BILL & MELINDA GATES MEDICAL RESEARCH INSTITUTE

MESA-TB

Statistical Analysis Plan: MRI-TBV02-202

Study Title:	A randomized, placebo-controlled, observer-blind, phase 2 study to evaluate safety and immunogenicity of the investigational M72/AS01$_E$ *Mycobacterium tuberculosis* (*Mtb*) vaccine in virally suppressed, antiretroviral-treated participants with human immunodeficiency virus (HIV)
Study Number:	Gates MRI-TBV02-202
Study Phase:	II
Sponsor:	Bill and Melinda Gates Medical Research Institute (Gates MRI), One Kendall Square, Building 600, Suite 6-301, Cambridge MA 02139
Version	Final
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Confidentiality Statement

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Study Title: A randomized, placebo-controlled, observer-blind, phase 2 study to evaluate safety and immunogenicity of the investigational M72/AS01$_E$ *Mycobacterium tuberculosis* (*Mtb*) vaccine in virally suppressed, antiretroviral-treated participants with human immunodeficiency virus (HIV)

Study Number: Gates MRI-TBV02-202

Prepared by: [redacted]
Principal Biostatistician, Biostatistics
MMS Holdings, Inc.

DocuSigned by:
[redacted]
Signer Name: [redacted]
Signing Reason: I am the author of this document
Signing Time: 22-Feb-2022 | 10:06:18 EST
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Reviewed by: [redacted]
Manager I Biostatistics
MMS Holdings, Inc.

DocuSigned by:
[redacted]
Signer Name: [redacted]
Signing Reason: I approve this document
Signing Time: 23-Feb-2022 | 02:39:29 EST
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Approved by: [redacted]
Head of Clinical Biometrics
Gates MRI

DocuSigned by:
[redacted]
Signer Name: [redacted]
Signing Reason: I approve this document
Signing Time: 22-Feb-2022 | 08:25:09 PST
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Approved by: [redacted]
Clinical Development Leader
Gates MRI

DocuSigned by:
[redacted]
Signer Name: [redacted]
Signing Reason: I approve this document
Signing Time: 22-Feb-2022 | 07:11:42 PST
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3 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviations	Definitions
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ART	anti-retroviral therapy
ATC	Anatomical Therapeutic Class
BMI	body mass index
CAPRISA	Centre for Aids Programme of Research in South Africa
CD4	cluster of differentiation 4
CD-40L	cluster of differentiation-40 ligand
CD8	cluster of differentiation 8
CFB	change from baseline
CI	confidence interval
CMI	cell-mediated immune responses
COVID-19	Coronavirus Disease 2019
CRO	contract research organization
CTMS	Clinical Trial Management System
CV	coefficient of variation
DBL	database lock
DMSO	Dimethyl Sulfoxide
eCRF	electronic case report form
ELISA	enzyme-linked immunosorbent assay
G	gamma
GMC	geometric mean concentration
HIV	human immunodeficiency virus
ICS	Intracellular cytokine staining

Abbreviations	Definitions
IDMC	Independent Data Monitoring Committee
IFN-γ	interferon gamma
IL-2	interleukin 2
IL-22	interleukin 22
ITT	intention to treat
M72/AS01$_E$	Candidate (experimental) TB vaccine
MCAR	missing completely at random
mITT	modified intention to treat
MedDRA	Medical Dictionary for Regulatory Activities
Mtb	*Mycobacterium tuberculosis*
PBMC	peripheral blood mononuclear cells
PD	protocol deviation
pIMD	potential immune-mediated diseases
PP	Per Protocol
PT	Preferred Term
QFT	QuantiFERON
QS-21	*Quillaja saponaria* Molina, fraction 21
REML	restricted maximum likelihood
RHI	Reproductive Health and HIV Institute
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SATVI	South African Tuberculosis Vaccine Initiative
SD	standard deviation
SI	International System of Units
SOC	System Organ Class
SUSAR	serious, unexpected, suspected adverse drug reactions
TB	Tuberculosis

Abbreviations	Definitions
TBL	total bilirubin
TNF-α	tumor necrosis factor alpha
ULN	upper limit of normal
WHO	World Health Organization

4 INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the framework of the statistical analyses, including the planned tables, listings and figures to assess the safety and immunogenicity of M72/AS01E *Mycobacterium tuberculosis* (*Mtb*) vaccine in virally suppressed, antiretroviral-treated participants with human immunodeficiency virus (HIV). The details in this SAP are based on Protocol Version 3.0, dated 26 February 2021 and Independent Data Monitoring Committee (IDMC) charter, version 1.0 dated 13 October 2020.

