GlaxoSmithKline	**Statistical Analysis Plan Approval**
Protocol Title:	Efficacy of GSK Biologicals' candidate tuberculosis (TB) vaccine GSK 692342 against TB disease, in adults living in a TB endemic region
eTrack study number	115616
eTrack abbreviated title	TUBERCULOSIS-018
Protocol version/date **Scope:**	Amendment 5 (29 January 2014) All analyses for the the triggered primary analysis and the end of study analysis pertaining to the above study
Version: **Date:**	Version 3: Amendment 1 17-OCT-2017
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LIST OF ABBREVIATIONS

AE	Adverse Event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATP	According-To-Protocol
BMI	Body Mass Index
CD4/8/40	Cluster of Differentiation 4/8/40
CD-40L	Cluster of Differentiation-40 Ligand
CEPL	Clinical and Epidemiology Project Lead
CI	Confidence Interval
CMI	Cell-Mediated Immune / Cell-Mediated Immunity
CRDL	Clinical Research and Development Lead
CRF	Case Report Form
CSR	Clinical Study Report
DBF	Database freeze
EOS	End of Study
EU	Elisa Unit
FDA	Food and Drug Administration
GMC	Geometric Mean Concentration
ICS	Intracellular Cytokine Staining
IDMC	Independent Data Monitoring Committee
IFN-γ	Interferon-gamma
IGRA	Interferon-Gamma Release Assay
IL-2/13/17	Interleukin-2/13/17
LL	Lower Limit

MedDRA	Medical Dictionary for Regulatory Activities
M72/AS01$_E$	*Mycobacterium tuberculosis* fusion protein M72 with GSK's proprietary adjuvant system containing MPL, QS21 with liposomes
Mtb	*Mycobacterium tuberculosis*
PAM	Pre-analysis meeting
pIMDs	Potential Immune Mediated Diseases
PT	Preferred Term
QFTG	QuantiFERON® TB Gold
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class
SS	Symptom sheet
TB	Tuberculosis
TFL	Table and Figures List
TNF-α	Tumour Necrosis Factor-alpha
TVC	Total Vaccinated Cohort
VE	Vaccine Efficacy

The analysis plan is divided into a section detailing the analyses to be performed in the Study Analysis Plan (SAP) and a Table and Figures List (TFL) describing the flow and format of tables, figures and listings to be included in the Clinical Study Report (CSR).

1. DOCUMENT HISTORY

Date	Version	Description	Protocol Version
07-MAR-2016	First Version	Case-driven analysis on 21 cases and End Of Study analysis	Amendment 5 dated 29 Jan 2014
31-MAR-2017	Second Version	Case-driven analysis on 21 cases and End Of Study analysis Update of maximum allowed interval: addition of extra 15 days margin in the two directions for Year 1, year 2, year 3. By this timing, the immune should not change much with such a difference in time since dose 2 Addition of analysis of vitamin D, of some risk factors	Amendment 5 dated 29 Jan 2014
17-OCT-2017	Third Version: amendment 1	Addition of the covariate BCG in the adjusted analysis of efficacy. Addition of the sensitivity analysis (primary endpoint requiring at least two positive results, on the same sputum or on different sputa) (plus conditional exact method for VE and CI) Event-triggered analysis when 21 cases are accrued will be replaced by "primary analysis will be performed when all subjects have completed 24 months of follow-up"	Amendment 5 dated 29 Jan 2014

2. INTRODUCTION

- Study TUBERCULOSIS-018 is an efficacy study with a follow-up of 3 years The triggered primary analysis will be conducted when all subjects have completed their Month 24 visit.
- In order to preserve the blinding of the study, the triggered primary analysis will be performed by statisticians external to the GSK-AERAS clinical teams and any of the investigator teams.

2.1. Overview of analyses

Table 1 and Table 2 present an overview of analyses to be performed for the triggered primary analysis and for the End of Study (EoS) analysis. For the list of endpoints, refer to Section 4. Case definitions of tuberculosis (TB) disease are described in Section 5. Total Vaccinated cohort (TVC) and according-to-protocol (ATP) populations are defined in Section 6. Risk period definitions are summarized and further explained in Section 10.

Table 1 Overview of analyses when all subjects have completed 24 months of follow-up

EFFICACY	Population	Risk Period	First or only episodes	Comments
Primary analysis	ATP	[30 days post dose 2 – time when all subjects have completed 24 months of follow-up]	Primary case definition	The analysis for the primary objective
Primary analysis	TVC	[day of first vaccination – time when all subjects have completed 24 months of follow-up]	Primary case definition	
Secondary analysis	ATP	[30 days post dose 2 – time when all subjects have completed 24 months of follow-up]	Second case definition	The analysis for the confirmatory secondary objective if the primary objective is met
Secondary analysis	TVC	[day of first vaccination – time when all subjects have completed 24 months of follow-up]	Second case definition	
Secondary analysis	ATP	[30 days post dose 2 – time when all subjects have completed 24 months of follow-up]	Third to fifth case definition	
Secondary analysis	TVC	[day of first vaccination – time when all subjects have completed 24 months of follow-up]	Third to-fifth case definition	
Exploratory analysis	ATP	[30 days post dose 2 – time when all subjects have completed 24 months of follow-up]	Fifth case definition with HIV negative status (exploratory endpoint)	
Exploratory analysis	TVC	[day of first vaccination – time when all subjects have completed 24 months of follow-up]	Fifth case definition with HIV negative status (exploratory endpoint)	
Sensitivity analysis	ATP	[30 days post dose 2 – time when all subjects have completed 24 months of follow-up]	Case definition for sensitivity analysis	Sensitivity analysis to complement the primary analysis

ATP = ATP cohort for efficacy
TVC = Total vaccinated cohort for efficacy

Table 2 Overview of End of Study analyses

EFFICACY	Population	Risk Period	First or only episodes
Primary analysis	ATP	[30 days post dose 2 – Month 36]	Primary case definition
Primary analysis	TVC	[day of first vaccination – Month 36]	Primary case definition
Secondary analysis	ATP	[30 days post dose 2 – Month 36]	Second case definition
Secondary analysis	TVC	[day of first vaccination – Month 36]	Second case definition
Secondary analysis	ATP	[30 days post dose 2 – Month 36]	Third to fifth case definition
Secondary analysis	TVC	[day of first vaccination – Month 36]	Third to fifth case definition
Exploratory analysis	ATP	[30 days post dose 2 – Month 36]	Fifth case definition with HIV negative status (exploratory endpoint)
Exploratory analysis	TVC	[day of first vaccination – Month 36]	Fifth case definition with HIV negative status (exploratory endpoint)
Sensitivity analysis	ATP	[30 days post dose 2 – Month 36]	Case definition. for sensitivity analysis

ATP = ATP cohort for efficacy
TVC = Total Vaccinated Cohort for efficacy

3. STUDY OBJECTIVES

3.1. Primary objective

- To evaluate the protective efficacy of two doses of the M72/AS01$_E$ candidate vaccine against **Definite pulmonary TB disease** not associated with HIV-infection, meeting the first case definition, as compared to placebo.

  Success criterion to be used for the primary objective:

  The lower limit (LL) of the 90% two-sided confidence interval (CI) for the vaccine efficacy (VE) (using a Cox regression model) against first occurrence of Definite pulmonary TB disease not associated with HIV-infection, meeting the first case definition, is above 0%

Refer to Section 4.1 for the definition of the primary endpoint and Section 5 for case definitions.

3.2. Secondary objectives

Efficacy:

- To evaluate the protective efficacy of two doses of the M72/AS01$_E$ candidate vaccine against **Definite Xpert MTB/Rif positive pulmonary TB disease** not associated with HIV-infection, meeting the second case definition, as compared to placebo.

  If the primary objective is met, this secondary objective will be analysed using the following success criterion:

  The LL of the 90% two-sided CI for the VE (using a Cox regression model) against first occurrence of Definite pulmonary TB disease not associated with HIV-infection, meeting the second case definition, is above 0%.

- To evaluate the protective efficacy of two doses of the M72/AS01$_E$ candidate vaccine against **Definite pulmonary TB disease** not associated with HIV-infection, meeting the third case definition, as compared to placebo.
- To evaluate the protective efficacy of two doses of the M72/AS01$_E$ candidate vaccine against **Microbiological pulmonary TB disease** meeting the fourth case definition, as compared to placebo.
- To evaluate the protective efficacy of two doses of the M72/AS01$_E$ candidate vaccine against **Clinical TB disease** meeting the fifth case definition, as compared to placebo.

Safety:

- To assess the safety and reactogenicity of two doses of the M72/AS01$_E$ candidate vaccine.

Immunogenicity:

- To assess the immunogenicity of two doses of the M72/AS01$_E$ candidate vaccine.

Refer to Section 4.2 for the definition of the secondary endpoints and Section 5 for case definitions.

4. ENDPOINTS

4.1. Primary endpoint

- Incident cases of **Definite Pulmonary TB disease** not associated with HIV-infection, meeting the first case definition.

  Over a period starting 1 month post dose 2 and lasting up to 35 months post last vaccination.

