applicable for BCG}])
  - For the previous calculation, only consider those doses where the days since dose x is ≥ 0 (therefore excluding the doses occurring after the relevant assessment/event) and determine the dose (1, 2 [not applicable for BCG]) for which the days since dose x (as calculated in the previous step) is a minimum.
  - Assign the dose selected in the previous step as the most recent vaccination as the specific dose determined in the previous calculation.
- Change from pre-vaccination:
  - Result at Study Day x – results at relevant pre-vaccination time point.
  - If a result/value is missing, change from pre-vaccination result will be presented as missing in the listing. That is, no imputation for a missing change will be performed.

- Shift in toxicity grade from pre-vaccination:
  - Toxicity grade at Study Day x – toxicity grade at relevant pre-vaccination time point.
  - If a toxicity grade is missing, shift in toxicity grade from pre-vaccination will be presented as missing in the listing. That is, no imputation for a missing shift will be performed.
  - If no toxicity grade is assigned to a specific visit the grade will be regarded as grade 0 for calculation purposes.

6.6. SOFTWARE VERSION

All analyses will be conducted using SAS® Version 9.4.

7. STATISTICAL CONSIDERATIONS

7.1. ADJUSTMENTS FOR COVARIATES AND FACTORS TO BE INCLUDED IN ANALYSES

Not applicable.

7.2. MULTICENTER STUDIES

This study is being conducted by multiple Investigators at multiple schools/regions in South Africa. No adjustment for school/region effect will be made. Generally, all schools/regions will be pooled by cohort and treatment group for analysis purposes.

7.3. MISSING DATA

Missing data will not be imputed. For the handling of partial or missing AE start dates, refer to APPENDIX 2: Partial Date Conventions.

7.4. MULTIPLE COMPARISONS/MULTIPLICITY

There will be no adjustment for multiplicity to control the Type 1 error rate over the two tests associated with the primary efficacy endpoint. The rationale for not performing this adjustment is related to the fact that the tests pertain to efficacy assessments of two unrelated vaccines (H4:IC31 and BCG). If these two evaluations were performed in two separate trials then no adjustment for multiplicity would be made. Thus, one should not be compelled to adjust for this multiplicity simply because the two evaluations are performed administratively in a single trial.

In addition, this is considered an intermediate test of biological effect study in the development of the vaccine and no definitive claims are being sought.

Multiplicity adjustment for immunology data will be performed by means of the Holm (Step-Down Bonferroni) method.

7.5. EXAMINATION OF SUBGROUPS

No subgroup analyses will be performed.

8. OUTPUT PRESENTATIONS

APPENDIX 1: Programming Conventions for Outputs describes the conventions for presentation of data in the TLFs.

The TLF shells provided together with this SAP describe the presentations for the final analysis and therefore the format and content of the TLFs to be provided by QuintilesIMS Biostatistics.

Note that verbatim terms, specifications (for example the reason a specific assessment was not done) and all variables in the TLF shells that contain the suffix (eCRF) contain verbatim text that may include spelling mistakes. Verbatim text will be presented in the listings 'as is' and no manual 'hard-coding' corrections of such data will be made.

For table presentations, the following treatment groups and cohorts will be presented:

- Treatment Group:
  - Placebo.
  - H4:IC31.
  - BCG.
  - Total.
- Cohort (if applicable):
  - All participants.
  - Safety and Immunogenicity Cohort.
  - Correlates Cohort.

9. DISPOSITION AND PREMATURE DISCONTINUATION

All participants who provide informed consent and were randomized to a treatment group and cohort will be accounted for in this study.

Participant disposition will be presented for the Randomized analysis set (unless otherwise specified).

The following tables are planned for presentation:

- Randomization by site.
- Participant disposition and primary reason for premature study discontinuation.

- Participant disposition and primary reason for premature treatment discontinuation (Safety analysis set).
- Protocol deviations.
- Analysis sets.

The following listings are planned for presentation:

- Participant disposition.
- Protocol deviations.
- Inclusion and/or exclusion exceptions at Study Day 0.
- Analysis sets.

The following variable will be collected at Screening on the System Enrollment eCRF:

- InForm participant number (12-digit):
  - First three digits are the standard study indicator ('044').
  - Next four digits are the study site indicator followed by a dash ('002-' or '014-').
  - Last five digits are a sequential participant number (00001 to 03000), uniquely assigned per participant.

The following disposition variables, as presented in the planned TLF shells, will be collected at Screening on the Informed Consent/Cohort Assignment eCRF:

- Date of informed consent.
- Date of informed assent.
- Date of randomization.

The following disposition variables, as presented in the planned TLF shells, will be collected during the study on the Disposition Study eCRF:

- Whether the participant completed the study:
  - Yes.
  - No.
- Primary reason for premature study discontinuation:
  - Lost to follow-up.
  - Withdrew consent.
  - Death.
  - Adverse Event.
  - Protocol deviation.
  - Study terminated by sponsor.
  - Other (specify).
- Date of study completion/premature discontinuation.

The following disposition variables, as presented in the planned TLF shells, will be collected during the study on the Disposition Treatment eCRF:

- Whether the participant completed study treatment:
  - Yes.
  - No.

- Primary reason for premature study treatment discontinuation:
  - Lost to follow-up.
  - Withdrew consent.
  - Death.
  - Adverse Event (specify).
  - Protocol deviation.
  - Study terminated by sponsor.
  - Physician decision (specify).
  - Other (specify).
- Date of treatment completion/premature discontinuation.

The following variable will be collected on the Exposure eCRF:

- Date of study vaccination(s).

The following protocol deviation variables, as presented in the planned TLF shells, will be collected throughout the study on the Protocol Deviations eCRF:

- Visit to which the protocol deviation is relevant.
- Protocol deviation category:
  - Informed consent not properly obtained.
  - Did not meet inclusion criteria or met exclusion criteria but entered in the study.
  - Developed withdrawal criteria during the study but not withdrawn.
  - Study vaccine dosing deviation.
  - Procedure(s) performed out of window.
  - Missed procedure(s).
  - Unintended unblinding (not applicable to the BCG treatment group).
  - Serious adverse event (SAE)/immediately reportable event (IRE) reporting.
  - Other (specify).
- Date of protocol deviation.
- Protocol deviation description.

The following variables, as presented in the planned TLF shells, will be collected prior to Screening on the Inclusion/Exclusion Criteria (IE) eCRF and collected at Day 0 on the Eligibility Verification (IEV) eCRF:

- Category:
  - Inclusion.
  - Exclusion.
- Criterion number.
- Date of criterion exception noted.

The following study visit variable, as presented in the planned TLF shells, will be collected throughout the study on the Date of Visit eCRF:

- Date of visit.

The following variables, as presented in the planned TLF shells, will be imported from an Aeras approved EXCEL spreadsheet created for the review of major protocol deviations as well as inclusion of participants in each analysis set:

- For each analysis set, included in analysis set (refer to Section 5: Analysis Sets for relevant analysis sets and definitions):
  - Yes.
  - No.
- For each analysis set, reason(s) for exclusion from analysis set (refer to Section 5: Analysis Sets for possible reasons for exclusion from each analysis set).

9.1. DERIVATIONS

Based on the aforementioned, the following variables, as presented in the planned TLF shells, will be derived:

- Treatment unblinded:
  - Based on unintended unblinding on the Protocol Deviation eCRF.
- Update the InForm participant number to the participant ID (8-digit):
  - Replace four digits from digit 4 to 7 with the 3-digit study site number, by removing the first digit ('002-' → '02-' and '014-' → '14-').
  - Last five digits kept as is.
    This participant ID will be used in all the listings, as presented in the relevant TLF shells.
- Total number of doses:
  - Per participant, determine the number of doses received.
  - If date of vaccination is available, the vaccination will be considered as administered.
- Age (years), sex, race:
  - Refer to Section 10: Demographic and Other Baseline Characteristics and Section 10.1: Derivations for details.

10. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

No inferential statistical testing will be performed for demographic or other Baseline characteristics.

The following table is planned for presentation (based on the Safety analysis set):

- Demographics and other Baselines characteristics.
  - Presented by means of the default summary statistics for quantitative and qualitative variables.
  - Percentage (%) of participants will be calculated relative to the total number of participants in the Safety analysis set per treatment group with data available (observed case).
  - This table will be repeated for the Modified Intent-to-treat analysis set, Per Protocol analysis set as well as the Safety and Immunogenicity Cohort (Safety analysis set).

The following listing is planned for presentation (based on the Randomized analysis set):

- Demographics and other Baseline characteristics.

The following demographic variables, as presented in the planned TLF shells, will be collected at Screening on the Demography eCRF:

- Date of birth.
- Sex:
  - Male (M).
  - Female (F).
- Race:
  - Asian.
  - Black.
  - White.
  - Coloured.
  - Other (specify).

The following variable, as presented in the planned TLF shells, will be collected at Screening on the Informed Consent/Cohort Assignment eCRF:

- Cohort assignment:
  - Safety and Immunogenicity Cohort.
  - Correlates Cohort.

The following demographic variable, as presented in the planned TLF shells, will be collected at Screening on the School Selection eCRF:

- School:
  - Drostdy.
  - Esselenpark Sekondêr.
  - Hexvallei Hoërskool.
  - Hexvallei Sekondêr.
  - Hoërskool Breërivier.
  - HS Goudini.
  - Montana Hoërskool.
  - Van Cutsem.
  - Vusisizwe.
  - Worcester Gimnasium.
  - Worcester Sekondêr.
  - Other (specify).

The following demographic variable, as presented in the planned TLF shells, will be collected at Screening on the Region Selection eCRF:

- Region:
  - Athlone.
  - Gugulethu.
  - New Crossroads.
  - Nyanga.
  - Old Crossroads.
  - Philippi East.
  - Philippi West.
  - Other (specify).

The following Baseline characteristic, as presented in the planned TLF shells, will be collected on the Height and Weight eCRF:

- Baseline body mass index (BMI) (kg/m^2).

10.1. DERIVATIONS

Based on the aforementioned the following variable, as presented in the planned TLF shells, will be derived:

- Age (years):
  - Calculated relative to the reference start date (Day 0 vaccination).
  - Age (years) = (date of Day 0 vaccination) – (date of birth)/365.25.

All listings, as presented in the relevant TLF shells, will include the following demographic information:

- Age (years).
- Sex.
- Race.

These demographic variables will be concatenated to form one demographic variable in the following format:

- Age (years)/Sex/Race:
  - For example: 17/M/WHITE.

11. MEDICAL HISTORY

Medical History will be presented for the Randomized analysis set.

The following listing is planned for presentation:

- Medical history.

Medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 16.1.

The following medical history variables, as presented in the planned TLF shells, will be collected on the Medical History (MH) and Interval Medical History (IMH) eCRFs during the study:

- Verbatim term (eCRF).
- Date started.
- Date stopped or ongoing.
- Comment (eCRF).

The following medical history coding variables, as presented in the planned TLF shells, will be included in the data transfers received from Data Management:

- System Organ Class.
- Preferred Term.

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

12. PRIOR AND CONCOMITANT MEDICATIONS

Concomitant medications will be presented for the Randomized analysis set.

The following listing is planned for presentation:

- Concomitant medications.

Concomitant medication will be coded with World Health Organization – Drug Dictionary (WHO-DD) Version 01DEC2013.

The following concomitant medication variables, as presented in the planned TLF shells, will be collected on the Prior and Concomitant Medication (CM) eCRF:

- Verbatim term (eCRF).
- Date started.
- Date stopped or ongoing.
- Dose and unit per administration.
- Frequency.
- Route of administration.
- Indication.

The following medication coding variables, as presented in the planned TLF shells, will be included in the data transfers received from Data Management:

- Preferred Term.
- Anatomical Therapeutic Chemical (ATC) Level 1 term.
- ATC Level 3 term.

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

13. STUDY VACCINATION

Administration of the study vaccine(s) will be presented for the Safety analysis set.

The following table is planned for presentation:

- Study vaccination administration:
  - Presented by treatment group by means of the default summary statistics for qualitative variables.
  - Percentage (%) of participants will be calculated relative to the total number of participants in the Safety analysis set per treatment group.

- The number and percentage (%) of participants who received all scheduled vaccinations will be presented.
- The number and percentage (%) of participants who received the second vaccination within the protocol-defined window will be presented. The denominator for the % will be based on the total number of participants in the Safety analysis set per treatment group (excluding BCG).

The following listing is planned for presentation (based on the Randomized analysis set):

- Study vaccination administration.

Study vaccinations will be administered on the study days as specified for each treatment group in Table 1: Planned Enrollment by Treatment Group and Cohort.

The following exposure variables, as presented in the planned TLF shells, will be collected on the Exposure Day 0 and Exposure Day 56 eCRFs:

- Study vaccination administered:
  - Yes.
  - No.
- Date and time of study vaccination.
- Full volume administered:
  - Yes.
  - No.
- Location (arm):
  - Left.
  - Right.

The following treatment deviation variables, as presented in the planned TLF shells, will be collected in collaboration with the clinical trial manager (CTM) with the Aeras/Quintiles Process Instruction: Treatment Deviation Identification and Authorization document:

- In accordance with randomization:
  - Yes.
  - No.
- Out of study window:
  - Yes.
  - No.

13.1. DERIVATIONS

Based on the aforementioned the following variables, as presented in the planned TLF shells, will be derived:

- Participants who received all scheduled vaccinations:
  - Yes:
    - For BCG treatment group participants if Day 0 study vaccination date is available.
    - For H4:IC31 or Placebo treatment group participants if Day 0 and Day 56 study vaccination dates are both available.

- No:
  - For BCG treatment group participants if Day 0 study vaccination date is not available.
  - For H4:IC31 or Placebo treatment group participants if Day 0 and/or Day 56 vaccination dates are not available.