5 TRIAL OBJECTIVES

5.1 Primary Objectives

The primary objective of this study is to assess the *safety and reactogenicity* of M72/AS01$_E$ vaccine (2-doses given one month apart) versus placebo in virally suppressed, antiretroviral-treated participants with HIV. The endpoints associated with this objective are: solicited adverse events (AEs) through 7 days post each dose of study intervention; unsolicited AEs through 28 days post each dose of study intervention; and serious adverse events (SAEs) through end of study.

5.2 Secondary Objectives

The secondary objectives of this study are to assess the following (in virally suppressed, antiretroviral-treated participants with HIV, for the M72/AS01$_E$ vaccination versus placebo):

- *safety*: The endpoints associated with this objective are: potential immune-mediated diseases (pIMDs) through end of study, safety laboratory assessments grade 3 or above through end of study.

- *humoral immunogenicity*: The endpoints associated with this objective are M72-specific antibody titers at Day 1, Day 29, Day 57, Day 210, and Day 390.

- *cellular immunogenicity*: The endpoints associated with this objective are frequency and magnitude of M72-specific cluster of differentiation 4 ($CD4^+$) and cluster of differentiation 8 ($CD8^+$) T-cell responses measured by expression of IFN-γ or IL-2 using intracellular cytokine staining (ICS) at Day 1, Day 57, and Day 390.

5.3 Exploratory Objectives

The exploratory objectives of this study are to assess the following (in virally suppressed, antiretroviral-treated participants with HIV, for the M72/AS01$_E$ vaccination versus placebo):

- *Cellular immunogenicity*: The endpoints associated with this objective are: (i) the frequency and magnitude of M72-specific CD4+ and CD8+ T-cell responses measured by expression of IFN-γ or IL-2 by ICS at Day 29 and Day 210, and (ii) the polyfunctionality of M72-specific CD4+ and CD8+ T-cell responses measured by co-expression of multiple functional markers by ICS at all timepoints.

- *HIV viral load* post-M72/AS01$_E$: The endpoint associated with this objective is frequencies of participants with confirmed HIV ribonucleic acid ([RNA] > 200 copies/mL) at Day 57, Day 210, and Day 390.

- *changes in $CD4^+$ T cell count* from baseline: The endpoint associated with this objective is the mean change in CD4+ T cell from baseline at Day 57, Day 210, and Day 390.

- *incidence of suspected TB disease and laboratory confirmed pulmonary TB disease:* The endpoints associated with this objective are: suspected TB during the study and laboratory-confirmed pulmonary TB during the study.

Other exploratory endpoints may include, but are not limited to, assessing functional antibody profiles in response to vaccination, vaccine-induced changes in innate and myeloid cell populations, and vaccine-induced changes in transcriptomic, proteomic or metabolomic profiles. Analyses associated with these endpoints are out of the scope of this SAP.

6 STUDY DESIGN CONSIDERATIONS

6.1 Study Design

This is a randomized, placebo-controlled, observer-blind, phase II study with two arms (M72/AS01$_E$ vaccine and saline placebo). An IDMC will be established to oversee the safety of this study. Participants will be randomly assigned equally to one of the two intervention groups in parallel for the duration of the study.

M72/AS01$_E$ group will receive 0.5 mL dose of M72/AS01$_E$ that contains 10µg M72 reconstituted with AS01$_E$, a GSK proprietary adjuvant system containing 25 µg MPL (3-O-desacyl-4-monophosphoryl lipid A produced by GSK), 25 µg QS-21 (*Quillaja saponaria* Molina, fraction 21). The vaccine will be administered at Day 1 and Day 29. Placebo group will receive one dose of 0.5 mL saline (0.9% NaCl) at Day 1 and Day 29.