Refer to Section 5 for case definitions

4.2. Secondary endpoints

Efficacy:

- Incident cases of **Definite Xpert MTB/Rif positive Pulmonary TB disease** not associated with HIV-infection, meeting the second case definition.

  Over a period starting 1 month post dose 2 and lasting up to 35 months post last vaccination.

- Incident cases of **Definite Pulmonary TB disease** meeting the third case definition.

  Over a period starting 1 month post dose 2 and lasting up to 35 months post last vaccination.

- Incident cases of **Microbiological Pulmonary TB disease** meeting the fourth case definition.

  Over a period starting 1 month post dose 2 and lasting up to 35 months post last vaccination

- Incident cases of **Clinical TB disease** meeting the fifth case definition.

  Over a period starting 1 month post dose 2 and lasting up to 35 months post last vaccination

Refer to Section 5 for case definitions.

Safety:

- Occurrence of serious adverse events (SAEs).

  During the entire study period

- Occurrence of unsolicited adverse events (AEs).

  During the 30-day follow-up period following vaccination (day of vaccination and 29 subsequent days after each vaccine dose)

- Occurrence of solicited local and general AEs in the safety and immunogenicity sub-cohort.

  During the 7-day follow-up period following vaccination (day of vaccination and 6 subsequent days after each vaccine dose)

- Occurrence of all Potential Immune Mediated Diseases (pIMDs).

  Over a period starting at Day 0 until 6 months post-dose 2.

- Occurrence of grade ≥ 2 haematological and biochemical levels, in the safety and immunogenicity sub-cohort, at:

  Days 0, 7, 30 and 37.

Immunogenicity:

- Evaluation of cell-mediated immune (CMI) responses with respect to components of the study vaccine, in the safety and immunogenicity sub-cohort:
  - Determined by the frequency of M72-specific CD4+/CD8+ T-cells per million cells identified after *in vitro* stimulation, as expressing any combination of immune markers among Cluster of Differentiation-40 Ligand (CD40L), interleukin-2 (IL-2), interferon-gamma (IFN-γ) andTumour Necrosis Factor-alpha (TNF-α)

  Timepoints: prior to dose 1 (Day 0) and post dose 2 (Day 60, Years 1, 2 and 3)
- Evaluation of humoral immune responses with respect to components of the study vaccine, in the safety and immunogenicity sub-cohort:
  - Determined by M72-specific antibody titres as measured by ELISA.
  - Determined by seropositivity rates as measured by ELISA.

  Timepoints: prior to dose 1 (Day 0) and post-dose 2 (Day 60, Years 1, 2 and 3).

5. CASE DEFINITIONS

First case definition – Definite pulmonary TB, not associated with HIV-infection

- A subject with clinical suspicion* of pulmonary TB disease, with *Mycobacterium tuberculosis* (Mtb) complex identified from a sputum specimen, taken before initiation of TB treatment, by Xpert MTB/RIF and/or microbiological culture and confirmed HIV-negative at the time of TB diagnosis.

Second case definition –Definite Xpert MTB/Rif positive pulmonary TB, not associated with HIV-infection

- A subject with clinical suspicion* of pulmonary TB disease, with Mtb complex identified from a sputum specimen, taken before initiation of TB treatment, by Xpert MTB/RIF and confirmed HIV-negative at the time of TB diagnosis**.**

Third case definition – Definite pulmonary TB, not associated with HIV-infection

- A subject with clinical suspicion* of pulmonary TB disease, with Mtb complex identified from a sputum specimen, taken up to four weeks after initiation of TB treatment, by Xpert MTB/RIF and/or microbiological culture and confirmed HIV-negative at the time of TB diagnosis.

Fourth case definition – Microbiological pulmonary TB

- A subject with clinical suspicion* of pulmonary TB disease, with Mtb complex identified from a sputum specimen, taken up to four weeks after initiation of TB treatment, by Xpert MTB/RIF and/or microbiological culture.

*Clinical suspicion of pulmonary TB is defined as a subject presenting with one or more of the following symptoms: unexplained cough > 2 weeks, unexplained fever > 1 week, night sweats, unintentional weight loss, pleuritic chest pains, haemoptysis, fatigue or shortness of breath on exertion.

Fifth case definition – Clinical TB

- A subject for whom a clinician has diagnosed TB disease and has decided to treat the patient with TB treatment. Note: for the purpose of the analysis the site PI is considered the clinician providing definite diagnosis.

Case Definition	Localisation	Culture Result	GeneXpert MTB/Rif	HIV status	Other
1st Case Def. Primary Objective*	Pulmonary	Either or both positive for at least one of the 3 sputum		Negative	Sample before TB treatment start
2nd Case Def.	Pulmonary	Any	Positive	Negative	
3rd Case Def.	Pulmonary	Either or both positive for at least one of the 3 sputum		Negative	Sample up to 4 week after TB treatment start
4th Case Def.	Pulmonary	Either or both positive for at least one of the 3 sputum		Negative or positive or unknown or not tested	
5th Case Def.	Any	Any	Any	Negative or positive or unknown or not tested	Subject is diagnosed as a TB case by the PI and the subject is treated for TB
Exploratory case definition: Modified 5th Case Def.	Any	Any	Any	Negative	Subject is diagnosed as a TB case by the PI and the subject is treated for TB
Case Def. for sensitivity analysis**	Pulmonary	At least 2 positive results among the 3 sputa, regardless of the method (GeneXpert and/or culture)		Negative	at least 1 sputum positive before TB treatment start and then the other positives maybe before or after TB treatment start

Def.: Definition
PI: Principal Investigator
*1st case definition: the suspicion of TB should be pulmonary, the status of HIV at the time of diagnosis of TB should be negative and the sample date of the sputum being culture or GeneXpert positive should be before the start date of TB treatment.
**Case Def. for sensitivity analysis: A subject with clinical suspicion of pulmonary TB disease, with Mtb complex identified *from at least two positive results* in a sputum specimen (at least one of those taken before the initiation of TB treatment) by Xpert MTB/RIF and /or microbiological culture and confirmed HIV negative at the time of diagnosis.

6. STUDY COHORTS/DATA SETS TO BE ANALYSED

6.1. Total vaccinated cohort

The TVC will include all vaccinated subjects for whom data are available.

The TVC for efficacy will include all vaccinated subjects who did not present with TB disease, according to any case definition, and did not have a GeneXpert-positive sputum at screening and will include all TB cases occurring post-dose 1.

The TVC analysis will be performed per treatment actually administered at dose 1.

6.2. According-to-protocol cohort for analysis of safety

The ATP cohort for analysis of safety will include all vaccinated and eligible subjects:

- Who did not have a GeneXpert-positive sputum at screening
- Who have received at least one dose of study vaccine according to their random assignment.
- For whom study vaccines have been administered according to protocol (administration site and route).
- Who have not received a vaccine that may lead to elimination from an ATP analysis.
- Who have received a vaccine (effective treatment number) without a temperature deviation.
- Who have received a vaccine (effective treatment number) before its expiration date.
- For whom the randomisation code has not been broken.
- Without randomisation failure.

For the analysis of solicited AEs and clinical laboratory observations, the ATP cohort for safety will include subjects from the safety and immunogenicity sub-cohort only.

6.3. According-to-protocol cohort for analysis of immunogenicity

The ATP cohort for immunogenicity will include all subjects from the safety and immunogenicity sub-cohort and from the ATP cohort for safety:

- Who are without selected protocol violation linked to the inclusion/exclusion criteria (whose age is not in 18-50 years, who are HIV+ at screening, who have negative Interferon-Gamma Release Assay (IGRA) at screening, or, who have a GeneXpert-positive sputum at screening) (note if rescreening, or double result at screening, use the last one for each of the considered test)

- Who received two vaccinations according to protocol procedures within specified intervals.
- Who complied with blood sampling schedules.
- Who did not present with TB disease, according to any definition, during the study.
- Who did not get HIV-infected during the study.
- Who had biochemistry and haematology values within normal range before any vaccination (exclude only if all values were out of range).
- For whom post vaccination blood samples are available.
- Who did not receive a vaccine/medication that may lead to elimination of an ATP analysis.
- Who did not present with a medical condition that may lead to elimination of an ATP analysis.
- Who signed the informed consent for the safety and immune sub-cohort.
- For whom the randomization code has not been broken.
- Without randomisation failure.

6.4. According-to-protocol cohort for analysis of efficacy

The ATP cohort for efficacy will include all subjects from the ATP cohort for safety:

- Who received 2 doses of M72/AS01$_E$ or placebo according to their random assignment.
- Received both vaccinations according to protocol procedures (correct site and route) within specified intervals.
- Who entered the evaluation period for efficacy starting one month post-dose 2, i.e. who have entered into the efficacy surveillance period.
- Who did not present with TB disease, according to any case definition, during the vaccination period (day of first vaccination up to 1 month post-dose 2).
- Who did not receive a vaccine/medication that the CRDL assesses as justifying elimination from the ATP analysis.
- Who did not present with a medical condition that the CRDL assesses as justifying elimination from the ATP analysis.
- Who have received a vaccine (effective treatment number) without a temperature deviation.
- Who have received a vaccine (effective treatment number) before its expiration date.
- For whom the randomization code has not been broken.
- Without randomisation failure.