- Study day of the Day 56 vaccination:
  - Calculated relative to Day 0 vaccination (refer to Section 6.1: Reference Start Date and Study Day).

- Participants who received the second vaccination within the protocol-defined window:
  - This is only applicable to the H4:IC31 and Placebo participants.
  - The allowable window for the Day 56 visit is 56-2 days until 56+14 days from the Day 0 vaccination.
  - Yes:
    - Study day of the Day 56 vaccination >= 54.

    AND
    - Study day of the Day 56 vaccination <= 70.
  - No:
    - Study day of the Day 56 vaccination < 54.

    OR
    - Study day of the Day 56 vaccination > 70.

14. EFFICACY OUTCOMES

14.1. PRIMARY EFFICACY

14.1.1. PRIMARY EFFICACY ENDPOINT

The primary efficacy endpoint is defined as QuantiFERON TB Gold-in-tube (QFT-GIT) conversion, at any time point after Day 84 through end of follow-up, from negative at Screening to positive, using the manufacturer's recommended threshold of ≥ 0.35 IU/mL.

14.1.2. ANALYSIS OF PRIMARY EFFICACY ENDPOINT

The following tables will be presented for the Modified Intent-to-treat analysis set:

- QFT-GIT results at each visit:
  - Number and percentage (%) of participants in each category per visit:
    - Negative.
    - Positive.
    - Missing.
  - Percentage (%) of participants will be calculated relative to the total number of participants in the Modified Intent-to-treat analysis set who have QFT-GIT assessments available per treatment group per visit.

- Compliance to QFT-GIT testing:
  - Number and percentage (%) of participants in each compliance category per visit:
    - Yes.
    - No.
    - Missing.
  - Percentage (%) of participants will be calculated relative to the total number of participants in the Modified Intent-to-treat analysis set expected to have a QFT-GIT assessment available per treatment group per visit (N1).

- QFT-GIT conversion rates, primary endpoint (therefore endpoints occurring after Day 84):
  - Number and percentage (%) of participants in each conversion status category:
    - Yes.
    - No.
    - Missing.
  - Hazard ratio (H4:IC31/comparator) presented:
    - Point estimates (based on the Cox regression model).
    - P-values for the comparison of the estimated hazard ratios of QFT-GIT conversion based on a one-sided log-rank test.
      - H4:IC31 versus Placebo.
      - BCG versus Placebo.
      - H4:IC31 versus BCG (at the request of the sponsor's partner).
  - Vaccine efficacy presented:
    - Point estimate (based on the hazard ratio estimates).
    - 80% two-sided CI based on the hazard ratio estimate from the Cox regression model.
  - This table will be repeated for the Per Protocol, Adjusted Modified Intent-to-treat (First Recall Positive Omit) analysis sets. This table will also be repeated for the adjudication approach (refer to Section 3.3: Changes to Analysis from Protocol).
  - As a sensitivity analysis the content of this table will be repeated in a separate table using interval censoring for the MITT analysis set.

- First QFT-GIT conversion by visit:
  - Number and percentage (%) of participants with first QFT-GIT conversion at each of the scheduled visits.
  - Number of participants at risk for first conversion at each scheduled visit.
  - At risk defined as participants with:
    - A negative QFT-GIT result at the preceding visit without a previous positive QFT-GIT result.
    - A QFT-GIT result available at the relevant visit.
  - This table will be repeated for the Per Protocol analysis set.

- Follow-up time until first QFT-GIT conversion:
  - Number of participants contributing to the total follow-up time (at risk).
  - Cumulative number of participants:
    - Censored (not due to a primary endpoint at the time of the last available non-positive QFT-GIT result).
    - With an event (primary endpoint).
  - The total follow-up time (person-months), as measured from Randomization (1 month = 4 weeks).
  - The Kaplan-Meier event rate presented at each relevant post-Day 84 visit.
  - This table will be repeated for the Per Protocol analysis set.

- Primary endpoints by school/region:
  - Number and percentage (%) of participants who experienced a primary endpoint in each school/region.
- Primary endpoints by site and sex:
  - Number and percentage (%) of participants who experienced a primary endpoint in each site/sex.

The following table will be presented for the Randomized analysis set:

- QFT-GIT conversion rates including all post-Day 0 conversions:
  - Number and percentage (%) of participants in each conversion status category:
    - Yes.
    - No.
    - Missing.
  - Two groups of conversion time points included:
    - Any QFT-GIT conversion (early [Day 84] or post-Day 84) (at risk participants include all participants).
    - Early (Day 84) conversion (at risk participants include all participants).
  - Hazard ratio (H4:IC31/comparator) presented:
    - Point estimates (based on the Cox regression model).
    - P-values for the comparison of the estimated hazard ratios of QFT-GIT conversion based on a one-sided log-rank test.
      - H4:IC31 versus Placebo.
      - BCG versus Placebo.
      - H4:IC31 versus BCG (included at the request of the sponsor's partner).
  - Vaccine efficacy presented:
    - Point estimate (based on the hazard ratio estimates).
    - 80% two-sided CI based on the hazard ratio estimate from the Cox regression model.

The following figures will be presented for the Modified Intent-to-treat analysis set:

- Time on study:
  - Kaplan-Meier plot per treatment group.
  - Cumulative follow-up time as measured from randomization (1 month = 4 weeks).
  - Event is defined as whichever occurs first:
    - Initial QFT-GIT conversion.
    - Early termination/study completion.
  - This figure will be repeated for the Per Protocol analysis set.
- Time to first post-Day 84 QFT-GIT conversion, primary endpoint:
  - Kaplan-Meier plots per treatment group for the following:
    - Time to first post-Day 84 QFT-GIT conversion.
  - Time to first QFT-GIT conversion will be presented in months, measured from Day 84 (1 month = 4 weeks).
    - Censored (at the time of the last available non-positive QFT-GIT result).
  - This figure will be repeated for the Per Protocol analysis set.
- Time to first post-Day 84 QFT-GIT conversion (interval-censored sensitivity analysis):
  - Survival function estimate plot per treatment group based on a life-table analysis.
  - Time to QFT-GIT conversion measured from Day 84.
  - Time to conversion will be presented in 6-month intervals.

The following figure will be presented for the Randomized analysis set:

- Time to First QFT-GIT Conversion (Early or Post-Day 84):
  - Kaplan-Meier plots per treatment group for the following:
    - Time to any QFT-GIT conversion (early or post-Day 84) measured from Day 0.
  - Time to QFT-GIT conversion will be presented in months, measured from Randomization (1 month = 4 weeks).
    - Censored (not due to a primary endpoint at the time of the last available non-positive QFT-GIT result).

The following listing will be presented for the Randomized analysis set:

- QuantiFERON results.

The following QuantiFERON variables, as presented in the planned TLF shells, will be collected on the QuantiFERON and QuantiFERON Re-valuation eCRFs:

- Date of sample collection.
- Qualitative results:
  - Negative.
  - Positive.
- Quantitative Result:
  - QFT-Nil (IU/mL).
  - QFT-Ag (IU/mL).
  - QFT-Mitogen (IU/mL).

14.1.3. DERIVATIONS

Based on the aforementioned, the following variables, as presented in the planned TLF shells, will be derived for post-vaccination visits and/or time points:

- QFT-GIT testing compliance derived per visit:
  - Yes: QFT-GIT assessment date is within the protocol-defined visit window.
  - No: QFT-GIT assessment date is outside the protocol-defined visit window.
  - Missing: The participant is expected to have a QFT-GIT assessment available.
  - Refer to APPENDIX 8: Protocol-defined Visit Windows for the relevant protocol-defined visit windows.
- QFT-GIT result classification at each visit (use the retest result if available). The Investigator's assessment will be used, which is based on the algorithm below.

QFT-GIT Result Classification	QFT_{Nil}	QFT_{Ag} - QFT_{Nil}	$QFT_{Mitogen}$ - QFT_{Nil}
Positive	≤ 8.0	≥ 0.35 (primary analysis threshold) and ≥ 25% of QFT_{Nil} value	Any
Negative		< 0.35 (primary	≥0.5

QFT-GIT Result Classification	QFT_{Nil}	QFT_{Ag} - QFT_{Nil}	$QFT_{Mitogen}$ - QFT_{Nil}
Indeterminate		analysis threshold) OR ≥ 0.35 (primary analysis threshold) and < 25% of QFT_{Nil} value	< 0.5
Indeterminate	> 8.0	Any	Any

- If the QFT-GIT result is indeterminate at any of the visits Day 84, M6, M9, M12, M15, M18, M21, M24, M27 or M30, the QFT-GIT test will be repeated (QUANT2 form in the eCRF used to record the result). If the repeat result is negative or indeterminate, the participant will continue with the study visits as if the participant did not convert, and the result for the corresponding visit will be deemed "negative".

- Any QFT-GIT conversion status:
  - The QFT-GIT conversion status is assigned hierarchically in the order provided below:
    - Yes: Participant has at least one positive QFT-GIT result classification, regardless of missing or indeterminate results at any other visit and regardless of at which visit the positive QFT-GIT result is recorded.
      - Post-Day 84 QFT-GIT conversion: First positive QFT-GIT result classification recorded post-Day 84.
      - Early QFT-GIT conversion: First positive QFT-GIT result classification recorded at Day 84.
    - No: Participant has no positive QFT-GIT result classification and the last available QFT-GIT result classification is negative.
    - Missing: Participant has no positive/negative/indeterminate QFT-GIT result classification available.

- Censored:
  - Participants who do not experience a primary endpoint or early conversion (early conversion is only applicable to the analyses based on the Randomized analysis set), will be censored at the date of their last available, non-positive QFT-GIT result.
  - The following SAS code will be implemented for all Kaplan-Meier analyses, where:

```
PROC LIFETEST DATA = <>;
      TIME Months*Censored(1);
      TEST Treatment_Group;
RUN;
```

    - Censored = 1 represents censored participant.
    - Censored = 0 represents participant who experienced an event.
    - Months represent the available follow-up time (months) per participant since:
      - Day 84 (applicable to analyses based on the mITT and PP analysis set).
      - Randomization (applicable to analyses based on the Randomized analysis set).

- Event:
  - Participants who experience a primary endpoint or early conversion will be indicated as having an event (depending on the relevant table, early converters will be included/excluded from the participants experiencing an event).

- Available follow-up time (months) until first QFT-GIT conversion:
  - The number of months of follow-up time will be derived for each participant based on the date of randomization/Day 84 (depending on the relevant table) and either the censor or event date.
  - 1 month = 4 weeks.
  - For the sensitivity analysis the follow-up time will be rounded to the nearest 6-month interval for any of the following visits:
    - Month 6.
    - Month 12
    - Month 18.
    - Month 24.
  - For the sensitivity analysis the following SAS code will be implemented:

```
PROC LIFETEST DATA = <>  METHOD=lt INTERVALS=(0 to 2 by 0.5)
PLOTS=(s);
      TIME Years*Censored(1);
      FREQ count;
RUN;
```

- Vaccine efficacy is derived as:
  - $VE = 1 - Hazard\ Rate\ Ratio\ (Vaccine/comparator)$
  - The hazard ratio is estimated based on the following Cox regression model:

```
PROC PHREG DATA = <>;
      MODEL Time to Event (Months) * Censor (1) = Treatment Group;
RUN;
```

    - Censor = 1 represents censored participant.
    - Censor = 0 represents participant who experienced an event.
    - Months represent the available follow-up time (months) per participant since randomization.
  - The 80% CI is based on the two-sided hazard ratio confidence interval and will be derived as:
    - $VE_{\text{lower limit}} = 1 - \text{Hazard ratio}_{\text{upper limit}}$
    - $\text{VE}_{\text{upper limit}} = 1 - Hazard\ ratio_{lower\ limit}$
  - The 95% CI is based on the two-sided hazard ratio confidence interval.

- For the sensitivity analysis, interval censoring will be used based on the following code:

```
PROC ICPHREG DATA = <>;
      MODEL (left, right) = Treatment Group /b=pch(NINTERVAL=X);
RUN;
```

    - Left represents left censoring value in months.
    - Right represents right censoring value in months.
    - Left and right censoring values are dependent on where the event is identified:

Visit at Which Primary Event Identified	Left Censoring Value	Right Censoring Value
M6	3	6
M12	6	12
M18	12	18
M24	18	24

14.2. SECONDARY EFFICACY

14.2.1. SECONDARY EFFICACY ENDPOINT

The secondary efficacy endpoint is defined as sustained QFT-GIT conversion without reversion:

- Occurrence of a primary endpoint.
- Sustained conversion without a change in QFT-GIT from positive to negative through 6 months after QFT-GIT conversion, also using the threshold of 0.35 IU/mL.
- Sustained conversion without a change in QFT-GIT from positive to negative through 6 months after QFT-GIT conversion, using the alternative threshold of 0.2 at any time point prior to conversion and > 0.70 at initial post-Day 84 QFT-GIT conversion, and maintains QFT-GIT > 0.7 for 6 months after initial conversion.

A participant will be considered as having a secondary endpoint (at the first conversion date), denoted here as '6-month sustained conversion (per protocol)', if that participant had three consecutive positive QFT-GIT results after Day 84.