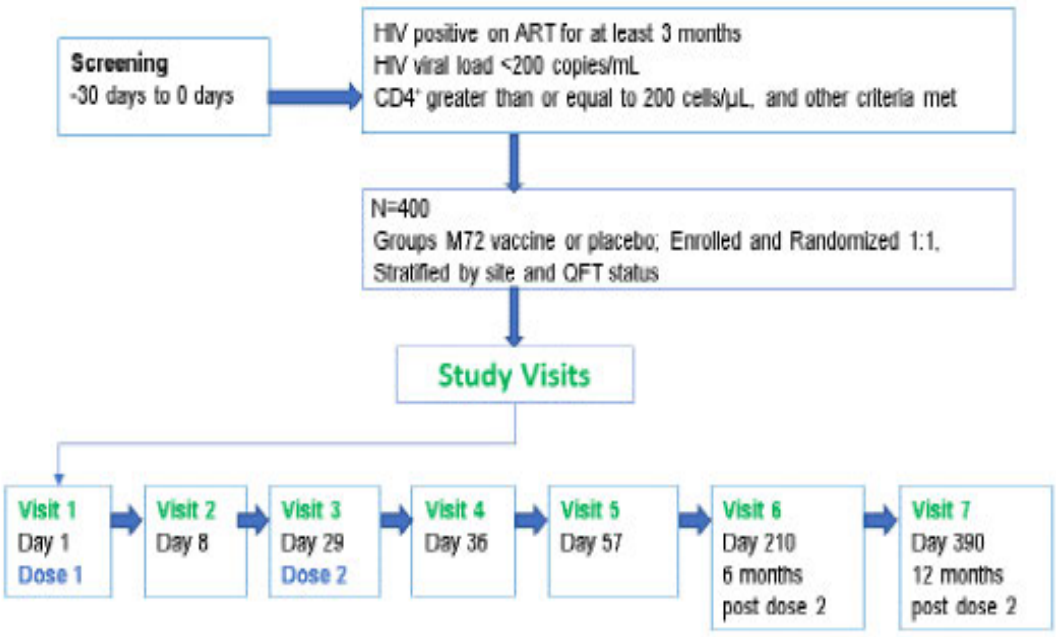
Participants, sponsor, investigators, clinical research organization (CRO) clinical team, laboratory, and clinical staff are blinded to intervention (M72/AS01$_E$ vs placebo). The investigational pharmacist preparing study interventions will be unblinded but will not perform other study duties.

Approximately 800 participants will be screened to enroll and randomize 400 participants 1:1 to receive either 2 doses of M72/AS01$_E$ or 2 doses of saline placebo at Day 1 and Day 29. Randomization will be stratified by study site and by screening QuantiFERON-tuberculosis (TB) Gold Plus (QFT) status (positive/negative). An indeterminate QFT test at the screening visit would render the participant ineligible for the study.

Per the protocol and sample size calculations, it is not necessary to test all participants for cellular immunogenicity. It is anticipated that approximately 140 participants will be randomly selected and tested (10 on Placebo and 60 on M72/AS01$_E$ for each QFT status [QFT+, QFT-]).

The study duration for each participant, after screening, is approximately 390 days, which includes 2 vaccinations 1 month apart, and 365 days of follow-up post dose 2. Approximately 6 sites in the Republic of South Africa (RSA) will participate in this study.

Figure 1: Outline of Study Procedures



6.2 Masking/Blinding

The study is 'observer-blinded' meaning that the vaccine recipient as well as those responsible for the evaluation of study endpoint data are unaware which intervention, M72/AS01$_E$ or placebo, was administered to a particular participant.

Only the following people will have access to treatment allocation while the study is blinded:

- Investigational pharmacists preparing the study interventions
- Biostatistician preparing the randomization list
- Biostatistician preparing the unblinded IDMC data
- IDMC members
- Unblinded study monitors.

Data that can lead towards unblinding individual study participants:

- randomization list
- humoral M72 -specific IgG antibodies
- intracellular cytokine staining (ICS) data

will not be shared with the study team until final database lock (DBL).

6.3 Planned Analyses for the Study

6.3.1 Independent Data Monitoring Committee (IDMC)

An IDMC will be established for the Gates MRI-TBV02-202 study as an independent advisory committee commissioned and charged with the responsibility of evaluating safety data at regular intervals and on an ad hoc basis as necessary, to ensure the rights and safety of the study participants are safeguarded and that potential risks to participant are minimized. The IDMC will play an important role in study oversight and will contribute to study compliance with Good Clinical Practice, as defined by current regulatory and clinical research best practices.

The independent IDMC will operate according to the most current version of the IDMC charter, specified in the introduction section of this document. The IDMC structure, participants and other details are provided in the charter and are not to be repeated in this document. The charter describes the scope of responsibilities of the IDMC and identifies its members. Additionally, it outlines the meeting schedule and format, provides procedures for ensuring confidentiality and maintaining the blind of the study team, and explains the administrative procedures that will be followed.

6.3.2 Interim Analysis

Not applicable. Interim analyses are not planned.