7. STUDY DESIGN AND PROCEDURES

Refer to latest version of the protocol.

8. GENERAL STUDY ASPECTS

Refer to latest version of the protocol.

9. PLANNING OF ACTIVITIES

Timeframe	Activities
FSFV	August 2014
During the study	Several analyses for IDMC, especially before last subject last dose 2
Before datalock point	Clean ATP efficacy

Before datalock point, a first check of the elimination codes to be assigned to subjects for the ATP cohort for efficacy (and safety) will be organised (draft Pre-Analysis Meeting PAM). After all subjects have completed 24 months of follow-up, the final PAM for the primary analysis will be organised.

Timeframe	Activities
Every 2 months	Case review
2-3 times/year	IDMC
When 18 primary TB cases are accrued	Weekly case review
From 21 primary TB cases are accrued until all subjects complete their M24 visit	Continuous review of the entire database by the data management and preparation of the triggered primary analysis
When all subjects have completed 24 months of follow-up	All analyses will be performed by an external statistician: efficacy analysis + IDMC + Analysis of safety with masking of single events
Month 36 (study completion)	All analyses

10. ANALYSIS OF EFFICACY

10.1. Time-to-event variables

The time-to-event variable will be the time elapsed from the time origin to the end date (end of the follow-up for that subject). In order to avoid mathematical problems which would occur in case the time variable equals zero when an event occurred the same day as the time origin, the first day counts as 1 thus the time to event is calculated as (end date – date of time origin + 1).

The time origin for the start of follow-up in the TVC for efficacy will be the date of the Day 0 visit (date of the first dose of study vaccine) and all cases occurring after Day 0 will be included in the analysis.

The time origin for the start of the follow-up in the ATP cohort for efficacy will be the date of 30 days post dose 2 and all cases occurring on or after 30 days post dose 2 will be included in the analysis.

Table 3 Time origin

Analysis	Cohort	Risk Period	Start
Triggered Primary Analysis	ATP	[30 days post dose 2 – time when all subjects have completed 24 months of follow-up]	30 days post dose 2 of M72/AS01$_E$ or placebo
Triggered Primary Analysis	TVC	[day of first vaccination-time when all subjects have completed 24 months of follow-up]	Day of first vaccination of M72/AS01$_E$ or placebo vaccine
End of study analysis	ATP	[30 days post dose 2 – Month 36]	30 days post dose 2 of M72/AS01$_E$ or placebo
End of study analysis	TVC	[day of first vaccination-Month 36]	Day of first vaccination of M72/AS01$_E$ or placebo vaccine

ATP = ATP cohort for efficacy
TVC = Total Vaccinated Cohort

10.2. Triggered Primary Analysis when all subjects have completed 24 months of follow-up

As explained in Section 9, the date of the last month 24 visit will be monitored. This calendar date will be defined as the database lock.

Cleaning of the required data will be performed as extensively as possible before that calendar date, but finalization of cleaning will occur during several weeks following this calendar date. Therefore the database freeze will only occur after end of cleaning of the data which will then be analysed. Therefore, the table below describes what will happen to data collected before the database lock, and between the database lock and the freezing.

A period of 6 weeks is planned between database lock and database freeze (DBF) in order to obtain laboratory confirmation of most of the TB suspicions that could remain unconfirmed at the time of database lock.

Table 4 Censoring rules for triggered primary analysis when all subjects have completed 24 months of follow-up

Scenario	Sub-scenario	End date and censoring
Subjects with a suspicion of TB before the data lock point** but unconfirmed by laboratory results	Laboratory results confirmed positively before database freeze	End date = date when suspicion of TB is identified Case = yes → not censored
Subjects with a suspicion of TB before the data lock point** but unconfirmed by laboratory results	Laboratory results confirmed negatively before database freeze	End date = data lock point** Case = no → censored
Subjects with a suspicion of TB before the data lock point** but unconfirmed by laboratory results	Laboratory results not confirmed before database freeze *	End date = date when suspicion of TB is identified Case = no → censored
Subjects with a suspicion of TB before the data lock point** and confirmed positively by laboratory results before the data lock point**		End date = date when suspicion of TB is identified Case = yes → not censored
Cases when suspicion of TB is identified with a date after the data lock point**.		End date = data lock point** Case = no → censored
Subjects having finished the study (month 36) before the data lock point** without being a case		End date = date of month 36 visit Case = no → censored
Subjects dropping-out before the data lock point** without being a case		End date = last contact date Case = no → censored
Subjects still on study and not yet a case by the time of the data lock point**.		End date = data lock point** Case = no → censored

*Should be with very small frequency due to the lapse of time (6 weeks) considered between database lock point and database freeze

**Data lock point = last subject M24 visit date

Note: In this table, only lab confirmation or not of the TB suspicion is considered, but there are other elements involved in the case definitions, elements which differ from case definition to case definition (ex: HIV status at time of TB diagnosis or timing of sputum sample with respect to TB treatment start). Therefor the censoring occurs for the non-cases at the date when last subject month 24 visit is completed (database lock point), or Month 36 visit or last contact date or date of suspicion if lab data is pending or date of positive lab result if not satisfying the considered case definition whichever comes first.

10.3. End of Study analysis (EOS)

For the analysis at the end of the study: for non-cases, the end date is the date of the last contact for drop-out or the date of the Month 36 visit for subjects who went up to the end of the study. The time is then considered as censored.

For the analysis at the end of the study, for the cases, the end date is the date when suspicion of TB was identified for TB cases 1 to 6.

Table 5 Censoring rules for EOS analysis

Scenario	End date and censoring
Cases	End date = date when suspicion of TB is identified Case = yes → not censored
Subjects having finished the study (Month 36) without being a case	End date = date of Month 36 visit Case = no → censored
Subjects dropping-out without being a case	End date = last contact date Case = no → censored

11. STATISTICAL METHODS

11.1. Overview of recruitment

A line plot of subject accrual by study centre for all subjects in the TVC population as of date of data cut-off will be presented. Time elapsed from study start will be presented on the x-axis; the cumulative number of subjects vaccinated at each time from start will be presented on the y-axis. The figure will plot subject accrual by study centre (e.g., using separate lines representing study centres) and total.

11.2. Demography, study cohorts and baseline characteristics

11.2.1. Study cohorts

The reasons why screened subjects are not enrolled will be displayed by treatment group.

The number of subjects who attended each study visit and the identification numbers of subjects who withdrew from the study along with the reason for withdrawal will be displayed per treatment group. As this gives a list of identification numbers per group, this will only be produced for the EOS analysis.

Reasons for drop-out from the study will also be summarised by vaccine group for both the triggered primary analysis when all subjects have completed their Month 24 visit and for the end of study analysis.

The age at the first vaccination and the intervals between visits defined in the protocol should be followed as closely as possible. Subjects falling outside of these intervals will be reviewed and excluded from the ATP immunogenicity analysis (code 2xxx) if they don't respect the maximum interval allowed and excluded from the ATP efficacy analysis for the interval between the 2 doses of the TB vaccine or placebo (code 3xxx):

Table 6 Intervals between study visits

Interval	Size of interval per protocol*	Maximum interval allowed	Elimination code
Visit 1 (screening) → Visit 2 (Day 0)	0-30 days	0 to 30 days	No elimination code
Visit 2 (Day 0)→ Visit 4 (Day 30)	26-35 days	26 to 50 days**	code 2080 and 3080
Visit 4 (Day 30)→Visit 6 (Day 60)	26-35 days	26 to 50 days**	code 2090
Visit 4 (Day 30)→Visit 7 (Month 12)	10 months -12 months	285 days- 380 days **	code 2090
Visit 4 (Day 30)→Visit 8 (Month 24)	22 months -24 months	645 days- 745 days **	code 2090
Visit 4 (Day 30)→Visit 9 (Month 36)	34 months -36 months	1005 days- 1110 days **	code 2090
Visit n → next contact	6 weeks -12 weeks	42 days- 84 days	No elimination code
Contact n→Contact n+1	6 weeks -12 weeks	42 days- 84 days	No elimination code

*Subjects may be eligible for inclusion in the ATP cohort for analysis if they make the study visit outside this interval.
** Subjects will not be eligible for inclusion in the ATP cohort for immunogenicity (code 2xxx) or efficacy (code 3xxx) analysis if they make the study visit outside this interval.

Table 7 Intervals between study visits specific for the safety and immunogenicity sub-cohort

Interval	Size of interval per protocol	Elimination code
Visit 2 (Day 0) - Visit 3 (Day 7)	6 days - 10 days	No elimination code
Visit 4 (Day 30)- Visit 5 (Day 37)	6 days - 10 days	No elimination code

The number and percentage of subjects included in each of the study cohorts as well as the reason(s) for elimination will be presented per treatment group: One table for subjects of the safety and immunogenicity sub-cohort to indicate those subjects who are eliminated from safety and/or immunogenicity analyses and one table for all the subjects to indicate those who are eliminated from safety and/or efficacy analyses.