14.2.2. ANALYSIS OF SECONDARY EFFICACY ENDPOINT

The following table will be presented for the Modified Intent-to-treat analysis set:

- QFT-GIT 6-month sustained conversion rates:
  - Number and percentage (%) of participants in each conversion status category:
    - Yes.
    - No.
    - Missing.
  - Hazard ratio (H4:IC31/comparator) presented:
    - Point estimates (based on the Cox regression model).
    - P-values for the comparison of the estimated hazard ratios of QFT-GIT 6-month sustained conversion based on a one-sided log-rank test.
      - H4:IC31 versus Placebo.
      - BCG versus Placebo.
      - H4:IC31 versus BCG (at the request of the sponsor's partner).
  - Vaccine efficacy presented:
    - Point estimate (based on the hazard ratio estimate).
    - 80% two-sided CI based on the hazard ratio estimate from the Cox regression model.
  - This table will be repeated for the alternative threshold value.
  - These tables (based on the original threshold as well as the alternative threshold) will be repeated for the Per Protocol analysis set. This table (based on the original threshold) will also be repeated for the Adjusted Modified Intent-to-treat (First Recall Positive Omit) analysis set and the adjudication approach (refer to Section 3.3: Changes to Analysis from Protocol).
  - As a sensitivity analysis both of these tables (original threshold and the alternative threshold outputs) will be repeated in separate tables using interval censoring for the MITT analysis set.

The following figures will be presented for the Modified Intent-to-treat analysis set:

- Time to 6-month sustained QuantiFERON conversion:
  - Kaplan-Meier plots per treatment group for the following:
    - Time to first of three consecutive post-Day 84 QFT-GIT positive results.
  - Time to sustained QFT-GIT conversion will be presented in months, measured from Day 84 (1 month = 4 weeks) to the date of the first of three consecutively positive QFT-GIT results.
  - Participants who do not convert are censored at their last negative QFT-GIT.
  - This figure will be repeated for the alternative threshold value.
  - Both these figures (original and alternative threshold outputs) will be repeated for the Per Protocol analysis set.

The following QuantiFERON variables, as presented in the planned TLF shells, will be collected on the QuantiFERON and QuantiFERON Re-valuation eCRFs:

- Date of sample collection.
- Qualitative results:
  - Negative.
  - Positive.
- Quantitative Result:
  - QFT-Nil (IU/mL).
  - QFT-Ag (IU/mL).
  - QFT-Mitogen (IU/mL).

14.2.3. DERIVATIONS

Based on the aforementioned, the following variables (refer to Section 14.1.2: Analysis of Primary Efficacy Endpoint), as presented in the planned TLF shells, will be derived at 3 and 6 months post first QFT-GIT conversion for participants who have a post-Day 84 QFT-GIT conversion (primary endpoint):

- QFT-GIT result classification (refer to Section 14.1.3: Derivations).
- QFT-GIT 6-month sustained conversion status:
  - Yes: At both 3 and 6 months following first QFT-GIT conversion, QFT-GIT result classifications are derived as positive.
  - No: At 3 and/or 6 months following first QFT-GIT conversion, QFT-GIT result classification is derived as negative.
  - Missing: None of the aforementioned QFT-GIT result classifications (yes, no) has been assigned at 3 or 6 months post-conversion, QFT-GIT result classification is derived as missing.
- Censored:
  - Participants who do not experience an initial QFT-GIT conversion will be censored at the date of their last available, non-positive QFT result.
  - Converters who do not have a sustained conversion will be censored at their last available QFT-GIT result.
  - Converters with only a 3-month post-conversion result and no 6-month post-conversion result will be censored at:
    - The initial conversion visit if the 3-month post-conversion result is positive.

- The 3-month post-conversion visit if that 3-month post-conversion result is negative.

o The following SAS code will be implemented for all Kaplan-Meier analyses, where:

```
PROC LIFETEST DATA = <>;
      TIME Months*Censored(1);
      TEST Treatment_Group;
RUN;
```

- Censored = 1 represents censored participants.
- Censored = 0 represented participants who experienced an event (sustained QFT-GIT conversion).
- Months represent the available follow-up time (months) per participant since Day 84.

- Event:
  - o Participants, who experience a sustained QFT-GIT conversion for three consecutive visits will be indicated as having an event.

- Vaccine efficacy is derived as:
  - o $VE = 1 - Hazard\ Ratio\ (Vaccine/comparator)$
  - o The hazard ratio is estimated based on the following Cox regression model:

```
PROC PHREG DATA = <>;
      MODEL Time to Event (Months) * Censor (1) = Treatment Group;
RUN;
```

- Censor = 1 represents censored participant.
- Censor = 0 represents participant who experienced an event.
- Months represent the available follow-up time (months) per participant since Day 84.

  - o The 80% CI is based on the two-sided hazard ratio confidence interval and will be derived as:
    - $VE_{\text{lower limit}} = 1 - \text{Hazard ratio}_{\text{upper limit}}$
    - $\text{VE}_{\text{upper limit}} = 1 - Hazard\ ratio_{lower\ limit}$
  - o The 95% CI is based on the two-sided hazard ratio confidence interval.

14.3. EXPLORATORY EFFICACY

14.3.1. EXPLORATORY EFFICACY ENDPOINT

The following exploratory analyses will be performed:

- Prevention of *Mtb* infection as measured by rates of reversion.
- Effect of alternative QFT-GIT test threshold values on rates of QFT-GIT conversion and reversion.
- To explore trends in QFT-GIT prolonged/sustained conversions and late reversions (i.e., more than 6 months post initial conversion) in early QFT-GIT converters (i.e., among those who converted at Month 6 or Month 12 of follow-up).

Some analyses are based on subsets of participants determined by a post-randomization event, and some involve participants who experience differential follow-up. Given these types of analyses have the potential to be biased, additional supportive analyses, such as principal stratification, may be utilized to better understand a potential vaccine effect.

14.3.2. ANALYSIS OF EXPLORATORY EFFICACY ENDPOINT

The following tables will be presented for the Modified Intent-to-treat analysis set:

- QuantiFERON levels (IU/mL) upon and following first positive QFT-GIT result:
  - Default summary statistics for QFT-GIT results at the following time points:
    - First positive QFT-GIT result:
      - The p-value based on the Mann-Whitney-Wilcoxon test will be used for pair-wise comparisons between treatment groups.
    - 3 months-post first positive QFT-GIT result:
      - Number and percentage (%) of participants with a negative QFT-GIT.
    - 6 months-post first positive QFT-GIT result:
      - Number and percentage (%) of participants with a negative QFT-GIT.
  - This table is to include all participants with at least one positive post-Day 84 QFT-GIT result.
  - This table will be repeated for the Per Protocol analysis set.
- First QuantiFERON reversion:
  - Number of participants with first QFT-GIT negative value within the following categories will be included:
    - Within 3 months post-conversion.
    - Within 6 months post-conversion.
    - At any time during follow-up.
  - At risk defined as participants with:
    - A primary endpoint.
    - A QFT-GIT result available at the relevant visit within 6 months (for the first two lines) or at any time post-initial conversion (for the third line) after the primary endpoint occurrence.
  - This table will be repeated for the Per Protocol analysis set.
- Alternative QFT-GIT thresholds:
  - Number and percentage of participants who EVER experienced the following alternative threshold values (i.e., at any post-Day 84 timepoint):
    - ≥ 0.20.
    - < 0.2 at any time point prior to conversion and > 0.70 at any time point post-Day 84.
    - > 0.70.
    - > 4.0.
  - Vaccine efficacy presented:
    - Point estimate (based on the conditional binomial distribution).
    - 95% CI (based on the conditional binomial Clopper-Pearson method with mid-p correction).
  - This table will be repeated for the Per Protocol analysis set.
- Trends in QFT-GIT sustained conversions and end-of-study reversions:
  - Number and percentage (%) of participants in each category:
    - Participants who were negative at Month 24 or the Month 24 call-back visit. Percentages (%) will be calculated based on the number of participants with non-missing Month 24 or Month 24 call-back values.
    - Participants who never converted or converted with reversion. Percentages (%) will be calculated based on the number of participants who did not have two missing QFT-GIT values within 6 months of post-initial conversion.

- Participants who never converted or converted with reversion and have non-positive (i.e., negative or missing) six-month post-initial-conversion QFT-GIT values. Percentages (%) will be calculated based on the number of participants who did not have two missing QFT-GIT values within 6 months of post-initial conversion.
- Participants who never converted or converted with reversion and have non-positive (i.e., negative or missing) end of study QFT-GIT values. Percentages (%) will be calculated based on the number of participants who did not have the following combination of QFT-GIT values: +/m/m, +/+/m/m or +/m/m/m where + = positive and m = missing.

o Comparisons of proportions between treatment groups for each category will be performed based on the Pearson chi-square test.
o Vaccine efficacy presented:
- Point estimate (based on the conditional binomial Clopper-Pearson method with mid-p correction).
- 95% CI (based on the conditional binomial Clopper-Pearson method with mid-p correction).

- QFT-GIT end of study sustained conversion rates:
  - o Number and percentage (%) of participants in each conversion status category:
    - Yes.
    - No.
    - Missing.
  - o Hazard ratio (H4:IC31/comparator) presented:
    - Point estimates (based on the Cox regression model).
    - P-values for the comparison of the estimated hazard ratios of QFT-GIT end of study sustained conversion based on a one-sided log-rank test.
      - H4:IC31 versus Placebo.
      - BCG versus Placebo.
      - H4:IC31 versus BCG (at the request of the sponsor's partner).
  - o Vaccine efficacy presented:
    - Point estimate (based on the hazard ratio estimate).
    - 80% two-sided CI based on the hazard ratio estimate from the Cox regression model.
  - o This table will be repeated for the Per Protocol analysis set.

- Participants who converted, reverted, and time to conversion among reverters and non-reverters:
  - o Number and percentage (%) of participants who:
    - Converted.
    - Converted and later reverted.
    - Converted and did not revert.
  - o The median time and the quartile 1 (Q1) and 3 (Q3) values will be displayed for:
    - Time to conversion among all converters.
    - Time to conversion among all reverters.
    - Time to conversion among non-reverters.
  - o This table will be repeated for the Per Protocol analysis set.

- QFT-GIT positivity patterns over time from initial conversion timepoint onwards:
  - o Number and percentage (%) of participants, summarized for the following patterns in the order specified below:
    - +/+/+/+
    - +/+/+
    - +/+/m

- +/m/+
- +/m/m/m
- +/+/+/-
- +/-/+/+
- +/+/-/+
- +/+/-
- +/-/+
- +/-/m
- +/-/-/+
- +/-/-
- +/-/+/-
- +/m/-/-
- +/-/-/-
- -/-/-/-
- This table will also be repeated for the Per Protocol analysis set.

- Clinical TB diagnosis:
  - Number and percentage of participants in each of the following categories:
    - Participants who received at least one TB work-up:
    - Bacteriologically-confirmed TB.
    - Clinical TB (based on the Investigator's assessment).
  - The total number of TB work-ups performed.
  - This table will be repeated for the Per Protocol analysis set.

The following figures will be presented for the Modified Intent-to-treat analysis set:

- Quantitative QFT-GIT results following initial conversion:
  - Box-and-whisker plots per treatment group for the following:
    - QFT-GIT result at 0, 3 and 6 months since first QFT-GIT conversion (reference line at 0.35 IU/mL to be included).
    - QFT-GIT Change from Baseline at 3 and 6 months since first QFT-GIT conversion (reference line at 0 IU/mL to be included).
    - The number of participants at 3 and 6 months since post-initial conversion whose results fell below 0.35 should also be displayed.
  - This figure will include all participants with at least one positive QFT-GIT result post-Day 84.
  - This figure will be repeated for the Per Protocol analysis set.

- Time to first QuantiFERON reversion:
  - Kaplan-Meier plot per treatment group.
  - Time to first reversion will be presented in months, measured from primary endpoint occurrence (1 month = 4 weeks).
  - Participants who do not revert (Month 24 call-back visit also considered) will be censored at the time of the last positive QFT-GIT result.
  - This figure will be repeated for the Per Protocol analysis set.

- Time to first QFT-GIT conversion among those who ever reverted (Month 24 call-back visit also considered):
  - Kaplan-Meier plots per treatment group for the following:
    - Time to post-Day 84 QFT-GIT conversion.

- Time to QFT-GIT conversion will be presented in months, measured from Day 84 (1 month = 4 weeks) to the date of the first QFT-GIT conversion of those who ever reverted.
- Participants who do not convert are censored at their last negative QFT-GIT.

This figure will be repeated for the Per Protocol analysis set.

- Time to end of study sustained QuantiFERON conversion:
  - Kaplan-Meier plots per treatment group for the following:
    - Time to first of three (M18 or M24 initial conversion) or four (M6 or M12 initial conversion) consecutive post-Day 84 QFT-GIT positive results.
  - Time to sustained QFT-GIT conversion will be presented in months, measured from Day 84 (1 month = 4 weeks) to the date of the first of three (M18 or M24 initial conversion) or four (M6 or M12 initial conversion) consecutively positive QFT-GIT results.
  - Participants who do not convert are censored at their last non-positive QFT-GIT.
  - This figure will be repeated for the Per Protocol analysis set.

The following listing will be presented for the randomized analysis set:

- Clinical TB diagnosis and assessment.
- QuantiFERON positivity patterns over time.
- Participants who QFT-GIT converted, reverted and then converted again.

The following QuantiFERON variables, as presented in the planned TLF shells, will be collected on the QuantiFERON and QuantiFERON Re-valuation eCRFs:

- Date of sample collection.
- Qualitative results:
  - Negative.
  - Positive.
- Quantitative Result:
  - QFT-Nil (IU/mL).
  - QFT-Ag (IU/mL).
  - QFT-Mitogen (IU/mL).

The following TB diagnosis variables, as presented in the planned TLF shells, will be collected on the TB Assessments – First Sputum Sample and TB Assessments – Second Sputum Sample eCRFs:

- Date of sputum sample collection.
- Sputum smear result:
  - Acid- Fast Bacilli (AFB) seen:
    - Scanty.
    - 1+.
    - 2+.
    - 3+.
  - No AFB seen.
  - No result.
- Sputum culture result:
  - Mycobacterium positive.
  - Mycobacterium negative.