6.4 Efficacy Analyses/Immunogenicity

Clinical efficacy of the M72/AS01$_E$ vaccine will not be measured in this study.

The study will evaluate the immunogenicity of the vaccine.

6.4.1 Humoral Immunogenicity

Blood samples for immunogenicity evaluation of M72 -specific IgG antibodies will be measured by enzyme-linked immunosorbent assay (ELISA) and will be collected on Day 1, Day 29, Day 57, Day 210, and Day 390/discontinuation visits. On Day 1 and Day 29 visits, samples will be collected prior to study intervention administration.

6.4.2 Cell-Mediated Immune Responses

Blood samples for cell-mediated immune (CMI) responses will be collected on Day 1, Day 29, Day 57, Day 210, and Day 390/discontinuation visits. On Day 1 and Day 29 visits, samples will be collected prior to study intervention administration. Peripheral blood mononuclear cells (PBMCs) will be isolated and analyzed using intracellular cytokine staining (ICS) to assess the frequency, magnitude and polyfunctionality of M72-specific CD4+ and CD8+ T-cell responses. M72-specific CD4+ and CD8+ T cells expressing multiple cytokines will be measured upon short-term in vitro stimulation of PBMCs.

6.4.3 Exploratory Endpoints

Assessments of HIV viral load (copies/mL) and CD4+ cell count will be performed at Screening, Day 1, Day 57, Day 210, and Day 390/discontinuation.

The incidence of suspected TB disease cases/events will be based on participants with at least one of the TB symptoms starting approximately 1 month post 2nd vaccination (Day 57). The incidence of laboratory-confirmed pulmonary TB cases/events will be based on participants with sputum Xpert MTB/RIF test results = MTB DETECTED starting approximately 1 month post 2nd vaccination (Day 57).

6.4.4 Other Exploratory Endpoints

Analysis related to assessing functional antibody profiles in response to vaccination, vaccine induced changes in innate and myeloid cell populations, and vaccine-induced transcriptomic, proteomic or metabolomic profiles will be analyzed separately by Gates MRI, and outside the scope of this SAP. No details of these analyses will be described within this SAP.

6.5 Safety Measures

Safety outcomes include solicited AEs (based on the review of diary card data), unsolicited AEs, all SAEs, AEs of special interest (pIMDs), vaccination-related SAEs, clinical laboratory assessments, vital signs, and physical examination.

7 STUDY POPULATIONS

7.1 Analysis Populations

Agreement and authorization of participants included/excluded from all populations will be obtained prior to any unblinding activities. A summary table containing the number of participants in each of the populations defined below along with any reasons for exclusions will be provided.

7.1.1 Randomized Population

All participants randomly assigned to study intervention, a randomization number and date. A participant will be programmatically included in the Randomized analysis population if the participant has a randomization number and date. Participants will be analyzed according to the intervention they were randomized to.

7.1.2 Safety Population

All participants randomly assigned to study intervention and who received at least one dose of study intervention. Participants will be summarized according to the actual intervention received.

If a participant received the same consistent intervention for both doses, but the actual intervention is different to the allocated intervention, then the participant will be summarized according to the intervention received.

If a participant did not receive consistent intervention for both doses (mixed intervention regimen) and the actual intervention for one of these doses is different to the allocated intervention, then the participant will be summarized as follows:

- For overall presentations: according to the following vaccine hierarchy: M72/AS01$_E$ followed by placebo.
- For by-dose presentations: according to the different interventions per the relevant doses.

7.1.3 Intention to Treat (ITT)

All participants randomly assigned to study intervention and who received the study intervention. Participants will be analyzed according to the intervention they were randomized.

7.1.4 Modified Intention to Treat (mITT) Population

All participants randomly assigned to study intervention, who received the study intervention (both doses) and who were randomly selected and tested for immunogenicity. Participants will be analyzed according to the intervention they actually received (for details refer to Section 7.1.2).

7.1.5 Per Protocol (PP) Population

All participants randomly assigned to study intervention, who received the study interventions as planned and did not substantially deviate from the protocol procedures. Critical and major protocol deviations will be evaluated individually by the sponsor to decide whether it has basis to exclude a participant from the PP population. If a participant is unblinded during the study, except for serious, unexpected, suspected adverse drug reactions (SUSAR), he/she will be excluded from all PP analyses. Participants will be analyzed according to the intervention they actually received (for details refer to Section 7.1.2).

7.1.6 PP Population for Cellular Immunogenicity

All participants in PP population randomly selected to have cellular immune assays performed.