For each activity, the minimum and maximum dates over all vaccinated subjects will be presented per treatment group.

Enrolment in each study site will be tabulated by group.

11.2.2. Demography and baseline characteristics

All the analyses in this section will be presented by treatment group, and also by study centres and treatment group and by country and treatment group.

Demography and baseline characteristics will be displayed in one table for all subjects in the TVC, in TVC for efficacy, in the ATP for efficacy and in the ATP for immunogenicity.

Categorical variables will be presented by percentages and numerical variables will be summarized by mean, standard deviation, minimum, Q1, median, Q3, and maximum. For the age, minimum and maximum will not be presented.

Demographic parameters (age at first vaccination, gender and race) will be presented by treatment group. The Body Mass Index (BMI) at baseline will be summarized by mean, standard deviation, minimum, Q1, median, Q3 and maximum by group for all subjects.

The percentage of subjects recently exposed (within the last 12 months) to a household contact diagnosed with and/or treated for pulmonary TB disease will be presented by treatment group.

The percentage of subjects diagnosed with diabetes at screening will be presented by treatment group.

The percentage of subjects diagnosed with a chronic pulmonary condition such as asthma, COPD at screening will be presented by treatment group.

The percentage of subjects with each of the 4 smoking histories will be presented by treatment group.

A variable indicating whether a subject was vaccinated with BCG and/or has a BCG scar (yes to one of the 2 questions) will be derived and summarized by treatment group.

11.3. Evaluation of study population during the study period

The Body Mass Index (BMI) will be summarized by mean, standard deviation, minimum, Q1, median, Q3 and maximum by group and at each timepoint when weight is measured (at baseline Day 0, at Month 12, at Month 24 and at Month 36). For the subjects who were identified as a case (whatever the definition), BMI and weight will be tabulated at baseline and at the time they meet any case definition.

The follow-up time will be summarized by mean, standard deviation, minimum, Q1, median, Q3 and maximum, by group.

All the enrolled subjects are HIV negative at entry due to the inclusion/exclusion criteria, the percentage of subjects becoming positive in each treatment group will be presented.

In case of positive HIV results, the CD4 count is measured. For those subjects, the descriptive statistics (N, mean, standard deviation, min, Q1, median, Q3, max) will be displayed by group.

11.4. Efficacy

11.4.1. Analysis

VE will be estimated from a Cox proportional hazard regression model (VE=1-hazard ratio) and 90% CIs and Wald p-value will be derived. The primary analysis will be unadjusted but secondary analyses will evaluate the effect of potential covariates.

At the case-driven analysis of efficacy (primary analysis), the success criterion for the primary objective is the following:

The LL of the 90% two-sided CI for the VE (using a Cox regression model) against first occurrence of Definite pulmonary TB disease not associated with HIV-infection, meeting the first case definition, is above 0%.

Kaplan-Meier survival curves for the vaccine and control groups will be presented together with p-values from the logrank test.

If the primary objective is met, the confirmatory secondary objective will be evaluated with the following success criterion:

The LL of the 90% two-sided CI for the VE (using a Cox regression model) against first occurrence of Definite pulmonary TB disease not associated with HIV-infection, meeting the second case definition, is above 0%.

For all other secondary efficacy objectives, Kaplan-Meier survival curves will be plotted and compared by means of the logrank test. The magnitude of the vaccine efficacy will be estimated using Cox regression.

For the primary case definition, the number and proportion of cases will be given by vaccine group and by the number of doses received (1 or 2).

11.4.2. Treatment of ties

In case of ties (i.e. more than one case at the same time, very unlikely with such a small incidence), the Breslow method will be used.

11.4.3. Covariates

The Cox regression methodology can take into account specific risk factors which might have been imbalanced, by chance, at the beginning of the trial between the vaccinated and control group.

As a secondary analysis, ATP analyses evaluating first or only episodes of first case definition will also be performed adjusting for other covariates. Covariates are:

- Country
- Gender
- Diabetes at screening
- Year of occurrence (time-dependent covariable, treated differently)
- Age: ≤25, >25
- The variable indicating whether a subject was vaccinated with BCG and/or has a BCG scar
- Smoking: currently smoker or not

Please find in the below table how the variable indicating whether a subject was vaccinated with BCG and/or has a BCG scar is defined based on data coming from the CRF

CRF categories for BCG history (previous BCG vaccination)	CRF categories for presence of a BCG vaccination scar	The covariate= subject was vaccinated with BCG and/or has a BCG scar
Yes	Yes	Yes
Yes	No	Yes
Yes	Not done	Yes
No	Yes	Yes
No	No	No
No	Not done	Unknown
Unknown	Yes	Yes
Unknown	No	Unknown
Unknown	Not done	Unknown

Please find in the below table how the current smoker is defined based on data coming from the CRF

Categories for smoking history in the CRF	Current smoker
Yes, currently smoking cigarettes every day	Yes
Yes, currently smoking cigarettes some days	Yes
No, currently not but previously regularly	No
No, currently not but never regularly	No

The VE will be given at each level of each of these covariates, like for a subgroup analysis. A forest plot will be given representing these VE and their 90% CI. This is really exploratory and requires caution in interpretation due to the low number of cases.

Due to the low number of cases, the decision to adjust for all the covariates all together or in a univariate way will be taken based on the outcome of the model fit (if standard deviation is too high, or coefficient is infinity or the model did not converge, then the adjustment will be univariate, covariate by covariate separately, [Harrell1984], [Harrell1996], [Peduzzi1996] Subjects with missing values for the covariates taken into account into the model will be not considered into the model.

For the year of occurrence, as it is a time-dependent covariate, this will be analysed through the piecewise Cox model.

```
proc phreg data=TB OUTEST=oo COVOUT;;
model fu_year*event(0)=treatt1 treatt2;
treatt1 = GROUP * (fu_year LE 1.5);
treatt2 = GROUP * (1.5 < fu_year );
run;
```

The hazard ratio and VE with the CI will be computed inside each interval. The 90% CI for the hazard ratio linked to the i interval is equal to exp (estimate of the coefficient for the i interval ± 1.645* standard error for the estimator of the coefficient for the i° interval)

11.4.4. Check of the assumption of the proportional hazards under the Cox regression

Cox regression assumes proportional hazards throughout the follow-up period. This assumption will be checked by including a time-varying covariate, an interaction between the treatment and the time-to-event. This can be done easily within proc phreg. If the interaction term between time and group is significant, the null hypothesis of proportionality is rejected.

Time Dependent Cox model

```
proc phreg data=TB_effic;
model fu_year*event(0)=GROUP treatt;
treatt=group*log(fu_year+1);   *+1 is useful to avoid problems at
time=0;
run;
```

If this assumption of proportion hazards is not respected,

We will further investigate other methods to investigate the variability of the VE over time using a more flexible time-dependent Cox model where we split the time into few intervals and we estimate the hazard ratio within each interval (piecewise Cox model). The problem of the piecewise Cox model is that results will depend on the chosen intervals. In our case, the follow-up time could be split into two periods due to the small number of cases, for example as following.

```
proc phreg data=TB OUTEST=oo COVOUT;;
model fu_year*event(0)=treatt1 treatt2;
treatt1 = GROUP * (fu_year LE 1.5);
treatt2 = GROUP * (1.5 < fu_year );
run;
```

The split will be decided based on the distribution of the cases over the study time later on following this rule: It will be the time where half of the events has been observed

The hazard ratio and VE with the CI will be computed inside each interval. The 90% CI for the hazard ratio linked to the i° interval is equal to exp (estimate of the coefficient for the i° interval ± 1.645* standard error for the estimator of the coefficient for the i° interval)

11.4.5. Methods for Confidence Intervals (CIs) for Vaccine Efficacy based on Cox regression

The CI for VE can then be derived from the Wald CI from Hazard Ratio. This method is implemented in the PHREG procedure of the SAS/STAT package (SAS V9.2).

11.5. Details on case definition 1

For subjects falling into case definition 1, the GeneXpert result (positive, negative/missing) will be cross tabulated with the culture result inside the 2 vaccine groups only for the end of study analysis.

11.6. Details on case whatever the definition

For the subjects who were identified as a case (whatever the definition), the percentage of cases with specific symptoms will be tabulated (not split by groups)

11.7. Assessment of cases versus baseline characteristics

The descriptive statistics (N, mean, standard deviation, min, Q1, median, Q3, max) of the age of the cases will be displayed without split by group for the triggered primary analysis but by group for the end of study analysis.

The distribution of the cases (n) will be given according to gender and according to country without any split by vaccine group for the triggered primary analysis but by group for the end of study analysis.