- Contaminated.
- No result.

- Differential test for positive Culture:
  - MTB.
  - Mycobacterium other than tuberculosis (MOTT) (specify).

- GeneXpert result:
  - Invalid.
  - No result.
  - MTB not detected.
  - MTB detected.

The following TB diagnosis variables, as presented in the planned TLF shells, will be collected on the TB Clinical Evidence eCRF:

- TB clinical signs and symptoms:
  - Unexplained cough for more than two weeks.
  - Fever for more than two weeks.
  - Night sweats for more than two weeks.
  - Unexplained weight loss.
  - Recent history of Hemoptysis.
  - Other (specify).

The following TB diagnosis variables, as presented in the planned TLF shells, will be collected on the Chest X-Ray eCRF:

- Chest x-ray performed:
  - Yes.
  - No.

- Chest x-ray result:
  - Normal.
  - Abnormal.

The following clinical TB diagnosis variable, as presented in the planned TLF shells, will be collected on the TB Case Assessment eCRF:

- Was a clinical case of TB diagnosed?

14.3.3. DERIVATIONS

Based on the aforementioned, the following variables, as presented in the planned TLF shells, will be derived for post-vaccination visits and/or time points:

- QFT-GIT result classification (refer to Section 14.1.3: Derivations). Substitute the primary analysis threshold value with the alternative threshold value.

- Available follow-up time (months) until QFT-GIT:
  - Months represent the available follow-up time (months) per participant since first QFT-GIT conversion.

- Negative at Month 24:
  - Participants who are negative at Month 24 or who initially converted at Month 6 or Month 12 and are negative at the ≥ 24 Month call-back visit.

- Prevention of conversion OR conversion with reversion:
  - Participants who are consistently negative OR
  - Participants who have a negative QFT-GIT value within six months after their initial conversion (i.e., +/-/-, +/+/-, +/-/+, +/m/-, +/-/m).

- Prevention of conversion OR conversion with reversion and non-positive (i.e. negative or missing) QFT-GIT results at six-months post-initial-conversion:
  - Participants who are consistently negative OR
  - Participants who have a negative QFT-GIT value at the last available testing timepoint within six months after their initial conversion (i.e., +/-/-, +/+/-, +/m/-, +/-/m).

- Prevention of conversion OR conversion with reversion and non-positive (i.e., negative or missing) QFT-GIT results at the end of the study:
  - Participants who are consistently negative throughout the study OR
  - Participants who initially converted at Month 18 or Month 24 (i.e., +/-/-, +/+/-, +/m/-, +/-/m) and later reverted OR
  - Participants who initially converted at Month 6 or Month 12 and have a call-back Month 24 visit that is negative (i.e., +/-/-/-, +/+/-/-, +/+/+/-, +/-/+/-, +/-/m/-, +/m/-/-, +/m/m/-, +/+/m/-).

- QFT-GIT end of study sustained conversion status:
  - Yes: At 3 and 6 months following first QFT-GIT conversion AND at the Month 24 call-back visit (if applicable), QFT-GIT result classifications are derived as positive.
  - No: At 3 and/or 6 months following first QFT-GIT conversion and/or at the Month 24 call-back visit (if applicable), QFT-GIT result classification is derived as negative.
  - Missing: None of the aforementioned QFT-GIT result classifications (yes, no) has been assigned at 3 or 6 months post-conversion or at the Month 24 call-back visit, QFT-GIT result classification is derived as missing.

- The confidence interval for VE is calculated using the conditional binomial method (Clopper-Pearson method with mid-p correction) as follows:
  The number of participants with a conversion (n_A) in one of the treatment groups (for example H4:IC31) and the number (n_B) of participants with a conversion in another treatment group (for example Placebo), are assumed to have Independent Poisson distributions with rate parameters λ_A and λ_B, respectively, but inference is conditional on the total number of conversions, $n = n_A + n_B$. Conditional on n, n_A has a Binomial distribution, Bin(n,π), where

$$\pi = \frac{\lambda_A F_A}{\lambda_A F_A + \lambda_B F_B} = \frac{\theta F_A}{\theta F_A + F_B}$$

  $\theta = \lambda_A \backslash \lambda_B$ and F_A and F_B are the total lengths of follow-up across all subjects in the relevant treatment groups (Treatment Group A/Treatment Group B), that is, F = Σ (Duration of VE Follow-up Period [Days]).

A point estimate and exact two-sides 95% CI (π_L,π_U) for π is then calculated (Clopper - Pearson method with mid-p correction) based on the number of participants with a conversion in one of the treatment groups (for example H4:IC31), relative to the total number of participants $n = n_A + n_B$ who had at a conversion in either of the two compared treatment groups. The following SAS® code will be used:

```
PROC FREQ DATA = <>;
        TABLE Events / BINOMIAL (midp P=0.05);
RUN;
```

Based on the exact 95% CI for π, an exact 95% CI (θ_L,θ_U), for the rate ratio θ is then calculated by solving the equations:

$$\frac{\theta_L F_A}{\theta_L F_A + F_B} = \pi_L$$

$$\frac{\theta_U F_A}{\theta_U F_A + F_B} = \pi_U$$

Solving θ_L and θ_U yields:

$$\theta_L = \left(\frac{\pi_L}{1 - \pi_L} \right)\left(\frac{F_B}{F_A} \right)$$

$$\theta_U = \left(\frac{\pi_U}{1 - \pi_U} \right)\left(\frac{F_B}{F_A} \right)$$

Finally, the exact 95% CI (VE_L, VE_U) for VE is calculated as

$VE_L = (1 - \theta_U)$

$VE_U = (1 - \theta_L)$

In summary, the VE point estimate and confidence limits for the aforementioned binomial proportion (π) will be substituted in the following formula in order to obtain the corresponding confidence limits for the VE:

$$VE = \left(\frac{(\pi) F_B}{(1 - \pi) F_A} \right)$$

Where the lower confidence limit for VE is obtained by substituting the upper confidence limit for π in the above formulae, and the upper confidence limit for VE is obtained by substituting the lower confidence limit for π in the above formula.

- Bacteriologically confirmed TB:
  - Positive culture result (Mycobacterium tuberculosis positive)
    OR
  - Positive GeneXpert result (MTB detected) (with or without clinical symptoms and/or positive chest x-ray).

15. IMMUNOGENICITY

15.1. PERIPHERAL BLOOD MONONUCLEAR CELLS (PBMC) INTRACELLULAR CYTOKINE STAINING (ICS)

The following tables are planned for presentation (based on the Safety analysis set, in the Safety and Immunogenicity Cohort):

- Percent antigen-specific T cell negative control-subtracted ANY cytokine response and change from Baseline.
  - Only the derived ANY cytokine combination will be included in this table.
  - This table will include descriptive statistics and 95% confidence interval (CI) for the median based on order statistics at each applicable visit as well as the change from Baseline per T cell and stimulation antigen (including a 'total' stimulation antigen for Ag85B and TB10.4 combined).
  - This table will be repeated for the negative-control ANY cytokine combination.
- Percent antigen-specific T cell negative-control subtracted Positive (G,2) cytokine response and change from Baseline.
  - Only the derived Positive (G,2) cytokine combination will be included in this table.
  - This table will include descriptive statistics and 95% confidence interval (CI) for the median based on order statistics at each applicable visit as well as the change from Baseline per T cell and stimulation antigen (including a 'total' stimulation antigen).
  - This table will be repeated for the negative control Positive (G,2) cytokine combination.
- Number (percentage) of responders based on the derived Positive (G,2) cytokine combination.
  - This is to include the number and percentage of responders (Refer to Section 15.1.2: Responder Status) at each visit per T cell and stimulation antigen.
  - Percentages are based on the number of participants in the Safety analysis set within each treatment group with data available to determine responder status.
  - P-values are also to be included and are based on a Fisher's EXACT test comparing each of the treatment groups.
- Comparisons of median negative control-subtracted ANY cytokine response.
  - Only the derived ANY cytokine combination will be included in this table.
  - This table will include the number of participants who have a negative control-subtracted negative-set-to-zero value available as well as the median of these values.
  - P-values based on the Wilcoxon-Mann Whitney test for pair-wise comparisons between treatment groups will be performed.
- Comparisons of median negative control-subtracted Positive (G,2) cytokine response.
  - Only the derived Positive (G,2) cytokine combination will be included in this table.
  - This table will include the number of participants who have a negative control-subtracted negative-set-to-zero value available as well as the median of these values.
  - P-values based on the Wilcoxon-Mann Whitney test for pair-wise comparisons between treatment groups will be performed.

The following figures are planned for presentation (based on the Modified Intent-to-treat analysis set):

- Antigen-specific negative control-subtracted ANY cytokine response:
  - Dot plot of antigen-specific negative control-subtracted ANY cytokine response per study day.
  - One figure will be prepared for each stimulation antigen, including the derived total (Ag85B and TB10.4) stimulation antigen response; the median response will be represented by a horizontal line per treatment group and study day.
  - Separate plots will be created per T cell (CD4+/CD8+).
  - This figure will be repeated for the negative control ANY cytokine combination.
  - Different symbols will be used to differentiate between responders (closed circles), non-responders (cross) and missing responder status (triangle) as based on the derived Positive (G,2) cytokine combination responder status.
- Antigen-specific negative control-subtracted Positive (G,2) cytokine response:
  - Dot plot of antigen-specific negative control-subtracted Positive (G,2) cytokine response per study day.
  - One figure will be prepared for each stimulation antigen, including the derived total (Ag85B and TB10.4) stimulation antigen response; the median response will be represented by a horizontal line per treatment group and study day.
  - Separate plots will be created per T cell (CD4+/CD8+).
  - This figure will be repeated for the negative control Positive (G,2) cytokine combination.
  - Different symbols will be used to differentiate between responders (closed circles), non-responders (cross) and missing responder status (triangle) as based on the derived Positive (G,2) cytokine combination responder status.
- Antigen-specific negative control-subtracted ANY cytokine median response:
  - Line plot of antigen-specific negative control-subtracted ANY cytokine median response per study day. Bars will be included, representing the first and third quartile per study day.
  - One figure will be prepared for each stimulation antigen, including the derived total (Ag85B and TB10.4) stimulation antigen response; the median response will be represented by a dot and connected with a horizontal line across study days per treatment group.
  - Separate plots will be created per T cell (CD4+/CD8+).
  - This figure will be repeated for the negative control ANY cytokine combination.
- Antigen-specific negative control-subtracted Positive (G,2) cytokine median response:
  - Line plot of antigen-specific negative control-subtracted Positive (G,2) cytokine median response per study day. Bars will be included, representing the first and third quartile per study day.
  - One figure will be prepared for each stimulation antigen, including the derived total (Ag85B and TB10.4) stimulation antigen response; the median response will be represented by a dot and connected with a horizontal line across study days per treatment group.
  - Separate plots will be created per T cell (CD4+/CD8+).
  - This figure will be repeated for the negative control Positive (G,2) cytokine combination.
- Total (Ag85B and TB10.4) negative control-subtracted ANY cytokine response:
  - Stacked bar plot of each stimulation antigen's median negative control-subtracted ANY cytokine response per study day.
  - Separate plots will be created per T cell (CD4+/CD8+).
- Total (Ag85B and TB10.4) negative control-subtracted Positive (G,2) cytokine response:

- Stacked bar plot of each stimulation antigen's median negative control-subtracted Positive (G,2) cytokine response per study day.
- Separate plots will be created per T cell (CD4+/CD8+).

- Antigen-specific negative control-subtracted polyfunctional profile plots:
  - Separate plots will be created per cytokine combinations of interest:
    - CD4+: IFN-g, IL-2, TNF, CD154.
    - CD4+: IFN-g, IL-2, IL-17, IL-22.
    - CD8+: IFN-g, IL-2, TNF, CD107a.
  - Dot plot of participants' negative control-subtracted cytokine response per single-gate on the left hand side. Dot plot of participants' negative control-subtracted ANY cytokine response on the right hand side. The median response will be represented by a horizontal line per treatment group and cytokine combination.
  - These figures will be repeated for the negative control.

The following listings are planned for presentation (based on the Safety analysis set):

- Percent antigen-specific T cell negative control-subtracted cytokine response and change from Baseline:
  - Only derived cytokine combinations will be included in this listing.

- Percent antigen-specific T cell negative control-subtracted ANY cytokine response and total (Ag85B and TB10.4) vaccine response:
  - Only derived cytokine combinations will be included in this listing.

- ICS responder status based on the Positive (G,2) response:
  - The responder status for each antigen will be displayed, including the overall status.

The following PBMC ICS variables, as presented in the planned TLF shells, will be contained in the data received from Aeras:

- Stimulation antigen:
  - Ag85B.
  - BCG.
  - TB10.4.
  - Negative control:
    - DMSO for Ag85B and TB10.4.
    - R10 for BCG.

- T cell:
  - CD4+.
  - CD8+.

- Cell counts and percentages (including a total cell count) for each possible combination (alone and in combination with all other cytokines) of the following cytokines per stimulation antigen, study day and participant:
  - IFN-γ (+/-).
  - TNF (+/-).
  - IL-2 (+/-).
  - IL-17A (+/-).
  - IL-22 (+/-).
  - CD154 (+/-).
  - CD107a (+/-).

15.1.1. DERIVATIONS

15.1.1.1. Negative control-subtracted Cytokine Response

The negative control results are sometimes referred to as the background data. For all immunology presentations, the negative control results are subtracted from the active stimulation antigen results. This result is referred to as the negative control-subtracted response.

15.1.1.2. Single Positive CD107a

The single positive CD107a cytokine combination (for example: APBNGN2N4N17NTN or APBNGN2N17N22NTN), per antigen, is excluded entirely from the Analysis Data Model (ADaM) ICS Result (ADZI) dataset.