7.2 Subgroups

The following subgroups will be used for safety analyses (refer to Section 15). The subgroups to be considered are as follows:

- Study site
- QFT Status (Positive, Negative) at baseline
- Gender (Male, Female)
- Body mass index (BMI) groups (≤ 25 kg/m^2, > 25 kg/m^2) at baseline
- Age (years): 16 - ≤ 24, ≥ 25 - ≤ 35 at baseline
- CD4 cell count < 350, CD4 cell count ≥ 350 at baseline

8 CHANGES IN CONDUCT OR PLANNED ANALYSES FROM THE PROTOCOL

Protocol definition for Per Protocol Population for Immunogenicity ("All participants in PP population randomly selected to have immunogenicity assays performed.") was revised to specify Per Protocol Population for Cellular Immunogenicity ("All participants in PP population randomly selected to have cellular immune assays performed.").

9 OVERALL STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

There are no formal statistical hypotheses to support the objectives of this study.

9.2 Determination of Sample Size

Sample size for safety: While there are no formal statistical hypotheses to support the objectives of this study, from a safety perspective it is intended that the study has sufficient power to detect with high probability at least 1 SAE, or 1 adverse event of special interest (AESI) if the true AE rate is relatively low (~1%). If *p* is the event probability then the table below shows the sample size needed to have a pre-specified power to observe an event. N can be calculated from the following equation: $(1\text{-p})^N$ = 1-power.

Power	**Event probability (p)**	**N = log (1-power)/log(1-p)**
80%	0.8%	log(1-0.8)/log(1-0.008) ~ 200 participants
85%	1.0%	log(1-0.85)/log(1-0.010) ~ 189 participants
90%	1.2%	log(1-0.9)/log(1-0.012) ~ 191 participants

Therefore a sample size of 200 participants vaccinated with M72/AS01$_E$ is needed to have an 80% chance to observe at least 1 AE if the true rate is at least 0.08%.

Sample size M72 immunogenicity: The sample size is not driven by the immunogenicity endpoints. The table below provides the power to show statistically significant differences in GMCs between the 2 treatment groups for varying sample sizes when the true differences are between 10% and 40% higher in the vaccine arm, and the coefficient of variation (CV) of the measurement is between 30% and 50%.

N		**True geometric mean increase in vaccine arm**			
per group	**CV**	**10%**	**20%**	**30%**	**40%**
50	30%	36.0	87.4	99.4	> 99.9
	40%	23.0	65.1	92.0	99.1
	50%	16.3	48.2	78.7	94.4
100	30%	62.3	99.2	> 99.9	> 99.9
	40%	42.2	90.8	99.9	> 99.9
	50%	29.5	77.0	97.5	> 99.9
150	30%	80.3	> 99.9	> 99.9	> 99.9
	40%	56.6	98.1	> 99.9	> 99.9
	50%	41.5	90.9	99.8	> 99.9
200	30%	90.0	> 99.9	> 99.9	> 99.9
	40%	68.8	99.7	> 99.9	> 99.9
	50%	53.0	97.0	> 99.9	> 99.9

With N = 200 per group, there is excellent power (≥ 97%) to show statistically significant differences in GMCs between the 2 treatment groups when the true differences are at least 20% higher in the vaccine arm, and CV of the measurement is as high as 50%. The table clearly shows that sample sizes lower than 200 per group are likely sufficient to show meaningful differences in immunogenicity between the vaccine and placebo groups. While samples will be collected and stored at all planned immunogenicity timepoints, strategies to test only a portion of participants for immunogenicity analyses may be considered. Final plans will be documented in a separate statistical analysis plan (SAP) prior to data unblinding.

A sample of size of 140 participants (60:10 in each intervention group for each QFT+/QFT-) will be used for cellular immunogenicity analyses. A sample size of 120 in M72/AS01$_E$ and 28 in placebo will have > 85% power to detect a difference in geometric mean concentrations (GMCs) of 20% assuming that the common standard deviation (CV of the difference) is 30% using a two group t-test with a 5% two-sided significance.

9.3 General Conventions

Frequency (n) and percentages (%) will be used to summarize categorical variables; mean, standard deviation (SD), median, minimum, and maximum will be used to summarize continuous variables.

Decimal precision for summary statistics of continuous variables will be based on the mean value. Typically, the mean will contain one more decimal place than actual values but the decimal precision may vary in order to obtain an organized and understandable table or listing. The median will contain the same number of decimal places as the mean, the SD will contain one more decimal place than the mean, and the minimum and maximum will contain one less decimal place than the mean.