11.8. Sensitivity analysis for the case definition 1

11.8.1. Sensitivity excluding single positives

During accrual of cases of active pulmonary TB in study TB-018, an unexpectedly high proportion of primary case definition was found to be positive by only one test out of six (3 real-time PCR and 3 cultures performed on sputa collected on different days)

The observations are hypothesized to correlate with intermittent shedding and low bacterial load in the sputa of early-onset active pulmonary TB. The primary objective of the study was concluded to remain appropriate (i.e. diagnosis confirmed by at least one positive GeneXpert or microbiological confirmation test, so it includes even single-positive result out of the 6 performed). However in view of the high number of single-positive cases, the team concluded that the primary analysis should be complemented by a sensitivity analysis excluding single-positive cases.

VE will be estimated from a Cox proportional hazard regression model (VE=1-hazard ratio) and 90% CIs and Wald p-value will be derived. The sensitivity analysis will be unadjusted and performed in the ATP cohort for efficacy. If needed, further exploratory analysis might be performed.

Kaplan-Meier survival curves for the vaccine and control groups will be presented together with p-values from the logrank test.

11.8.2. Conditional exact method for VE and its CI (instead of the cox regression)

VE will consider the exact inference on the relative risk conditionally to the total number of TB cases (according to each case definition) observed and time at risk.

This method computes an exact confidence interval (CI) around the rate ratio (ratio of the event rates in the vaccinated versus control group) and takes into account the sum of the time at risk of the subjects within each group.

RR is defined as the ratio of the incidence rates of the vaccine group over the placebo group.

VE = 1 – RR.A forest plot will be given representing the VE at each level of each of the covariates (see section 11.4.3) (and their 90% CI) using this conditional exact method. This is really exploratory and requires caution in interpretation due to the low number of cases.

For technical details, see section 16.

11.9. Immunogenicity

11.9.1. Cohorts and safety and immunogenicity sub-cohort

The primary analysis will be based on the ATP cohort for analysis of immunogenicity, which includes subjects from the safety and immunogenicity sub-cohort only. If, in any vaccine group, the percentage of vaccinated subjects with immunogenicity results excluded from the ATP cohort for analysis of immunogenicity is 5% or more, a second analysis based on the TVC, including subjects from the safety and immunogenicity sub-cohort only, will be performed to complement the ATP analysis.

11.9.2. Lab assays for immunogenicity

The following tables describe the lab assays that will be performed for immunogenicity assessment:

Table 8 Humoral Immunity (Antibody determination)

System	Component	Method	Kit/Manufacturer	Unit	Cut-off	Laboratory
Serum	*Mycobacterium tuberculosis*.M72 Ab.IgG	ELISA	Not Applicable	ELISA unit per millilitre	2.8	CEVAC or as designated by GSK Biologicals

Table 9 Cell-Mediated Immunity (CMI)

System	Component	Challenge	Method	Unit	Cut-off	Laboratory
Whole blood	CD4+/CD8+ T-cells expressing at least two immune markers (CD40L and/or IL-2 and/or TNF-α and/or IFN-γ) and any combination among CD40L, IFN-γ, IL-2 and TNF-α	M72	ICS - intracellular Cytokine Staining	Number of events per million cells	N/A	GSK or as designated by GSK

11.9.3. CMI and humoral immune responses

11.9.3.1. M72-specific CD4+/CD8+ T-cells expressing at least two different immune markers (IFN-γ and/or IL-2 and/or TNF-α and/or CD40L)

The following parameters will be tabulated at Days 0, 60 and Years 1, 2 and 3:

- Descriptive statistics of the frequency of M72-specific CD4+/CD8+ T-cells per million cells identified after *in vitro* stimulation expressing at least two different immune markers (IFN-γ and/or IL-2 and/or TNF-α and/or CD40L) after background subtraction for each treatment group.
- A box and whiskers plot of the frequency of M72-specific CD4+/CD8+ T-cells expressing at least two different immune markers (IFN-γ and/or IL-2 and/or TNF-α and/or CD40L) for the M72/AS01$_E$ group.

- Comparison of the frequency of M72-specific CD4+/CD8+ T-cells expressing at least two different immune markers (IFN-γ and/or IL-2 and/or TNF-α and/or CD40L) between PRE and all time points for the M72/AS01$_E$ group.
- Comparison of the frequency of M72-specific CD4+/CD8+ T-cells expressing at least two different immune markers (IFN-γ and/or IL-2 and/or TNF-α and/or CD40L) between PII(D60) and all time points for the M72/AS01$_E$ groups.
- Percentage of responders for M72-specific CD4+/ CD8+ T-cells expressing at least two different immune markers (IFN-γ and/or IL-2 and/or TNF-α and/or CD40L) for treatment group, according to different responder definitions (see Section 12.2.2)

P-value below 5% will be used to identify events that are recognised as worthy of further investigation and such comparisons should be considered as purely exploratory. Such a caution is driven by the problem of unadjustment for multiplicity of tests, potentially a lack of power and that the clinical/biological relevance of the difference is not accounted for.

11.9.3.2. M72-specific CD4+/CD8+ T-cells expressing any combination of immune markers among IFN-γ, TNF-α, IL-2 and CD40L

The following parameters will be tabulated at Days 0, 60 and Years 1, 2 and 3:

- Descriptive statistics of the frequency of M72-specific CD4+/CD8+ T-cells per million cells identified after *in vitro* stimulation expressing any combination of immune markers among CD40L, IFN-γ, IL-2 and TNF-α, after background subtraction for each treatment group.
- A box and whiskers plot of the frequency of M72-specific CD4+/CD8+ T-cells expressing any combination of immune markers among CD40L, IFN-γ, IL-2 and TNF-α, for M72/AS01$_E$ group.
- Descriptive statistics of the frequency of M72-specific CD4+/CD8+ T-cells expressing any combination of immune markers among IFN-γ, TNF-α and IL-2 for each treatment group.
- A box and whiskers plot of the frequency of M72-specific CD4+/CD8+ T-cells expressing any combination of immune markers among IFN-γ, TNF-α and IL-2 for the M72/AS01$_E$ group.
- Descriptive statistics of the frequency of M72-specific CD4+/CD8+ T-cells expressing at least IL-2 for each treatment group (total IL-2).
- Descriptive statistics of the frequency of M72-specific CD4+/CD8+ T-cells expressing at least IFN-γ for each treatment group (total IFN-γ).
- Descriptive statistics of the frequency of M72-specific CD4+/CD8+ T-cells expressing at least TNF-γ for each treatment group (total TNF-α).
- Box and whiskers plots of the frequency of M72-specific CD4+/CD8+ T-cells expressing at least IL-2, at least IFN-γ or at least TNF-α for the M72/AS01$_E$ group.

- Comparison of M72-specific CD4+ cells expressing at least IL-2, at least IFN-γ or at least TNF-α between PRE-and all timepoints for the M72/AS01$_E$ group.
- Comparison of M72-specific CD4+ cells expressing at least IL-2, at least IFN-γ and at least TNF-α between PII(D60) and all timepoints for the M72/AS01$_E$ group.

P-value below 5% will be used to identify events that are recognised as worthy of further investigation and such comparisons should be considered as purely exploratory. Such a caution is driven by the problem of adjustment for multiplicity of tests, potentially a lack of power and that the clinical relevance of the difference is not accounted for.

11.9.3.3. Humoral immune responses

For anti-M72 antibody responses, the following parameters will be tabulated at Days 0, 60 and Years 1, 2 and 3:

- Geometric mean concentrations (GMCs) and seropositivity rates with 95% CIs for each treatment group.
- Evolution of GMCs and 95% CIs will be presented graphically for the M72/AS01$_E$ group.
- Comparison of log (antibody concentrations) between PRE and all post-vaccination timepoints for the M72/AS01$_E$ group
- GM of ratios of anti-M72 antibody titres at each post-vaccination timepoint over pre vaccination will be tabulated with 95% CI for each treatment group.

11.10. Reactogenicity

11.10.1. Cohorts

The primary analysis will be based on the TVC. If, in any vaccine group, the percentage of vaccinated subjects excluded from the ATP cohort for analysis of safety is more than 5%, a second analysis based on this ATP cohort for analysis of safety will be performed to complement the TVC analysis.

Analyses of solicited (local and general) AEs and clinical laboratory observations will be performed for the safety and immunogenicity sub-cohort only.

11.10.2. Exposure

An overview of the number of vaccine doses received will be displayed by treatment group

11.10.3. Compliance

The compliance in retuning symptoms sheets (SS) will be described in the safety and immunogenicity sub-cohort.

The number of doses administered, the number of doses not given according-to-protocol, the number of SS transcribed for local and general symptoms, and the compliance for local and general symptoms will be tabulated by treatment group. Compliance (%) is defined as the number of (local/general) SS completed divided by the number of doses administered for a specified group. The number of doses not given according-to-protocol is the number of doses administered at wrong site, or administered using a wrong route as compared to the protocol specifications (per protocol, site is deltoid and route is intramuscular)

11.10.4. All symptoms

This analysis will be performed in the safety and immunogenicity sub-cohort.

- The percentage of subjects with at least one local AE (solicited and/or unsolicited), with at least one general AE (solicited and/or unsolicited) and with any AE during the solicited follow-up period (Day 0 to Day 6) will be tabulated by treatment group with exact 95% CI after each vaccine injection and overall.
- The percentage of doses followed by at least one local AE (solicited and/or unsolicited), by at least one general AE (solicited and/or unsolicited) and by any AE will be tabulated by treatment group, overall vaccination course, with exact 95% CI.