Since there are 126* cytokine combinations (128* cytokine combinations in total, excluding the all negative and the single positive CD107a cytokine combinations) available to be presented on a polyfunctional figure, it would not be possible to present all combinations on a single figure. Therefore, a subset of four cytokines is to be presented on one figure. The figure presenting the IFN-g, IL-2, TNF and CD107a subset only include 14 polyfunctional combinations on the x-axis instead of the usual 15 combinations, since the last column (IFN-g - IL-2- TNF- CD107a+) is omitted from the figure.

15.1.1.3. Total Number of Cells

The ICS Total number of cells per participant, per day, per T cell, per antigen does include all 128* cytokine combinations, therefore the single positive CD107a cytokine combination is included in the ICS Total number of cells. The ICS Total number of cells for each cell type is available in the RAW data file and is not recalculated as the sum of all cytokine combinations. The ICS Total number of cells from the RAW dataset:

- Time/Singlets/Viable CD3+/Lymphocytes/Aggregate 1/Aggregate 2/CD4+,Count for CD4.
- Time/Singlets/Viable CD3+/Lymphocytes/Aggregate 1/Aggregate 2/CD8+,Count for CD8.

15.1.1.4. ANY Response

The 'ANY' (%) result per participant, T cell type, stimulation antigen and visit are derived as:

- $\sum Cell\ percentages\ (\%)\ that\ respond\ (positive)\ at\ the\ cytokine\ level.$

The single positive CD107a and all negative combinations should be excluded from this derivation.

15.1.1.5. Total Stimulation Antigen Result

The total stimulation antigen result per participant, T cell type and visit is derived as:

- $\sum 'ANY'(\%)\ results\ of\ Ag85B\ and\ TB10.4\ \ antigens\ (excluding\ negative\ control\ and\ BCG).$

15.1.1.6. Positive (G,2)

The 'Positive (G,2)' (%) result per participant, T cell type, stimulation antigen and visit is derived as:

- $\sum Cell\ percentages\ (\%)\ where\ IFN-g\ and/or\ IL-2\ are\ positive.$

15.1.2. RESPONDER STATUS

To determine the responder status the following steps will be followed:

- Per participant, T cell type, stimulation antigen (including negative control) and visit, derive:
  - Positive (G,2).
  - Negative (G,2):
    - *Total Cell Count – Positive (G,2).*
  - The applicable cytokines are: IFN-g (G) and IL-2 (2).
- These results and the negative control results (positive and negative cell counts) will then be compared at each visit per participant, T cell type and stimulation antigen, using the Fisher's EXACT test (refer to Section 5.8.5: Fisher's Exact Test in the Figure guidelines).
- P-values will be adjusted for multiplicity by using PROC MULTTEST (Holm Method). The p-values are adjusted across antigens, therefore at a T cell type, by visit-level for each participant.
- Step 1: Determine whether the number of cells responding to the active antigen stimulation is statistically significantly more than the number of cells responding to the negative control stimulation at Baseline (Day 0).
  - One-sided adjusted p-value >= 0.05 indicates that the number of cells responding to the active antigen stimulation is not statistically more than the number of cells responding to the negative control stimulation.
    - Participant is classified as a non-responder at Baseline (Day 0).
  - One-sided adjusted p-value < 0.05 indicates that the number of cells responding to the active antigen stimulation is statistically more than the number of cells responding to the negative control stimulation.
    - Participant is classified as a responder at Baseline (Day 0).
- Step 2: Determine whether the number of cells responding to the active antigen stimulation is statistically significantly more than the number of cells responding to the negative control stimulation, at Day 70.
  - One-sided adjusted p-value >= 0.05 indicates that the number of cells responding to the active antigen stimulation is not statistically more than the number of cells responding to the negative control stimulation.
    - Participant is classified as a non-responder at Day 70.
  - One-sided adjusted p-value < 0.05 indicates that the number of cells responding to the active antigen stimulation is statistically more than the number of cells responding to the negative control stimulation
    - Participant is classified as a responder at Day 70.

- Determine the responder status post-Baseline when taking Baseline (Day 0) into account:

Baseline (Determined in Step 1)	Day 70 (Determined in Step 2)	Responder Status
Non-responder	Non-responder	Non-responder
Non-responder	Responder	Responder
Responder	Non-responder	Non-responder
Responder	Responder	Determine responder status by means of the odds ratio

- Determine the odds ratio for results at Baseline. If the negative control positive count is zero, the odds ratio will be undefined. In these cases the positive negative control count should be imputed to 1 in order to determine an odds ratio.
- Determine the odds ratio for results at Day 70. If the negative control count is zero, the odds ratio will be undefined. In these cases the positive negative control count should be imputed to 1 in order to determine an odds ratio.
- Perform the Breslow-Day test:
  - Test for homogeneity of odds ratio at Day 70 and Baseline (Day 0).
  - P-value >= 0.05 indicates that the odds ratio at Baseline (Day 0) and Day 70 do not differ statistically significantly.
    - Participant classified as a non-responder at the relevant post-Baseline visit.
  - P-value < 0.05 indicates that the odds ratio at Baseline (Day 0) and Day 70 visit differ statistically significantly.
    - Difference in log odds ratio should be evaluated in order to determine the responder status at Day 70.
- Calculate the difference in the log of the odds ratios at Day 70 and Baseline (Day 0).
  - Difference in log odds ratio = log(odds ratio at Day 70) - log(odds ratio at Baseline [Day 0]).
- Determine the responder status based on the Breslow-Day and difference in log odds ratio for cases where the Baseline (Day 0) and Day 70 visit was determined as responders:

Breslow-Day test p-value	Difference in log odds ratio	Responder status
>= 0.05	<0	Non-responder
>=0.05	>0	Non-responder
<0.05	<0	Non-responder
<0.05	>0	Responder

The aforementioned steps will be implemented to determine the data record-level response per participant, T cell type, stimulation antigen (excluding negative control) and visit. In order to determine the response per participant at a day-level and therefore across T cell type and stimulation antigen, the following conventions will be used:

- Per participant and visit, if all records have a record-level responder status of non-responder, the day level responder status is determined as a non-responder.

- Per participant and visit, if at least one of the records has a record-level responder status of responder, the day-level responder status is determined as responder.

The overall responder status is determined as a single responder status per participant across T cell types, stimulation antigens and visits and the following conventions will be used to determine the overall responder status:

- Per participants, if all days have a day-level responder status of non-responder the overall responder status is determined as non-responder.
- Per participants, if at least one of the days has a day-level responder status of responder, the overall responder status is determined as responder.

As the Baseline responder status is used to determine the post-Baseline responder status, it might be possible that not all participants have sufficient data at Baseline (Day 0) or the relevant post-Baseline visit (Day 70) to determine the responder status. These participants will be presented in the figures by means of a different symbol (i.e. triangle) to indicate that the responder status could not be determined.

15.2. WHOLE BLOOD ICS

The following tables are planned for presentation (based on the Safety analysis set, in the Safety and Immunogenicity Cohort). Aeras will be responsible for performing this analysis.

- Percent antigen-specific T cell negative control-subtracted cytokine response and change from Baseline.
- Number (percentage) of responders.
- Comparisons of median negative control-subtracted cytokine response.

These tables will be provided for the following cytokine combinations (including repeat tables for the negative control for each cytokine combination):

- CD4 cells producing Positive (G,2,T,17,22) cytokine combination.
- CD4 cells producing Positive (G,2,T) cytokine combination.
- CD8 cells producing Positive (G,2,T,17,22) cytokine combination.
- CD8 cells producing Positive (G,2,T) cytokine combination.
- CD4 cells producing Positive (17) cytokine combination.
- CD4 cells producing Positive (22) cytokine combination.

The following listings are planned for presentation (based on the Safety analysis set):

- Percent antigen-specific T cell negative control-subtracted cytokine response and change from Baseline:
  - Only derived cytokine combinations will be included in this listing.
- Percent antigen-specific T cell negative control-subtracted cytokine response and total (Ag85B and TB10.4) vaccine response:
  - Only derived cytokine combinations will be included in this listing.
- ICS responder status based on each derived cytokine response:
  - The responder status for each antigen will be displayed, including the overall status.

The following whole blood ICS variables, as presented in the planned TLF shells, will be contained in the data:

- Stimulation antigen:
  - Ag85B.
  - BCG.
  - TB10.4.
  - Negative control:
    - UNS.
- T cell:
  - CD4+.
  - CD8+.
- Cell counts and percentages (including a total cell count) of the following cytokines per stimulation antigen, study day and participant:
  - IFN-γ and/or TNF and/or IL-2.
  - IFN-γ and/or TNF and/or IL-2 and/or IL-17 and/or IL-22.
  - IL-17.
  - IL-22.

15.2.1. DERIVATIONS

15.2.1.1. Positive (G,2,T,17,22)

The 'Positive (G,2,T,17,22)' (%) result per participant, T cell type, stimulation antigen and visit is derived as:

$\sum Cell\ percentages\ (\%)\ where\ IFN-g\ and/or\ IL-2\ \ and\ /\ or\ TNF\ and\ /\ or\ IL\text{-}17\ and\ /\ or\ IL\text{-}22\ are\ positive.$

15.2.1.2. Positive (G,2,T)

The 'Positive (G,2,T)' (%) result per participant, T cell type, stimulation antigen and visit is derived as:

$\sum Cell\ percentages\ (\%)\ where\ IFN-g\ and/or\ IL-2\ \ \text{and}\ /\ or\ TNF\ are\ positive.$

15.2.1.3. Positive (17)

The 'Positive (17)' (%) result per participant, stimulation antigen and visit for CD4 T cells is derived as:

$\sum Cell\ percentages\ (\%)\ where\ IL-17\ \ is\ positive.$

15.2.1.4. Positive (22)

The 'Positive (22)' (%) result per participant, stimulation antigen and visit for CD4 cells is derived as:

$\sum Cell\ percentages\ (\%)\ where\ IL-22\ \ is\ positive.$

15.2.2. RESPONDER STATUS

The same method as for the PBMC ICS analysis will be used (refer to Section 15.1.2: Responder Status). Substitute 'Positive (G,2)' with each applicable derived cytokine combination.

16. SAFETY OUTCOMES

Summary and presentation of safety data will be based on the Safety analysis set, unless otherwise noted.

16.1. ADVERSE EVENTS (AES)

Adverse events (AEs) will be coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 16.1.

The following AE variables, as presented in the planned TLF shells, will be collected on the Adverse Event (AE) eCRF:

- Verbatim term (eCRF).
- Date started.
- Date stopped.
- Serious:
  - Yes.
  - No.
- Severity (refer to Section 16.1.2.1: Severity).
- Relationship to study vaccination (refer to Section 16.1.2.2: Relationship to Study Vaccination).
- Outcome:
  - Resolved.
  - Resolved with sequelae.
  - Ongoing.
  - Death.
- Did the AE cause the participant to discontinue from the study:
  - Yes.
  - No.
- Was treatment given:
  - Yes.
  - No.
- Is the AE of special interest:
  - Yes.
  - No.
- System Organ Class (SOC).
- Preferred Term (PT).

The following AE variables, as presented in the planned TLF shells, will be collected on the SAE Report eCRF:

- Seriousness criterion:
  - Death.
  - Life-threatening.
  - Hospitalization.
  - Congenital anomaly/birth defect.
  - Involved persistent disability/incapacity.
  - Other important medical condition.
  - Prolonged hospitalization.

16.1.1. DERIVATIONS

Based on the aforementioned, the following variable, as presented in the planned TLF shells, will be derived:

- Study day of the most recent vaccination:
  - Calculated relative to Day 0 vaccination (refer to Section 6.1: Reference Start Date and Study Day).
- Relative days (start and stop):
  - Calculated relative to most recent vaccination (refer to Section 6.1: Reference Start Date and Study Day).
- Dose at onset (most recent vaccination):
  - Refer to Section 16.1.8: Adverse Event (AE) Dose at Onset (Most Recent Vaccination).
- Time of onset:
  - Derived based on the relative days (start) as either of the following categories:
    - Day 0 to Day 3.
    - Day 4 to Day 7.
    - Day 8 to Day 14.
    - >= Day 15.
  - For the overview of unsolicited AEs by severity, time of onset and relationship table, AEs with missing time to onset will be considered.

16.1.2. ALL ADVERSE EVENTS (AES)

The following tables are planned for presentation:

- Overview of AEs:
  - Number and percentage (%) of participants in each of the following categories (participants with multiple events in each category are counted only once in each category):
    - Any AE.
    - Any solicited AE.
    - Local solicited AE.
    - Systemic solicited AE.
    - SAE.
    - SAE with outcome of death.
    - Related AE.

- Severe AE.
- Related, severe AE.
- AE leading to premature study discontinuation.
- Adverse events of special interest (AESI).

- Percentage (%) of participants will be calculated relative to the total number of participants in the Safety analysis set per treatment group and cohort.
- 95% CIs:
  - Calculated for single proportion using mid-p binomial option (Clopper-Pearson method with mid-p correction).
- Number of events in each of the aforementioned categories (participants with multiple events in each category are counted multiple times in each category).
- This output will be repeated for the Safety and Immunogenicity Cohort as well as the Correlates Cohort.

All AE incidence tables will be sorted by:

- SOC (descending frequency of total number of participants with events reported).
- PT (descending frequency of total number of participants with events reported within each SOC).

All AE incidence tables presented by PT only will be sorted by:

- PT (descending frequency of total number of participants with events reported).