Unless otherwise specified, the denominators for percentages will be the number of participants in each intervention group with non-missing data for the variable of interest.

The day of receiving first dose of study intervention is defined as Study Day 1 or Day 1. All other study days will be computed relative to Day 1. For event on or after Day 1, study day for a particular event or visit will be calculated as $Date_{event} - Date_{Day\ 1} + 1$. For events before Day 1, study day for a particular event will be calculated as $Date_{event} - Date_{Day\ 1.}$ Day 0 will not be used.

In addition to the conventional study day described above, for certain data domains, a relative day to the most recent vaccination will be derived as $Date_{event} - Date_{most\ recent\ vaccination} + 1$. To determine the most recent vaccination, derive the difference in the start date of the event and all the available study vaccination dates as $Date_{event} - Date_{Vaccination}$. The vaccination with the smallest non-negative value will be deemed the most recent vaccination.

For a given parameter (eg, y) change from baseline (CFB) will be calculated as $y_t - y_b$ where y_t is a given participant's value t minutes, hours or days post-baseline and y_b is a given participant's value at Baseline. CFB will be computed for participants with both a Baseline value and a post-baseline value. If a participant is missing a post-baseline value, there will be no imputation of the missing value. Only observed data will be used for post-baseline analyses. For parameters

which are not fully numeric, CFB will not be computed and values will be summarized in a listing.

9.4 Baseline definition

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 laboratory assessments fall on the date of study vaccination and the time of the assessment is missing, the applicable assessment will be considered as Baseline. However, AEs starting on the reference start date (date of study vaccination) will be considered as treatment-emergent, therefore post-baseline.

9.5 Handling of Missing Data

Missing data will not be imputed.

Missing immunogenicity values are considered missing completely at random (MCAR) and therefore will not contain information that impact the result of the analysis (i.e., not informative). Imputation methods will therefore not be used.

9.6 Pooling Strategy for Study Sites

This study is being conducted at 6 sites within South Africa. Generally, all sites will be pooled by intervention for analysis purposes. Summaries by site will be included for relevant endpoints. Details are provided in the relevant sections.

9.7 Visit Windows/Unscheduled Visits

Additional visit windowing will not be applied Appendix 2 includes Study Visit Intervals as per study schedule of assessments. Unscheduled visits will not be included in by-visit summaries or analysis, but may contribute to the Baseline value and worst post-baseline assessments. 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.

10 STATISTICAL ANALYSIS METHODS

10.1 Disposition

All participants who provide informed consent will be accounted for in this study.

The number of participants screened, number of screening failures, and the number of participants randomized will be summarized for all screened participants per site and overall. Participant disposition and withdrawals (including reasons for study and intervention discontinuation as provided on the electronic case report form [eCRF]), number and percentage of participants in each analysis population, reason(s) for exclusion from each analysis population and critical and major protocol deviations will be summarized and listed for the randomized analysis population.

Protocol deviations will be programmatically determined by data management. Deviations which cannot be determined programmatically will be collected within IQVIA's clinical trial management system (CTMS) and provided together with the programmatically determined deviations to MMS Statistics on a monthly basis. It is expected that the two methods of identifying protocol deviations will not overlap.

Summary results for participant disposition, analysis populations, and protocol deviations will be presented overall and by study site.

10.2 Demographics and Baseline Characteristics

Demographic data and other baseline characteristics will be summarized using descriptive statistics only, for the Randomized and Safety populations. Summary results will be presented overall and by study site. The denominators for percentages will be the number of participants in each intervention group with non-missing data available for the variable of interest.

Explicitly the following characteristics will be summarized:

- Age (years)
- Age (years): 16-19, 20-24, 25-29, 30-35
- Sex (Male, female)
- Childbearing potential (if female)
- Race (Asian, Asian Indian, Black, Southern African Coloured, White, Other, Mixed Race)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Reported, Unknown)
- Weight (kg)

- Height (cm)
- Body mass index (BMI) (kg/m^2)
- Body mass index (BMI) groups (≤ 25 kg/m^2, > 25 kg/m^2)

BMI (kg/m^2) will be calculated using the following formula:

$$BMI = \frac{weight\ (kg)}{height\ (m) \times height\ (m)}$$

- QFT Status (Positive, Negative)
- CD4 (cells/mm^3): < 200, 200-349, 350-499, ≥ 500
- HIV ribonucleic acid ([RNA] ≤ 200 copies/mL, [RNA]> 200 copies/mL)

10.3 Treatment Compliance and Exposure

Participants will be administered 2 doses of vaccination. The date and time of each vaccination administration will be listed for each participant. A summary of participants treated, number and percentage of participants who received both doses and number of participants who received only the first dose will also be provided. Diary compliance will be calculated as described in the respective Section 15.3.