The same tabulations will be done for grade 3 AEs and for AEs causally related to vaccination.

11.11. Solicited symptoms

The analysis of solicited symptoms will be performed in the safety and immunogenicity sub-cohort.

The number and percentage of subjects reporting each individual solicited local (any, grade ≥ 2, grade 3) and general (any, related to vaccination, grade ≥ 2, grade 3, grade ≥ 2 related to vaccination and grade 3 related to vaccination) AE during the solicited follow-up period will be tabulated by treatment group with exact 95% CI.

The number and percentage of doses followed by each individual solicited local (any, grade ≥ 2 and grade 3) and general (any, related to vaccination, grade ≥ 2, grade 3, grade ≥ 2 related to vaccination and grade 3 related to vaccination) AE will be tabulated by treatment group, overall vaccination course, with exact 95% CI.

The percentage of doses followed by each individual solicited local and general (any, grade 3) AE will be presented in a bar chart by treatment group, overall vaccination course (2 doses combined), with exact 95% CI.

Occurrence of fever will also be reported per 0.5°C cumulative increments.

The number of days with a solicited symptom during the solicited follow-up period will also be presented by treatment group. The same tabulations will be done for grade 3 AEs and for general AEs with relationship to vaccination.

The number of days with a solicited symptom during the solicited follow-up period and beyond will also be presented by treatment group. The same tabulations will be done for grade 3 AEs and for general AEs with relationship to vaccination.

The number of solicited local and general symptoms ongoing beyond the 7-day post-vaccination period is given by treatment group as well as descriptive statistics (Q1, median, Q3) concerning the time-to-resolution (in days from the last day of the follow-up period to the last day the symptom was observed).

11.12. Large swelling reaction

In case a subject had a large swelling reaction after dose 1, the dose 2 should not be given to this subject. Therefore the summary is not per dose, but overall per subject whether the report of large swelling is after dose 1 or dose 2.

To check this per-protocol requirement, we will produce a list of subjects having reported large swelling reaction after dose 1, and received dose 2 nevertheless.

The number and percentage of subjects who experienced a large swelling reaction during the 30-day post-dose-1 vaccination period will be tabulated by treatment group with two-sided exact 95% CI.

The number and percentage of subjects who experienced a large swelling reaction during the 30-day post-dose-2 vaccination period will be tabulated by treatment group with two-sided exact 95% CI.

The number and percentage of subjects reporting large swelling reaction during the 30-day post vaccination period will be tabulated by treatment group with two-sided exact 95% CI.

The duration (=AE end date- AE start date+1) and the size of the large swelling reaction will be summarised by descriptive statistics such as mean, standard deviation, and minimum, Q1, median, Q3 and maximum values.

The presence of a large swelling reaction in a subject indicates with a high probability that the subject comes from the TB vaccine group but we will not eliminate any of these subjects from none of the ATP cohort (for efficacy, immunogenicity and safety).

11.13. Unsolicited symptoms

The proportion of subjects/doses with at least one report of unsolicited AE classified by the Medical Dictionary for Regulatory Activities (MedDRA) reported during the 30-day follow-up period (Days 0 to 29) will be tabulated with exact 95% CI by treatment group.

The same tabulations will be done for grade 3 AEs, AEs related to vaccination, grade 3 events related to vaccination and AEs resulting in a medically attended visit.

As only the subjects part of the safety and immunogenicity sub-cohort have a diary card to collect the solicited AEs, those symptoms (redness, swelling, pain at injection site, fever, headache, respiratory symptoms, malaise, myalgia)) reported for the other subjects were recorded in the Case Report Form (CRF) section on unsolicited symptoms. Therefore to assess the impact of this situation, the following analyses will be proposed:

- The same analysis will be produced for the subjects with diary cards (part of the safety and immunogenicity sub-cohort).
- The proportion of subjects/doses with at least one report of unsolicited AE classified by MedDRA reported during the 7-day follow-up period (Days 0 to 7) will be tabulated with exact 95% CI by treatment group. Idem for grade 3 AEs, AEs related to vaccination, grade 3 events related to vaccination.
- The proportion of subjects/doses with at least one report of unsolicited AE classified by MedDRA reported after the 7-day follow-up period (Days 7 to 29) will be tabulated with exact 95% CI by treatment group. Idem for grade 3 AEs, AEs related to vaccination, grade 3 events related to vaccination.

The proportion of subjects with at least one report of unsolicited AE associated to the respiratory system classified by the MedDRA reported during the 90-day post-vaccination follow-up period (on or after Day 0 to Day 89) will be tabulated with exact 95% CI by treatment group, for all subjects in the TVC population.

The same tabulation will be done for, grade 2 or 3 AE associated to the respiratory system, grade 3 AE associated to the respiratory system, AE associated to the respiratory system related to vaccination, grade 2 or 3 AE associated to the respiratory system related to vaccination and grade 3 AE associated to the respiratory system related to vaccination.

The proportion of subjects with at least one report of grade 3 unsolicited AE associated to the respiratory system classified by the MedDRA reported during the 30-day post-vaccination follow-up period (on or after Day 0 to Day 29) will be tabulated with exact 95% CI by treatment group, for all subjects in the TVC population

Note that the list of preferred terms (PTs) “associated to the respiratory system” is actually the list of PTs which map to the MedDRA System Organ Class (SOC) of “Respiratory, thoracic or mediastinal conditions” regardless if this is their primary SOC or not.

11.14. Serious adverse events

Percentage of subjects reporting the occurrence of SAEs classified by MedDRA Primary S O C and P T will be tabulated with exact 95% CI by treatment group.

The same tabulations will be done for SAEs with causal relationship to vaccination and for fatal SAEs.

As reporting periods for AE, SAEs and related SAE differ, these tabulations will be done for events occurring during the 30-Day (Days 0-29) post vaccination, during the period from Day 0 to Month 7 and during the entire study period as indicated in the following table.

	Post vaccination period considered		
	30-day post-vaccination period	From Day 0 to Month 7	From Day 0 to end of study*
SAEs	X	X	X**
Related-SAE(s)	X	X	X
Fatal SAE(s)			X

* For the triggered primary analysis: it will be from day 0 to database freeze
** performed only for the CTR tables

11.15. Potential Immune Mediated Diseases (pIMDs)

The proportion of subjects with at least one report of pIMDs classified by the MedDRA reported during the study period up to 6 months post-dose 2 will be tabulated with exact 95% CI by treatment group.

11.16. Concomitant medication

The number and percentage of subjects with concomitant medication(s), with antipyretics and with immunosuppressant within 30 days post-vaccination will be tabulated with exact 95% CI by treatment group. Concomitant medications will be classified in antipyretics and immunosuppressant according to MedDRA.

11.17. Haematological and biochemical parameters

The analysis of haematological and biochemical parameters will be performed on the safety and immunogenicity sub-cohort.

The frequency distribution of values below and above the site-specific normal ranges will be tabulated per treatment group at each scheduled timepoint (Day 0, Day 7, Day 30 and Day 37).

In addition, change from baseline will also be tabulated by treatment group.

Number and percentage of subjects outside the normal range by severity grading for haematology and biochemistry will be tabulated by treatment group.

For subjects with at least one grade 3 or 4 laboratory value for a specific biochemistry or haematology parameter (TVC), all the values for this specific laboratory parameter will be given for this subject at all timepoints when lab assessments are done

For the toxicity grading scale for haematology and biochemistry, the Food and Drug Administration (FDA) grading for prophylactic vaccine trials was used (Guidance for Industry - Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials – Sep 2007):

Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Alanine Aminotransferase	[1.1 – 2.6[x ULN	[2.6 – 5.1[x ULN	[5.1 – 10.001[x ULN	≥ 10.001 x ULN
Aspartate Aminotransferase	[1.1 – 2.6[x ULN	[2.6 – 5.1[x ULN	[5.1 – 10.001[x ULN	≥ 10.001 x ULN
Creatinine (mg/dL)	[1.5 – 1.8[	[1.8 – 2.1[	[2.1 – 2.51[	≥ 2.51
Haemoglobin (Change from baseline) (g/dL)	[0.1 – 1.6[	[1.6 – 2.1[	[2.1 – 5.1[	≥ 5.1
Haemoglobin (Decrease) (Female) (g/dL)	[11 – 12.1[	[9.5 – 11[	[8 – 9.5[	< 8.0
Haemoglobin (Decrease) (Male) (g/dL)	[12.5 – 13.6[	[10.5 – 12.5[	[8.5 – 10.5[	< 8.5
Leukocytes (White Blood Cells) (Decrease) (/mm^3)	[2500 – 3501[	[1500 – 2500[	[1000 – 1500[	< 1000
Leukocytes (White Blood Cells) (Increase) (/mm^3)	[10800 – 15001[	[15001 - 20001[	[20001 - 25001[	≥ 25001
Platelets (Decrease) (/mm^3)	[125000 – 140001[	[100000 – 125000[	[25000 – 100000[	< 25000
Bilirubin – when accompanied by any increase in Liver Function Test; increase by factor	1.1 – 1.25 x ULN	1.26 – 1.5 x ULN	1.51 – 1.75 x ULN	> 1.75 x ULN
Bilirubin – when Liver Function Test is normal; increase by factor	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.0 – 3.0 x ULN	> 3.0 x ULN

ULN = upper limit of the normal range.