The following incidence table will be presented by SOC and PT:

- Incidence of AEs:
  - Number and percentage (%) of all participants with AEs summarized by SOC and PT.
  - Includes all AEs within the post-vaccination reporting windows (refer to Section 16.1.9: Adverse Event (AE) Post-vaccination Reporting Window for details on the derivation of post-vaccination reporting window).
  - This table will be repeated for the Safety and Immunogenicity Cohort.
- Incidence of AEs by dose (refer to 16.1.8: Adverse Event (AE) Dose at Onset (Most Recent Vaccination)).

The following incidence table is planned for presentation by PT only:

- Incidence of AEs:

The following listings are planned for presentation:

- Solicited and unsolicited non-serious AEs.
- AE comments.

16.1.2.1. Severity

Severity will be reported on the Adverse Events eCRF as mild, moderate or severe (increasing severity).

Missing severities will not be regarded as ‘worst case’ severity. If any missing severity is present in the data transfer, the severity will remain missing and will be counted under the missing category in the by-severity tables. Participants with multiple events in each SOC/solicited AE category and PT are counted only once in each SOC/solicited AE category and PT at highest severity.

For the overview of unsolicited AEs by severity, time of onset and relationship table, AEs with missing severity will be considered. The participant will be counted in the missing category if the all severities are reported as missing for the relevant participant.

The following incidence tables are planned for presentation by SOC and PT:

- Incidence of AEs by highest severity.
- Incidence of AEs by highest severity by dose (refer to 16.1.8: Adverse Event (AE) Dose at Onset (Most Recent Vaccination)).

The following listing will be presented:

- Adverse events of toxicity grade 3/4:
  - An AE of toxicity grade 3/4 is any AE for which the severity is indicated as severe.

16.1.2.2. Relationship to Study Vaccination

Relationship to study vaccination will be reported on the Adverse Events eCRF as definite, probable, possible, unlikely or not related (decreasing relationship).

The relationship to study vaccination will be reported as either related or not related:

- Related AE if relationship to study vaccination is reported as:
  - Definite.
  - Probable.
  - Possible.
- Not related AE if relationship to study vaccination is reported as:
  - Unlikely.
  - Not related.

Missing relationship to study vaccination will not be regarded as 'worst case' relationship to study vaccination. If any missing relationship to study vaccination is present in the data transfer, that relationship to study vaccination is to remain missing and will be counted in the missing category in the by-relationship tables. Participants with multiple events in each SOC/solicited AE category and PT are counted only once in each SOC/solicited AE category and PT at the strongest relationship.

For the overview of unsolicited AEs by severity, time of onset and relationship table, AEs with missing relationship to study vaccine will be considered. The participant will be counted in the missing category if the all relationship to study vaccine is reported as missing for the relevant participant.

The following incidence tables are planned for presentation by SOC and PT:

- Incidence of related AEs.
- Incidence of related AEs by dose (refer to 16.1.8: Adverse Event (AE) Dose at Onset (Most Recent Vaccination)).
- Incidence of related AEs by highest severity.
- Incidence of related AEs by highest severity and dose (refer to 16.1.8: Adverse Event (AE) Dose at Onset (Most Recent Vaccination)).

The following incidence tables are planned for presentation by PT only:

- Incidence of related AEs.

16.1.3. UNSOLICITED ADVERSE EVENTS (AEs)

The following overview table is planned for presentation:

- Overview of unsolicited AEs by severity, time of onset and relationship:
  - Number and percentage (%) of participants in each of the following categories (participants with multiple events in each category are counted only once in each category, worst case/shortest time to onset):
    - Severity (refer to Section 16.1.2.1: Severity).
    - Time of onset (refer to Section 16.1.1: Derivations).
    - Relationship (refer to Section 16.1.2.2: Relationship to Study Vaccination).
  - Number of events in each of the aforementioned categories (participants with multiple events in each category are counted multiple times in each category).
  - Includes all unsolicited AEs, SAEs as well as AEs of special interest within the post-vaccination reporting window (refer to Section 16.1.9: Adverse Event (AE) Post-vaccination Reporting Window for details on the derivation of the post-vaccination reporting window).
  - 95% CIs:
    - Calculated for single proportion using mid-p binomial option (Clopper-Pearson method with mid-p correction).
  - This table will be repeated for the Safety and Immunogenicity Cohort as well as the Correlates Cohort.

16.1.4. SOLICITED AND INJECTION SITE ADVERSE EVENTS (AEs)

In the database all AEs were reported as either solicited or unsolicited, however the database categorization will not be used to report AEs as either solicited or unsolicited. All AEs will be assigned as either solicited or unsolicited based on the PT (refer to APPENDIX 3: Solicited and Injection Site Adverse Event (AE)) and post-vaccination reporting window (refer to Section 16.1.9: Adverse Event (AE) Post-vaccination Reporting Window for a description of the post-vaccination reporting windows).

Local and systemic solicited AE incidence tables will be presented as follows:

- Solicited AE category (local, systemic).
- PT (descending frequency of total number of participants with events reported within each solicited AE category).

The following incidence tables will be presented by PT only:

- Incidence of solicited AEs.
- Incidence of related solicited AEs.
- Incidence of related solicited AEs by dose at onset (refer to Section 16.1.8: Adverse Event (AE) Dose at Onset (Most Recent Vaccination) for details on the derivation of dose at onset):
  - Number and percentage (%) of participants with AEs summarized by solicited AE category and PT.

- Includes all solicited AEs within the post-vaccination reporting window (refer to Section 16.1.9: Adverse Event (AE) Post-vaccination Reporting Window for details on the derivation of the post-vaccination reporting window).
- BCG treatment group will only include Dose 1 at onset AEs.

- Incidence of solicited AEs per cohort and dose at onset (refer to Section 16.1.8: Adverse Event (AE) Dose at Onset (Most Recent Vaccination) for details on the derivation of dose at onset):
  - Number and percentage (%) of participants with AEs summarized by solicited AE category and PT.
  - Includes all solicited AEs within the post-vaccination reporting window (refer to Section 16.1.9: Adverse Event (AE) Post-vaccination Reporting Window for details on the derivation of the post-vaccination reporting window).
  - BCG treatment group will only include Dose 1 at onset AEs.

- Incidence of local solicited AEs by severity and dose at onset:
  - Number and percentage (%) of participants with AEs summarized by solicited AE category and PT.
  - Includes all local solicited AEs within the post-vaccination reporting window (refer to Section 16.1.9: Adverse Event (AE) Post-vaccination Reporting Window for details on the derivation of the post-vaccination reporting window).
  - BCG treatment group will only include Dose 1 at onset AEs.
  - This table will be repeated for systemic solicited AEs and related systemic solicited AEs.

16.1.5. SERIOUS ADVERSE EVENTS (SAEs)

An SAE is any AE for which serious event is indicated as 'yes' on the Adverse Event eCRF.

The following listing is planned for presentation by treatment group:

- SAEs.
- SAEs with an outcome of death.

The following incidence table is planned for presentation by SOC and PT:

- Incidence of serious adverse events by dose.
- Incidence of serious adverse events with outcome of death.

16.1.6. ADVERSE EVENTS OF SPECIAL INTEREST (AESI)

An AESI is any AE for which AE of special interest is indicated as 'yes' on the Adverse Events eCRF. Refer to APPENDIX 4: Adverse Events of Special Interest (AESIs) for the list of AEs considered to be of special interest.

The following listing is planned for presentation by treatment group:

- Adverse events of special interest (AESI).

16.1.7. ADVERSE EVENTS LEADING TO PREMATURE STUDY DISCONTINUATION

An AE leading to premature study discontinuation is any AE for which did the AE cause the participant to discontinue from the study recorded as 'yes'

The following listing is planned for presentation by treatment group:

- Adverse events leading to premature study discontinuation.

16.1.8. Adverse Event (AE) Dose at Onset (Most Recent Vaccination)

A dose at onset will be assigned for all AEs and is defined as the most recent dose prior to the onset of the AE:

- Post any dose (combination of the AEs starting after the Day 0 and Day 56 vaccinations).
- Post-dose 1 (AEs starting after the Day 0 vaccination).
- Post-dose 2 (AEs staring after the Day 56 vaccination):
  - Only applicable to H4:IC31 and Placebo treatment groups.

The assignment of the dose at onset will be based on the following algorithm:

- Calculate the difference in the AE start date (as collected on the Adverse Events eCRF) and all available study vaccination dates (as collected on the Exposure Day 0 and Exposure Day 56 eCRFs):
  - Days since dose x: (AE start date – study vaccination dose x date [where x= 1 or 2]).
- From the previous calculation, only consider those doses where the days since dose x is >=0 and determine the dose (1 or 2) for which the days since dose x (as calculated in the previous step) is a minimum.
- Assign the dose selected in the previous step as the dose at onset as the specific dose determined in the previous calculation.

16.1.9. Adverse Event (AE) Post-vaccination Reporting Window

All SAEs and AESIs will be collected through database lock.

All unsolicited AEs will be collected during the 28-day reporting window following each study vaccination. The reporting window is defined in terms of the relevant scheduled study visit coinciding with the 28-day window following the relevant dose.

Solicited systemic adverse events will be collected during the 7-day reporting window following each study vaccination (diary cards will be used for 7 days following each study vaccination for the Safety and Immunogenicity Cohort only).

Solicited and unsolicited local injection site reaction adverse events will be collected:

- BCG treatment group:
  - 84-day reporting window following study vaccination.
- H4:IC31 and Placebo treatment groups:
  - 28-day reporting window following each vaccination.

Refer to Table 4: General Adverse Event (AE) Post-vaccination Reporting Windows below for the relevant post-vaccination reporting windows as defined in terms of scheduled study visits:

Table 4: General Adverse Event (AE) Post-vaccination Reporting Windows

Adverse Event Type	Treatment Group	Dose at Onset	Post-vaccination Reporting Window	
			Scheduled Study Visit	Protocol Specified Visit Window
Unsolicited AE	All	Day 0	Study Day 28	28 days following Study Day 0
	H4: IC31 Placebo	Day 56	Study Day 84	28 days following Study Day 56
Local Solicited AEs	BCG	Day 0	Study Day 84	84 days following Study Day 0
	H4: IC31 Placebo	Day 0	Study Day 28	28 days following Study Day 0
	H4: IC31 Placebo	Day 56	Study Day 84	28 days following Study Day 56
Systemic Solicited AEs	All	Day 0	Study Day 7	7 days following Study Day 0
	H4: IC31 Placebo	Day 56	Study Day 63	7 days following Study Day 56
SAEs and AEs of special interest	All	All	-	Through database lock

If the relevant scheduled study visit occurred within the protocol specified visit window, all AEs with start date through the relevant scheduled study visit will be included in the reporting period. If the relevant scheduled study visit occurred outside the protocol specified visit window, only include AEs with start date through either 7, 28 or 84 days will be included.

16.2. INJECTION SITE REACTION ASSESSMENT

Injection site reaction assessments will be presented for the Safety analysis set.

The following injection site reaction assessment listing is planned for presentation:

- Injection site reaction assessment.

The following injection site reaction variables will be collected throughout the study on the eCRFs:

- Date and time of assessment.
- Injection site reaction assessment:
  - Pain.
  - Redness.
  - Swelling.
  - Ulceration.
  - Drainage.
  - Abnormality photo taken.
  - Axillary lymphadenopathy.

- Present:
  - Yes:
    - Measurement (mm) for relevant assessments.
  - No.

16.2.1. DERIVATIONS

The following variables, as presented in the planned TLF shells, will be derived:

- Any time point:
  - Per study vaccination and injection site reaction the worst case result is selected as the any timepoint assessment.
  - Worst case assessment is defined as the largest measurement (mm) for assessments with measurements or the presence of the reaction if o measurements are available.
- Overall time point:
  - Per injection site assessment the worst case result is selected as the overall assessment.
  - Worst case assessment is defined as for the any timepoint assessment per study vaccination.

16.3. LABORATORY EVALUATIONS

The following tables are planned for presentation (based on the Safety analysis set for the Safety and Immunogenicity Cohort):

- Quantitative laboratory results and change from Baseline:
  - Presented by means of default summary statistics for quantitative variables.
  - Change from Baseline will be presented as well.
- Shift in laboratory grades from Baseline:
  - Shift will be presented in terms of the number of participants with an increased toxicity grade from the Baseline result (refer to APPENDIX 7: Toxicity Grading Criteria):
    - 0 grades (no change in grade compared to Baseline or grade decreased).
    - 1 grade.
    - 2 grades.
    - 3 grades.
    - 4 grades (only applicable to certain tests).
  - N1 is defined as the total number of participants with an assessment available at both Baseline and post-baseline time points.
  - Due to the fact that the toxicity grading for Urine Erythrocytes is “Normal”, “Grade 1” or “Grade 2/3/4”, it is not possible to determine if there was an increase. Therefore Urine Erythrocytes will not be included in this table. The toxicity grading will be displayed in the listing.

The following listings are planned for presentation (based on the Randomized analysis set):

- Quantitative laboratory results.
- Qualitative laboratory results.
- Laboratory reference ranges by system and test (no analysis set applicable to this listing).

Refer to APPENDIX 5: Laboratory Assessments for a list of laboratory assessments.

The following laboratory variables, as presented in the planned TLF shells, will be collected during the study on the Hematology (HEMA), Chemistry (CHEM), Urinalysis (URIN), Pregnancy Test (PREG) and HIV Tests (HIVT) eCRFs:

- Date of sample collection.
- Time of sample collection (only applicable to pregnancy test results).
- Test.
- Reported results and unit.

All conversion of original to standard units will be completed by Data Management within the database prior to transfer to Biostatistics. All laboratory data will be summarized in the standard unit.

16.3.1. TOXICITY GRADING CRITERIA

The toxicity grades will be assigned based on the protocol-specific criteria specified in APPENDIX 7: Toxicity Grading Criteria. For some assessments grade 3 or 4 cannot be assigned programmatically, but rather are based on clinical judgment, therefore they are not assigned for the purpose of analysis.