11 HUMORAL IMMUNOGENICITY ANALYSIS

Humoral immunogenicity analyses will be performed on the PP Population.

11.1 Geometric mean concentrations (GMCs)

The following analyses/summaries will be produced:

- GMCs and associated 95% CI will be obtained for each group and timepoint 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. 95% CI for the GMCs will then be estimated by exponential transformation of the 95% CI for the mean of the log-transformed concentration.
- GMCs and 95% CIs will also be presented graphically for the M72/AS01$_E$ group by timepoint.
- The primary analysis will be for comparison of GMCs between intervention groups using a linear mixed effect model, including fixed effects for treatment and time, and a random effect for participant. Individual M72-specific IgG antibody concentrations will be log-transformed. GMCs and 95% CIs will be estimated from the model as the back-transformed mean estimate.
- An additional analysis will be employed to compare log (antibody concentrations) between pre and all post-vaccination timepoints for each vaccination for the M72/AS01$_E$ group by timepoint and GM of ratios of anti-M72 antibody concentrations at each post-vaccination timepoint over pre vaccination will be tabulated with 95% CI for each intervention group and post-vaccination time point. SAS PROC TTEST/PAIRED will be used for this analysis.
- If sufficient data (for example ≥ 5 participants per category and intervention group), 95% CI for GMCs will be presented by subgroups (Section 7.2) for each timepoint separately.

11.2 Seropositivity Rates

Seropositivity rates with 95% CIs for each intervention group and timepoint will be calculated as follows:

- The cut-off value for M72-specific antibody concentrations will be 2.8 EU/mL (pending assay validation).
- A seronegative participant is a participant whose antibody concentration is below the cut-off value. A seropositive participant is a participant whose antibody concentration is greater than or equal to the cut-off value. The seropositivity rate is defined as the percentage of seropositive participants among participants with anti-M72 antibody data for the particular timepoint analyzed.
- Seropositivity rates will be plotted by timepoint and intervention group.

- All CIs computed will be two-sided 95% CIs. The 95% CIs for a proportion within an intervention group and timepoint will be based on the mid-p method.
- An additional analysis to compare seropositivity rates between intervention groups will be performed as follows: a generalized linear mixed effect model will be used, including fixed effects for treatment and time, and generalized estimating equations will be used to account for the dependence in the longitudinal binomial response data.

Other data considerations for the anti-M72 antibody data are included in Appendix 6. If sufficient data (for example ≥ 5 participants per category and intervention group), seropositivity rates will be presented by subgroups (Section 7.2) for each timepoint separately.

12 CELL-MEDIATED IMMUNE RESPONSE ANALYSES

Cell-mediated immune response analyses will be performed using PP population for Cellular Immunology.

The cellular immunogenicity of M72/AS01$_E$ vaccination frequency, magnitude and polyfunctionality of M72-specific CD4+ and CD8+ T-cell responses measured by ICS pre- and post-vaccination through the end of the study based on results from 18-color intracellular cytokine staining will be assessed.

The responder status (detailed in Appendix 7) will be based on the derived Positive (Gamma [G],2) cytokine combination, which is derived for each participant, T cell type (CD4+, CD8+), stimulation antigen and visit, as follows:

Positive (G,2) = ∑ Results where IFN-gamma and/or IL-2 are positive.

The negative control used for this analysis will be Dimethyl Sulfoxide (DMSO). If more than one DMSO value is available per visit, then the average of the available DMSO values will be used for derivation and presentation purposes.

DMSO-subtracted cytokine response values will be derived as (Active stimulation antigen results – DMSO results).

A total antigen value will be derived as follows:

Total antigen = ∑ Results across active antigens for the Positive (G,2) derived cytokine combination.

The following information will be summarized in tables for the PP population for Cellular Immunogenicity:

- %Antigen-specific T cell DMSO-subtracted Positive (G,2) cytokine responses per antigen (for the active antigens, including a total antigen) per visit. Repeat this table for the DMSO responses.
- The number and percentage of responders per active antigen (including an overall responder assessment). A p-value, based on a Fisher's EXACT test comparing the 2 treatment groups will be included.
- Comparisons of median DMSO-subtracted Positive (G,2) cytokine response values. A p-value, based on the Wilcoxon-Mann Whitney test for pair-wise comparisons between treatment groups will be included.