The bilirubin grading scale at a given time-point will depend on the liver function tests (ALT and AST) at the corresponding time-point. When both liver function tests are normal, i.e. when ALT and AST are grade 0 according to the FDA grading (reference: *FDA Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (September 2007))*, the "Bilirubin – when Liver Function Test is normal" scale will be applied while when at least one of the liver function tests (ALT or AST) is grade 1 or above, the "Bilirubin – when accompanied by any increase in Liver Function Test" scale will be applied. In the descriptive analysis, the bilirubin grades will be presented together regardless of the scale used.

Vitamin D is measured at screening in all subjects of the immuno and safety sub-cohort. Levels will be summarized by mean, standard deviation, minimum, Q1, median, Q3 and maximum by group at baseline inside the safety and immunogenicity sub-cohort.

The number and percentage of subjects with vitamin D deficiency in the immune and safety sub-cohort will be tabulated where Vitamin D deficiency is defined as serum 25(OH) D concentrations : < 20 ng/mL.

One laboratory parameter is analysed independently of the sub-cohort:

HbA1C is measured in confirmed TB cases. For those subjects, the descriptive statistics (N, mean, standard deviation, min, Q1, median, Q3, max) will be displayed by group.

11.18. Performance of culture and GeneXpert test

For all the suspicions of pulmonary TB, the result (positive/negative) for GeneXpert will be tabulated by result for culture (positive/negative) for all the pairs of results which are both available, without split by vaccine group.

This cross table will be performed without split by vaccine group as well for all suspicions which lead to treatment for TB and then further split with respect to timing of the sputum sample, so when sputum sample is taken on or before TB treatment start and separately when sputum sample is taken after TB treatment start.

12. STATISTICAL CALCULATIONS

12.1. Demography

12.1.1. Derived and transformed data

Age at the reference activity will be computed as the number of units between the date of birth and the reference activity. In case of partial dates of any of these 2 dates, the following reference dates will be used:

- 15th of month, if only the day is missing.
- 30th of June, if the day and month are missing.

12.2. Immunogenicity

12.2.1. Handling of missing data

For a given subject and a given immunogenicity measurement, missing or non-evaluable measurements will not be replaced.

Therefore, an analysis will exclude subjects with missing or non-evaluable measurements.

12.2.2. Derived and transformed data

Serology data

- The cut-off value for M72-specific antibody concentrations is 2.8 EU/mL.
- The assay cut-off is the value below which there is no quantifiable result available. For an assay with a specific ‘cut-off’, numerical immunogenicity results are derived from a character field (rawres):
  - If rawres is ‘NEG’ or ‘-’ or ‘(-)’, numeric result = cut-off/2,
  - if rawres is ‘POS’ or ‘+’ or ‘(+)’, numeric result = cut-off,

- if rawres is '< value' and value ≤ cut-off, numeric result = cut-off/2,
- if rawres is '< value' and value > cut-off, numeric result = value,
- If rawres is '> value' and value < cut-off, numeric result = cut-off/2,
- if rawres is '> value' and value ≥ cut-off, numeric result = value,
- if rawres is '≤ value' or '≥ value' and value < cut-off, numeric result = cut-off/2,
- if rawres is '≤ value' or '≥ value' and value ≥ cut-off, numeric result = value,
- if rawres is a value < cut-off, numeric result = cut-off/2,
- if rawres is a value ≥ cut-off, numeric result = rawres,
- if rawres is a value ≥ cut-off, numeric result = rawres,
- otherwise the numeric result is left blank.

- A seronegative subject is a subject whose antibody concentration is below the cut-off value.
- A seropositive subject is a subject whose antibody concentration is greater than or equal to the cut-off value.
- The seropositivity rate is defined as the percentage of seropositive subjects.
- The GMC calculations will be performed by taking the anti-log of the mean of the log10 concentration transformations. Antibody concentrations below the cut-off of the assay will be given an arbitrary value of half the cut-off for the purpose of GMC calculation.

ICS data (CD4+/CD8+ T-cells per 10^6 cells expressing at least two different immune markers [IFN-γ and/or TNF-α and/or IL-2 and/or CD40L])

- To compute the frequency of M72-specific CD4+ T-cells expressing at least 2 immune markers among IL-2, IFN-γ, TNF-α and CD40-L, there are two methods:

  Method 1:

  - Background reduction: stimulated minus background value. If the difference is < 0, then the value 1 was given.
  - Sum all the combinations with at least 2 immune markers.

  Method 2:

  - Sum of all the combinations with at least 2 immune markers for the stimulated frequencies.
  - Sum of all the combinations with at least 2 immune markers for the background frequencies.
  - Stimulated minus background value. If the difference is < 0, then the value 1 was given.

The method 2 will be used for the analysis of CD4+ T-cells polypositives.

- ICS data will be expressed as M72-specific CD4+/CD8+ T-cells per million CD4+ or CD8+ T-cells, respectively.
- A responder will be defined as a subject:
  - Whose post-vaccination frequency of cells is higher than the 95th percentile of pre-vaccination frequencies of all subjects;
  - Whose post-vaccination frequency of cells is at least 2 times/at least 3 times/at least 4 times his/her frequency of cells at pre-vaccination.

ICS data (CD4+/CD8+ T-cells expressing any combination of immune markers among IFN-γ, TNF-α, IL-2 and CD40L])

The following steps will be performed:

- Subtraction of background value for each subject,
- Replacement of negative or null value by 1,
- Calculation of new combinations of immune markers without the CD40L marker:

  CD40L was included in the ICS assay but the signal contributed by CD40L was not taken into account in this analysis.

  For example: IL-2 single positive = (IL-2$^+$) + (IL-2$^+$/CD40L$^+$)
- Calculation of M72-specific CD4+/CD8+ T-cells expressing at least IL-2 or at least IFN-γ or at least TNF-α:

  The frequency of M72-specific CD4+/CD8+ T-cells expressing at least a given immune marker represents the sum of single, double, triple, quadruple positive CD4+/CD8+ T-cells for that given immune markers

  For example: Total IL2 = (IL2+) + (TNF+/IL2+) + (IFN+/IL2+) + (IL2+/CD40L+) + (IL2+/TNF+/IFN+) + (IL2+/CD40L+/IFN+) + (IL2+/TNF+/CD40L+) + (IL2+/TNF+/IFN+/CD40L+).

12.2.3. Methodology for computing CIs

All CIs computed will be two-sided 95% CIs.

- The exact 95% CIs for a proportion within a group will be the Clopper-Pearson exact CI. [Clopper. 1934].
- The 95% CI for GMCs will be obtained within each group separately. The 95% CI for the mean of log-transformed concentration will be first obtained assuming that log-transformed values were normally distributed with unknown variance. The 95% CI for the GMCs will then be obtained by exponential transformation of the 95% CI for the mean of the log-transformed concentration.

12.3. Safety

12.3.1. Handling of missing data

Solicited symptoms

- For a given subject, missing or non-evaluable measurements will not be replaced. Therefore the analysis of solicited symptoms based on the TVC in the safety and immunogenicity sub-cohort will include only vaccinated subjects with documented safety data (i.e., symptom screen completed). More specifically the following rules will be used:
  - Subjects who documented the absence of a solicited symptom after one dose will be considered as not having that symptom after that dose.
  - Subjects who documented the presence of a solicited symptom and fully or partially recorded daily measurement over the solicited period will be included in the summaries at that dose and classified according to their maximum observed daily recording over the solicited period.
  - Subjects who documented the presence of a solicited symptom after one dose without having recorded any daily measurement will be assigned to the lowest intensity category at that dose (i.e. 37.5°C for fever or grade 1 for other symptoms).
  - Subjects without symptom sheets documented after one dose will be excluded at that dose.

Unsolicited AEs and concomitant medications

- All vaccinated subjects will be included in the analyses. Subjects who did not report the event or the concomitant medication will be considered as subjects without the event or the concomitant medication, respectively.

12.3.2. Derived and transformed data

For some solicited symptoms (fever, swelling, redness), a precise measure is recorded and at the time of data analysis, a severity coding is used to define several levels of severity.

The maximum intensity of fever and local injection site swelling and redness will be scored as follows:

Symptoms	Grade	Scale
Fever (Oral or Axillary temperature)	0	< 37.5°C
	1	[37.5°C – 38°C]
	2	] 38°C – 39.5°C]
	3	> 39.5°C
Swelling, Redness	0	<20 mm
	1	[20 mm; 50 mm]
	2	]50 mm; 100 mm]
	3	>100 mm

Note that for all tables described in this section, the way the percentage of subjects is derived will depend on the event analysed (see table below for details). As a result, the N value will differ from one table to another.