Refer to APPENDIX 5: Laboratory Assessments for a list of tests for which toxicity grades will be programmatically assigned.

16.4. VITAL SIGNS

Vital signs will be presented for the Safety analysis set.

The following tables are planned for presentation:

- Vital signs and change from pre-vaccination:
  - Presented by means of default summary statistics for quantitative variables.
  - Change from pre-vaccination will be presented as well.
- Shift in vital signs toxicity grades from pre-vaccination (Study Day 0 or Study Day 56 [not applicable to BCG]):
  - Shift will be presented in terms of the number of participants with an increased toxicity grade from the pre-vaccination results (refer to):
    - 0 grades (no change in grade compared to Baseline or grade decreased).
    - 1 grade.
    - 2 grades.
    - 3 grades.
  - N1 is defined as the total number of participants with an assessment available at both the relevant pre- and post-vaccination time points who received the applicable study vaccine dose.

The following listing is planned for presentation (based on the Randomized analysis set):

- Vital signs results.

The following vital signs variables, as presented in the planned TLF shells, will be collected on the Vital Signs, Vital Signs - Pre-vaccination and Vital Signs - Post-vaccination eCRFs:

- Result and unit for each of the following test:
  - Axillary temperature (˚C).
  - Pulse rate (beats per minute).
  - Systolic and diastolic blood pressure (mmHg).

16.4.1. TOXICITY GRADING CRITERIA

The toxicity grades will be assigned based on the protocol-specific criteria specified in APPENDIX 7: Toxicity Grading Criteria. Grade 4 cannot be assigned programmatically but rather is based on clinical judgment, therefore not assigned for the purpose of analysis.

Refer to APPENDIX 6: Vital Signs Assessments for a list of tests for which toxicity grades will be programmatically assigned.

16.4.2. PRE-VACCINATION AND POST-VACCINATION TIME POINTS

Refer to Table 4: Vital Signs Pre-and Post-vaccination Time Points below for details on the relevant pre-and post-vaccination time point for the vital signs assessments.

Study Vaccination	Pre-vaccination Time Point	Post-vaccination Time Point
Dose 1	Study Day 0 (Pre-vaccination)	Study Day 0 (Post-vaccination)
Dose 2 (not applicable to BCG)	Study Day 56 (Pre-vaccination)	Study Day 56 (Post-vaccination)

16.5. PHYSICAL EXAMINATION

Physical examination data will be presented for the Randomized analysis set.

The following listing is planned for presentation:

- Abnormal physical examination findings:
  - Only include physical examination results where the result is indicated as abnormal.

The following physical examination variable, as presented in the planned TLF shells, will be collected on the Physical Examination eCRF:

- Date of assessment.
- Verbatim term (and abnormality description if applicable).

16.6. PREGNANCIES

Pregnancies will be presented for the Safety analysis set.

The following listing is planned for presentation:

- Reported pregnancies.

The following pregnancy variables, as presented in the planned TLF shells, will be collected on the Pregnancy Notification eCRF:

- Pregnancy test:
  - Date of test.
  - Type:
    - Serum.
    - Urine.
  - Result:
    - Positive.
    - Negative.
- Current pregnancy information:
  - Estimated conception date.
  - Estimated delivery date.
- Current pregnancy outcome:
  - Date of delivery/outcome.
  - Outcome:
    - Normal.
    - Abnormal.
- Health status of mother.
- Health status of child.
- Additional information.

16.6.1. DERIVATIONS

Based on the aforementioned the following variable, as presented in the planned TLF shells, will be derived:

- Study day of the most recent vaccination:
  - Calculated relative to Day 0 vaccination (refer to Section 6.1: Reference Start Date and Study Day).
- Relative day:
  - Calculated relative to most recent vaccination (refer to Section 6.1: Reference Start Date and Study Day).

17. DATA NOT SUMMARIZED OR PRESENTED

The following eCRF data will not be presented:

- Immediately Reportable Event eCRF:
  - Immediately reportable events would be reported as part of the relevant domain's analysis.

18. REFERENCES

Aeras C-040-404 Study Protocol Version 5.0, dated 25 July 2016.

Aeras C-040-404 Electronic Case Report Form Version 6.0, dated 22APR2015.

Aeras C-040-404 Primary Analysis Note to File dated 25 April 2016.

APPENDIX 1. PROGRAMMING CONVENTIONS FOR OUTPUTS

Refer to the latest version of the relevant TLF shells.

STUDY VISITS

All study visits will be indicated as Visit in the relevant outputs (TLFs). The visits will be presented in the following order:

- Screening.
- Day x, where x = 0, 3, 7, 28, 56, 63, 70, 84.
- Month x, where x = 6, 9, 12, 15, 18, 21, 24, 27, 30.
- Any Time Point (if relevant).

FOOTNOTES

Footnotes will be ordered as follows:

- Non-standard abbreviations, separated by a full stop.
- n = Number of participants… N = Total number of participants… % = Percentage of participants.
- Definitions.
- Footnotes pertaining to statistical methodology.
- If coding is presented, the version of the coding dictionary used.
- Study-specific footnotes to clarify data points within the specific presentation.

OUTPUT HEADERS

Refer to the relevant set of TLF shells for the specific output header format.

OUTPUT FOOTERS

Refer to the relevant set of TLF shells for the specific output footer format.

DECIMAL PRECISION

All values will be rounded using the SAS® function ROUND, as the last step prior to presentation. All computed percentages (%) will be presented using one decimal place. If the original data has N decimal places (as derived

from the raw data), then the summary statistics for quantitative data are to contain the following number of decimal places (with a maximum of 3 places):

- Minimum and maximum: N.
- Mean and median: (N+1).
- Standard deviation: (N+2).

All p-values will be presented with 4 decimal places, if less than 0.0001 (after rounding to 4 decimal places) the p-value will be displayed as <0.0001. Odds ratios will be presented to 3 decimals and CIs will be presented to 2 decimals.

DATES & TIMES

Dates will be displayed as DDMMMYYYY. Times will be displayed as HH:MM (24-hour clock).

SPELLING FORMAT

English US.

LISTINGS

All listings will be sorted primarily by treatment group, in the order specified as applicable to the specific listing.

PRESENTATION NOTES

- In all listings, participants will be identified by means of the 16-digit participant identifier.
- Output margins should be top 1.5 inch and 1 inch on left, right and bottom.
- Each TLF will be produced as a separate stand-alone document.
- If separate presentations are required for analysis set or subgroups then these should be presented as stand-alone.
- All spelling is to adhere to English (US).
- All TLFs will be presented in a landscape format, as far as is feasible.
- The content of all tables and listings will be uppercase (excluding titles, column headers and footnotes), that is the 'Reported Term' in the medical conditions listing, for example.
- For all AE/CM/MH listings all coded terms will not be presented in uppercase, but rather as coded (sentence case) for differentiation from verbatim terms.

- The margin, page size and line size specifications as stipulated below will be used for the presentation of all TLFs:

	Landscape	**Portrait**
Paper Size	U.S. Letter (8.5 x 11 inch)	U.S. Letter (8.5 x 11 inch)
Margins (Inches):		
Top	1.25	1
Bottom	1	1
Left	1	1.25
Right	1	1
Header (Inches)	0.5	0.5
Footer (Inches)	0.5	0.5
SAS® Specifications:		
PAGESIZE	46 (8 point size, Courier)	67 (8 point size, Courier)
	41 (9 point size, Courier)	60 (9 point size, Courier)
LINESIZE	134 (8 point size, Courier)	93 (8 point size, Courier)
	119 (9 point size, Courier)	82 (9 point size, Courier)

APPENDIX 2. PARTIAL DATE CONVENTIONS

Imputation will only be performed for partially or completely missing AE start dates. Imputed AE start dates will not be presented in the listings and are only used to assign AEs to the relevant post-vaccination reporting window.

AE Start Date				
Day	**Month**	**Year**	**Criterion**	**Action**
Missing	Known	Known	AE start month and year are the same as the month and year of only one study vaccination (Day 0 or Day 56)	Assign the missing day as the day of the relevant study vaccination in the coinciding month and year
			AE start month and year are the same as the month and year of more than one study vaccination (Day 0 or Day 56)	Assign the missing day as the day of the earliest study vaccination in the coinciding month and year
			AE start month and year are not the same as the month and year of any of the study vaccinations (Day 0 or Day 56) and known to be in between study vaccinations	Assign the missing day as the first day of the month
			AE start month and year are not the same as the month and year of any of the study vaccinations (Day 0 or Day 56) and known to be prior to all study vaccinations	Assign the missing day as the last day of the month
			AE start month and year are not the same as the month and year of any of the study vaccinations (Day 0 or Day 56) and known to be after all study vaccinations	Assign the missing day as the first day of the month
Missing	Missing	Known	AE start year is the same as the year of only one study vaccination (Day 0 or Day 56)	Assign the missing day and month as the day and month of the relevant study vaccination in the coinciding year
			AE start year is the same as the year of more than one study vaccination (Day 0 or Day 56)	Assign the missing day and month as the day and month of the earliest study vaccination in the coinciding year
			AE start year is not the same as the year of any of the study vaccinations (Day 0 or Day 56) and known to be prior to all study vaccinations	Assign the missing day and month as 31 December

AE Start Date			Criterion	Action
Day	**Month**	**Year**		
			AE start year is not the same as the year of any of the study vaccinations (Day 0 or Day 56) and known to be after all study vaccinations	Assign the missing day and month as 01 January
Missing	Missing	Missing	-	Assign the missing date as the date of Dose 1 of study vaccination

APPENDIX 3. SOLICITED AND INJECTION SITE ADVERSE EVENT (AE) PREFERRED TERMS AND CODES

Relevant Treatment Group	Solicited or Injection Site AE	Solicited AE Category	Preferred Term	Preferred Term Code
Placebo H4:IC31 BCG	Solicited AE	Systemic	Pyrexia	10037660
			Myalgia	10028411
			Arthralgia	10003239
			Fatigue	10016256
			Headache	10019211
			Decreased appetite	10061428
			Urticaria	10046735
			Chills	10008531
			Lymphadenopathy	10025197
BCG	Injection site AE	Local	Vaccination site pain	10068879
			Vaccination site erythema	10059079
			Vaccination site swelling	10069620
			Vaccination site ulcer	10069621
			Vaccination site discharge	10069560
Placebo H4:IC31	Injection site AE	Local	Injection site pain	10022086
			Injection site erythema	10022061
			Injection site swelling	10053425
			Injection site ulcer	10022105
			Injection site discharge	10065600

APPENDIX 4. ADVERSE EVENTS OF SPECIAL INTEREST (AESIS)

Events, which are potentially immune, mediated are AESIs and include the following:

Acute disseminated encephalomyelitis (ADEM)	Myelitis/Transverse Myelitis
Addison's Disease	Myocarditis
Anti-neutrophil Cytoplasmic Antibody (ANCA)-associated Vasculitis	Nephritis
Ankylosing Spondylitis	Optic neuritis
Anti-phospholipid Syndrome	Pericarditis
Autoimmune Bullous Skin Diseases	Polymyalgia Rheumatica
Autoimmune Hemolytic Anemia	Polymyositis
Autoimmune Hepatitis	Primary Biliary Cirrhosis
Autoimmune Thrombotic/Thromboembolic Conditions	Primary Sclerosing Cholangitis
Basedow's Disease	Psoriasis
Behcet's Syndrome	Psoriatic Arthritis
Bell's Palsy	Raynaud's Phenomenon
Carditis	Rheumatoid Arthritis
Celiac Disease	Sarcoidosis
Crohn's Disease	Scleroderma
Cutaneous Lupus	Sjogren's Syndrome
Demyelinating Disease	Spondylo-arthropathy
Dermatomyositis	Stevens-Johnson Syndrome
Diabetes Mellitus, Insulin Dependent (IDDM)	Systemic Lupus Erythematosus
Erythema Nodosum	Temporal Arteritis
Glomerulonephritis	Thyroiditis
Guillain Barre Syndrome	Tolosa-Hunt Syndrome
Grave's Disease	Ulcerative Colitis
Idiopathic Thrombocytopenic Purpura (ITP)	Ulcerative Proctitis
Inflammatory Bowel Disease (non-specific)	Uveitis
Juvenile Rheumatoid Arthritis	Vasculitis
Mixed Connective Tissue Disease	Vitiligo
Multiple Sclerosis	Wegener's Granulomatosis
Myasthenia Gravis	

APPENDIX 5. LABORATORY ASSESSMENTS

System Test	Reported Unit	Conversion Factor	SI Unit	Toxicity Abnormality*
Hematology				
Basophils	10^9/L	1	10^9/L	-
Eosinophils	10^9/L	1	10^9/L	-
Hematocrit	Fraction of one	1	Fraction of %	-
	L/L	1	Fraction of %	-
Hemoglobin	g/dL	10	g/L	Hemoglobin -decreased
Lymphocytes	10^9/L	1	10^9/L	-
Monocytes	10^9/L	1	10^9/L	-
Neutrophils	10^9/L	1	10^9/L	-
Platelet count	10^9/L	1	10^9/L	Platelets - decreased
White blood cell (WBC) count	10^9/L	1	10^9/L	WBC - decreased
				WBC - increased
Chemistry				
Alkaline phosphatase	U/L	1	U/L	Alkaline phosphatase - increased
ALT	U/L	1	U/L	ALT (SGPT) - increased
AST	U/L	1	U/L	AST (SGOT) - increased
Blood urea nitrogen	mg/dL	0.357	mmol/L	BUN - increased
	mmol/L	1	mmol/L	
Creatinine	μmol/L	1	μmol/L	Creatinine - increased
Total bilirubin	μmol/L	1	μmol/L	Total bilirubin - increased
Urinalysis				
Blood	No standardization performed for the urinalysis laboratory assessments			-
Glucose				-
Protein				Proteinuria, random collection
Leucocytes				-
Erythrocytes				Hematuria
Epithelial cells				-

*Refer to APPENDIX 7: Toxicity Grading Criteria.

APPENDIX 6. VITAL SIGNS ASSESSMENTS

Test	Unit	Toxicity Abnormality*
Axillary body temperature	˚C	Fever
Pulse rate	bpm	-
Blood pressure: Diastolic	mmHg	Hypertension
Blood pressure: Systolic	mmHg	Hypertension
Height	cm	-
Weight	kg	-
BMI	kg/m^2	-

*Refer to APPENDIX 7: Toxicity Grading Criteria.

APPENDIX 7. TOXICITY GRADING CRITERIA

ESTIMATING SEVERITY GRADE

Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Clinical adverse event NOT identified elsewhere in this AE Grading Table	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Medical or operative intervention indicated to prevent permanent impairment, persistent disability, or death

CARDIOVASCULAR

Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Hypertension Adult > 17 years (with repeat testing at same visit)	140 – 159 mmHg systolic OR 90 – 99 mmHg diastolic	160 – 179 mmHg systolic OR 100 – 109 mmHg diastolic	≥ 180 mmHg systolic OR ≥ 110 mmHg diastolic	Life-threatening consequences (e.g., malignant hypertension) OR Hospitalization indicated (other than emergency room visit)
Hypertension Pediatric ≤ 17 years (with repeat testing at same visit)	NA	91st – 94th percentile adjusted for age, height, and gender (systolic and/or diastolic) 146 - 168 mmHg systolic OR 91 - 102 mmHg diastolic	≥ 95th percentile adjusted for age, height, and gender (systolic and/or diastolic) ≥168 mmHg systolic OR ≥102 mmHg diastolic	Life-threatening consequences (e.g., malignant hypertension) OR Hospitalization indicated (other than emergency room visit)
Hypotension	NA	Symptomatic, corrected with oral fluid replacement	Symptomatic, IV fluids indicated	Shock requiring use of vasopressors or mechanical assistance to maintain blood pressure

SKIN – DERMATOLOGICAL

Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Cutaneous reaction – rash	Localized macular rash	Diffuse macular, maculopapular, or morbilliform rash OR Target lesions	Diffuse macular, maculopapular, or morbilliform rash with vesicles or limited number of bullae OR Superficial ulcerations of mucous membrane limited to one site	Extensive or generalized bullous lesions OR Stevens-Johnson syndrome OR Ulceration of mucous membrane involving two or more distinct mucosal sites OR Toxic epidermal necrolysis (TEN)
Pruritus (itching – no skin lesions) (See also Injection Site Reactions: Pruritus associated with injection)	Itching causing no or minimal interference with usual social & functional activities	Itching causing greater than minimal interference with usual social & functional activities	Itching causing inability to perform usual social & functional activities	NA

INFECTION

Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Infection (any other than HIV infection)	Localized, no systemic antimicrobial treatment indicated AND Symptoms causing no or minimal interference with usual social & functional activities	Systemic antimicrobial treatment indicated OR Symptoms causing greater than minimal interference with usual social & functional activities	Systemic antimicrobial treatment indicated AND Symptoms causing inability to perform usual social & functional activities OR Operative intervention (other than simple incision and drainage) indicated	Life-threatening consequences (e.g., septic shock)

SYSTEMIC

Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Acute systemic allergic reaction	Localized urticaria (wheals) with no medical intervention indicated	Localized urticaria with medical intervention indicated OR Mild angioedema with no medical intervention indicated	Generalized urticaria OR Angioedema with medical intervention indicated OR Symptomatic mild bronchospasm	Acute anaphylaxis OR Life-threatening bronchospasm OR laryngeal edema
Chills	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA
Fatigue Malaise	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Incapacitating fatigue/ malaise symptoms causing inability to perform basic self-care functions
Fever (axillary)	38.0 – 38.4°C 100.4 – 101.1°F	38.5 - 40°C 101.2 - 104°F	>40°C >104°F	NA
Pain (indicate body site) DO NOT use for pain due to injection (See Injection Site Reactions: Injection site pain) See also Headache, Arthralgia, and Myalgia	Pain causing no or minimal interference with usual social & functional activities	Pain causing greater than minimal interference with usual social & functional activities	Pain causing inability to perform usual social & functional activities	Disabling pain causing inability to perform basic self-care functions OR Hospitalization (other than emergency room visit) indicated

Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Unintentional weight loss	NA	5 – 9% loss in body weight from baseline	10 – 19% loss in body weight from baseline	≥ 20% loss in body weight from baseline OR Aggressive intervention indicated [e.g., tube feeding or total parenteral nutrition (TPN)]

INJECTION SITE REACTIONS

Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Injection site pain (pain without touching) Or Tenderness (pain when area is touched)	Pain/tenderness causing no or minimal limitation of use of limb	Pain/tenderness limiting use of limb OR Pain/tenderness causing greater than minimal interference with usual social & functional activities	Pain/tenderness causing inability to perform usual social & functional activities	Pain/tenderness causing inability to perform basic self-care function OR Hospitalization (other than emergency room visit) indicated for management of pain/tenderness
Injection site reaction (localized) Adult > 15 years	Erythema OR Induration of 5x5 cm – 9x9 cm (or 25 cm2 – 81cm2)	Erythema OR Induration OR Edema > 9 cm any diameter (or > 81 cm2)	Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage	Necrosis (involving dermis and deeper tissue)
Injection site reaction (localized) Pediatric ≤ 15 years	Erythema OR Induration OR Edema present but ≤ 2.5 cm diameter	Erythema OR Induration OR Edema > 2.5 cm diameter but < 50% surface area of the extremity segment (e.g., upper arm/thigh)	Erythema OR Induration OR Edema involving ≥ 50% surface area of the extremity segment (e.g., upper arm/thigh) OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage	Necrosis (involving dermis and deeper tissue)

Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Pruritus associated with injection See also Skin: Pruritus (itching - no skin lesions)	Itching localized to injection site AND Relieved spontaneously or with < 48 hours treatment	Itching beyond the injection site but not generalized OR Itching localized to injection site requiring ≥ 48 hours treatment	Generalized itching causing inability to perform usual social & functional activities	NA

GASTROINTESTINAL

Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Anorexia*	Loss of appetite without decreased oral intake	Loss of appetite associated with decreased oral intake without significant weight loss	Loss of appetite associated with significant weight loss	Life-threatening consequences OR Aggressive intervention indicated [e.g., tube feeding or total parenteral nutrition (TPN)]
Diarrhea	Transient or intermittent episodes of unformed stools OR Increase of ≤ 3 stools over baseline per 24-hour period	Persistent episodes of unformed to watery stools OR Increase of 4 – 6 stools over baseline per 24-hour period	Bloody diarrhea OR Increase of ≥ 7 stools per 24-hour period OR IV fluid replacement indicated	Life-threatening consequences (e.g., hypotensive shock)
Nausea	Transient (< 24 hours) or intermittent nausea with no or minimal interference with oral intake	Persistent nausea resulting in decreased oral intake for 24 – 48 hours	Persistent nausea resulting in minimal oral intake for > 48 hours OR Aggressive rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)
Vomiting	Transient or intermittent vomiting with no or minimal interference with oral intake	Frequent episodes of vomiting with no or mild dehydration	Persistent vomiting resulting in orthostatic hypotension OR Aggressive rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)

Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Headache	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Hospitalization indicated (other than emergency room visit) OR Headache with significant impairment of alertness or other neurologic function
Insomnia	NA	Difficulty sleeping causing greater than minimal interference with usual social & functional activities	Difficulty sleeping causing inability to perform usual social & functional activities	Disabling insomnia causing inability to perform basic self-care functions

* Note that, while the grading scale provided for Unintentional Weight Loss may be used as a guideline when grading anorexia, this is not a requirement and should not be used as a substitute for clinical judgment.

RESPIRATORY

Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Bronchospasm (acute)	FEV1 or peak flow reduced to 70 – 80%	FEV1 or peak flow 50 – 69%	FEV1 or peak flow 25 – 49%	Cyanosis OR FEV1 or peak flow < 25% OR Intubation
Dyspnea or respiratory distress Adult ≥ 14 years	Dyspnea on exertion with no or minimal interference with usual social & functional activities	Dyspnea on exertion causing greater than minimal interference with usual social & functional activities	Dyspnea at rest causing inability to perform usual social & functional activities	Respiratory failure with ventilatory support indicated

Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Dyspnea or respiratory distress Pediatric < 14 years	Wheezing OR minimal increase in respiratory rate for age	Nasal flaring OR Intercostal retractions OR Pulse oximetry 90 – 95%	Dyspnea at rest causing inability to perform usual social & functional activities OR Pulse oximetry < 90%	Respiratory failure with ventilatory support indicated

MUSCULOSKELETAL

Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Arthralgia See also Arthritis	Joint pain causing no or minimal interference with usual social & functional activities	Joint pain causing greater than minimal interference with usual social & functional activities	Joint pain causing inability to perform usual social & functional activities	Disabling joint pain causing inability to perform basic self-care functions
Arthritis See also Arthralgia	Stiffness or joint swelling causing no or minimal interference with usual social & functional activities	Stiffness or joint swelling causing greater than minimal interference with usual social & functional activities	Stiffness or joint swelling causing inability to perform usual social & functional activities	Disabling joint stiffness or swelling causing inability to perform basic self-care functions
Myalgia (non-injection site)	Muscle pain causing no or minimal interference with usual social & functional activities	Muscle pain causing greater than minimal interference with usual social & functional activities	Muscle pain causing inability to perform usual social & functional activities	Disabling muscle pain causing inability to perform basic self-care functions

LABORATORY: HEMATOLOGY

Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Hemoglobin (Hgb)*	10.0 – 10.9 g/dL 6.18 – 6.79 mmol/L OR Any decrease 2.5 – 3.4 g/dL 1.58 – 2.13 mmol/L	9.0 – 9.9 g/dL 5.55 - 6.17 mmol/L OR Any decrease 3.5 – 4.4 g/dL 2.14 – 2.78 mmol/L	7.0 – 8.9 g/dL 4.34 - 5.54 mmol/L OR Any decrease ≥ 4.5 g/dL ≥ 2.79 mmol/L	< 7.0 g/dL < 4.34 mmol/L
Platelets, decreased	100,000 – 124,999/mm3 100.000 x 109 – 124.999 x 109/L	50,000 – 99,999/mm3 50.000 x 109 – 99.999 x 109/L	25,000 – 49,999/mm3 25.000 x 109 – 49.999 x 109/L	< 25,000/mm3 < 25.000 x 109/L
WBC, decreased	2,000 – 2,500/mm3 2.000 x 109 – 2.500 x 109/L	1,500 – 1,999/mm3 1.500 x 109 – 1.999 x 109/L	1,000 – 1,499/mm3 1.000 x 109 – 1.499 x 109/L	< 1,000/mm3 < 1.000 x 109/L
WBC, increased	10,800 – 15,000/mm3 10.8 – 15.0 x 109/L	15,001 – 20,000/mm3 15.1 – 20.0 x 109/L	20,001 – 25,000/mm3 20.1 – 25.0 x 109/L	>25,000/mm3 >25.0 x 109/L

*The decrease is a decrease from Baseline

LABORATORY: CHEMISTRY

Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Alkaline Phosphatase	1.25 – 2.5 x ULN†	2.6 – 5.0 x ULN†	5.1 – 10.0 x ULN†	> 10.0 x ULN†
ALT (SGPT)	1.25 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10.0 x ULN	> 10.0 x ULN
AST (SGOT)	1.25 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10.0 x ULN	> 10.0 x ULN
Blood urea nitrogen (BUN)	23 – 26 mg/dL 8.3 – 9.5 mmol/L	27 – 31 mg/dL 9.6 – 11.2 mmol/L	>31 mg/dL >11.2 mmol/L	Requires dialysis
Creatinine – elevated	1.5 – 1.7 mg/dL 121 - 145 umol/L	1.8 – 2.0 mg/dL 146 – 170 umol/L	2.1 – 2.5 mg/dL 171 – 208 umol/L	>2.5 mg/dL or requires dialysis >208 umol/L or requires dialysis
Bilirubin (Total)	1.1 – 1.5 x ULN	1.6 – 2.5 x ULN	2.6 – 5.0 x ULN	> 5.0 x ULN

LABORATORY: URINALYSIS

Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Hematuria (microscopic)	5 – 10 cells/mm3 +	> 10 cells/mm3 ++/+++	Gross, with or without clots OR with RBC casts ++/+++	Transfusion indicated ++/+++
Proteinuria, random collection	1 +	2 – 3 +	4 +	NA
Proteinuria, 24 hour collection ≥ 10 years	200 – 999 mg/24 h 0.200 – 0.999 g/d	1000 – 1999 mg/24 h 1.000 – 1.999 g/d	2000 – 3500 mg/24 h 2.000 – 3.500 g/d	> 3500 mg/24 h > 3.500 g/d

APPENDIX 8. PROTOCOL-DEFINED VISIT WINDOWS

Visit	Visit Window
Day 84	84 ± 7 days from Day 0
Month 6	168 ± 14 days from Day 0
Month 8	168 ± 14 days from Day 56
Month 9/12	84/168 ± 14 days from initial conversion at Month 6
Month 12	336 ± 14 days from Day 0
Month 15/18	84/168 ± 14 days from initial conversion at Month 12
Month 18	504 ± 14 days from Day 0
Month 21/24	84/168 ± 14 days from initial conversion at Month 18
Month 24	672 ± 14 days from Day 0
Month 27/30	84/168 ± 14 days from initial conversion at Month 30