Event	N used for deriving % of subjects for Vaccination phase
Concomitant vaccination	All subjects with study vaccine administered
Solicited general symptom	All subjects with at least one solicited general symptom documented as either present or absent (i.e. symptom screen completed)
Solicited local symptom	All subjects with at least one solicited local symptom documented as either present or absent (i.e. symptom screen completed)
Unsolicited symptom	All subjects with study vaccine administered
Concomitant medication	All subjects with study vaccine administered

12.4. Decimal descriptions

The following decimal description will be used for the demography, immunogenicity and safety/ reactogenicity.

Display Table	Parameters	Number of decimal digits
Demographic characteristics	Mean, median age	1
Demographic characteristics	SD (age)	2
Reactogenicity	Mean, Min, Q1, Median, Q3, Max for duration	1
All summaries	% of count, including LL & UL of CI	1
All summaries	p-value	3

13. CONDUCT OF ANALYSES

13.1. Sequence of analyses

All analyses will be conducted on data as clean as possible.

- A triggered primary analysis will be performed when all subjects have completed the Month 24 visit. Efficacy, immunogenicity and safety data available by that time will be analysed
- A final analysis of the primary epoch including all efficacy, safety and immunology data will be performed at the end of the study, i.e. when all Month 36 visits have been completed.

Description	Analysis ID (SDD sub-folder)
Triggered Primary analysis when all subjects have completed the Month 24 visit	E1_01
Final analysis up to Month 36	E1_02

13.2. Blinding

The study is 'double-blinded' meaning that the vaccine recipient as well as those responsible for the evaluation of study endpoint data are unaware which treatment, M72/AS01$_E$ or control vaccine, was administered to a particular subject. It also means that data monitors and GSK and AERAS central staff are blinded to treatment allocation and the database kept at GSK does not contain information that can lead towards un-blinding individual trial subjects (randomization list, immunogenicity data). As the primary objective, can be analysed before trial end, specific procedures are in place to continue the trial in a blinded way. The data cleaning is performed in a blinded way and the data analysis will be performed by statisticians external to the GSK-AERAS clinical teams and the investigator groups. Moreover, analysis outputs will be checked and blinded wherever applicable for GSK and AERAS (In the tables, the external statistician will, in case of a distribution of 15 vs 0 for an unsolicited AE, put 15 in each of the 2 columns with a double star to indicate that here one of the 2 groups has 15 subjects and 0 the other, not letting us know in which group.) and no individual subjects data will be generated and distributed before formal un-blinding of the trial. No individual listings, no identification numbers by group (for example for the drop-out tables) will be produced at the triggered primary analysis when all subjects have completed their Month 24 visit. Those will only be produced for the end of study analysis.

For the IDMC, the analysis output will be fully unblinded (no double star).

If required in order to fully grasp the risk/benefit of the vaccine during the review of the primary results, specific table(s) or even specific row(s) will be unblinded after discussion, agreement and documentation. We expect blinding stars to appear in few tables, mainly for events with very small incidence.

13.2.1. Demography tables

In order to preserve the blind of the study with respect to demography outputs, tabulations that present categories only in 1 treatment group will be blinded by presenting the total number in both treatment groups as *n* indicating there are n such subjects / events in 1 of the treatment groups. In addition, the next lowest frequency occurrence (>0) will be blinded. For those tables that will be produced by site, in addition to the categories blinded out in the overall tables additional categories where there is a n to 0 imbalance will be starred out.

13.2.2. Safety tables

In order to preserve the blind of the study with respect to safety outputs, tabulations that present AEs only in 1 treatment group will be blinded by presenting the total number of AEs (n) in both treatment groups as *n* indicating there are n such events in 1 of the treatment groups.

13.2.3. Efficacy tables

In the event that in one or several levels of the covariables all events are observed in one treatment group, the results will be blinded for the affected level(s) and for one additional level in order to avoid indirect un-blinding. The additional blinded level will be selected based on the lowest number of events (>0) among the remaining levels.

VE estimates for the blinded levels will not be presented and will not be included in forest plots.

13.3. Interpretation of analyses

For the analysis of the primary objective, a predefined success criterion and an appropriate type I error control are defined. The confirmatory secondary objective will be analysed only if the primary objective is met. Because of this hierarchy, the type I error is controlled. All other analyses will be descriptive with the aim to characterise the difference in TB incidence, reactogenicity and immunogenicity between groups. These descriptive analyses should not be interpreted.

The triggered primary analysis of efficacy is the analysis where all the alpha is spent.

The sensitivity analysis is for hypothesis generation and thus not confirmatory.

13.4. Statistical considerations for interim analyses

No interim analysis of efficacy is planned.

14. CHANGES FROM PLANNED ANALYSES

The maximum allowed interval between visits was added to the per-protocol interval.

One criterion to be included in the ATP cohort of safety and to be included in the TVC for efficacy has been added:

- Who did not have a GeneXpert-positive sputum at screening

Two criteria to be included in the ATP cohort of safety and efficacy have been added:

- Who have received a vaccine (effective treatment number) without a temperature deviation
- Who have received a vaccine (effective treatment number) before its expiration date.

One criterion to be included in the ATP cohort of safety and efficacy has been removed:

- With sufficient data to perform an analysis of safety (at least one dose administered with safety follow-up).

To be in the ATP cohort for immunogenicity, the subjects have to be in the ATP cohort for safety in addition to be from the safety and immunogenicity sub-cohort.

Three criteria to be included in the ATP cohort of immunogenicity have been added:

- That are without protocol violation linked to the inclusion/exclusion criteria
- Who did not present with TB disease, according to any definition, during the study
- Who did not get HIV-infected during the study

To be in the ATP cohort for efficacy, the subjects have to be in the ATP cohort for safety.

The graph of the accrual of cases was added.

Analysis of baseline characteristics was added.

The analysis of vitamin D and vitamin D deficiency was added.

The evaluation of study population during the study period was added.

The analysis of efficacy will be conducted in the ATP cohort for efficacy and in the TVC whatever the percentage of enrolled subjects excluded from the ATP cohort of efficacy.

The sixth case definition consisting of fifth case definition with HIV negative status (exploratory endpoint) was added.

The details on how the time-to-event and the censoring at the triggered primary analysis when all subjects have completed their M24 visit and at the EOS analysis were added.

The details on the adjustment of analysis of vaccine efficacy by covariate and the list of covariates were given as well as the test one the hypothesis of proportional hazards.

The cross table for subjects falling into case definition 1, of the GeneXpert result (positive, negative/missing) with the culture result inside the 2 vaccine groups only for the end of study analysis was added.

The assessment of cases versus baseline characteristics for the primary analysis was added

The sensitivity analysis of the efficacy has been added.

The analysis of geometric mean of ratios of anti-M72 antibody titres at each post-vaccination timepoint over pre vaccination was added.

The analysis of the performance of culture and GeneXpert test was added.

Analysis of the frequency of M72-specific CD4+/CD8+ T-cells expressing any combination of immune markers among IFN-γ, TNF-α and IL-2 was added.

Analysis of the frequency of M72-specific CD4+/CD8+ T-cells expressing at least IL-2, at least IFN-γ, at least TNF-α for each treatment group was added.

The analysis of large swelling reaction was added.

The analysis of unsolicited AE associated to the respiratory system was added.

In view of the high number of single-positive cases, the team concluded that the efficacy evaluation of the M72/AS01$_E$ vaccine candidate would benefit of prolonged endpoint accrual (i.e. until 24 months of follow-up) in order to perform the primary analysis on a more representative clinical spectrum of TB. Therefore, the team chose that the triggered analysis will be performed when all subjects have completed the Month 24 visit, which was allowed and considered in the protocol.

VE will be estimated from a Cox proportional hazard regression model

The way to keep unblinding at the level of the individual subject at the triggered primary analysis when all subjects have completed their M24 visit was detailed.

15. REFERENCES

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16. ANNEX: HOW THE CONFIDENCE INTERVAL FOR VE IS COMPUTED WITH THE CONDITION EXACT METHOD

The Vaccine Efficacy (VE) can be estimated by:

$$VE = 1 - \frac{n1/N1}{n2/N2} = 1 - \frac{n1}{r * n2}$$

where n1 = number of cases in the vaccinated group

N1 = follow-up time the vaccinated group

n2 = number of cases in the control group

N2 = follow-up time in the control group

$$r = \frac{N1}{N2}$$

Conditionally to the total number of cases n = n1+ n2 and r, let p denote the proportion of cases in the vaccine group,

$$VE = 1 - \frac{n1}{n} * \frac{n}{r * (n - n1)} = 1 - p * \frac{1}{r * (1 - p)} = 1 - \frac{p}{r * (1 - p)}$$

where p = n1/n is binomially distributed.

Therefore, there is a monotonic link between VE, the true vaccine efficacy, and p, the true proportion of subjects in the vaccine group among the total cases in the two groups.

The CI for vaccine efficacy can then be derived from the exact CI from p (obtained by Clopper-Pearson method for computation of exact CIs for one proportion)