The following information will be presented in figures for the PP population for Cellular Immunogenicity:

- %Antigen-specific T-cell DMSO-subtracted Positive (G,2) response of each participant per visit, in the form of a dot plot. The median response, per treatment group, will be presented by a horizontal line. Responders will be indicated by an 'x' (or colored square for visibility) and non-responders by an open circle. Treatment groups will be plotted next to each other per visit, and also in a different color. Separate plots per T cell will be created.
- %Antigen-specific DMSO-subtracted Positive (G,2) median responses per visit, in the form of a line plot. The first and third quartile per visit will also be included as bars. Each stimulation agent will be displayed on a separate page. The median responses per treatment group will be presented by a dot and connected by a horizontal line across the visits. Separate plots will be provided for each T cell type.
- Median DMSO-subtracted Positive (G,2) responses for each stimulation antigen per visit, by means of a stacked bar plot. Separate plots will be provided for each T cell type.
- %Antigen-specific DMSO-subtracted polyfunctional plots, by means of a dot for each participant's value for each cytokine combination. Only cytokine combinations where at least 3 of the applicable markers are positive will be included. Separate outputs for the following different polyfunctional combinations per applicable T cell type will be provided:
    - CD4+: IFN-gamma, IL-2, TNF, CD40L
    - CD8+: IFN-gamma, IL-2, TNF

A listing of the %DMSO-subtracted values and the applicable changes from Baseline per T cell type and antigen will be presented for the Positive (G,2) combination as well as the IFN-gamma, IL-2, TNF, CD40L polyfunctional combinations where at least 3 of these markers are positive. In addition, the responder status for each antigen per participant will also be listed.

13 HIV VIRAL LOAD AND CD4 COUNTS POST-M72/AS01$_E$ VACCINATION

Analyses of HIV viral load and CD4 counts will be performed using the Safety Population. Additional analyses will be performed using PP Population and PP Population for Cellular Immunogenicity.

HIV viral load: To assess HIV viral load post-M72/AS01$_E$ vaccination frequencies of participants with confirmed HIV ribonucleic acid ([RNA] > 200 copies/mL) at Day 57, Day 210, and Day 390 will be presented. 95% CIs for a proportion within an intervention group and timepoint will be computed using Clopper-Pearson mid-p CI and compared between intervention groups using Fisher's exact test. The analyses will be repeated by subgroups in Section 7.2 if there is sufficient data (≥ 5 participants per category and intervention group).

CD4 counts: The analysis of the change from baseline in CD4 counts will be performed on observed data, using a mixed model with intervention group and visits as fixed effects and baseline CD4 counts as a covariate. The treatment × visit term will also be fitted. An unstructured covariance matrix will be used to model the within-subject errors. Restricted maximum likelihood (REML) based on repeated measures approach will be used. Analyses will be implemented using SAS PROC MIXED. Example of SAS code is provided in the Appendix 5. Summary results will be presented by timepoint. The 95% confidence intervals will be presented for the LSMEAN estimates and their differences. CD4 count data may be transformed if necessary to support the normality assumption inherent in the method.

14 SUSPECTED TB DISEASE AND LABORATORY-CONFIRMED PULMONARY TB

The number and percentage of participants with TB signs and symptoms post vaccination, with suspected TB disease noted by the investigator on the CRF, and with laboratory-confirmed pulmonary TB based on sputum Xpert MTB/RIF test results = MTB DETECTED will be performed using Safety Population and presented by study visit.

For the incidence of suspected TB disease, cases will be defined as any participant with suspected TB disease noted by the investigator on the CRF starting approximately 1 month post 2nd vaccination (Day 57). The incidence rate of suspected TB symptoms (or 100 Person-years rate) will be calculated as the number of participants reporting at least one case in a treatment group divided by the sum of follow-up period expressed in years in the same treatment group, and multiplied by 100.

For the incidence of laboratory-confirmed pulmonary TB, cases will be defined as any participant with sputum Xpert MTB/RIF test results = MTB DETECTED starting approximately 1 month post 2nd vaccination (Day 57). The incidence rate of laboratory-confirmed pulmonary TB (or 100 Person-years rate) will be calculated as the number of participants reporting at least one case in a treatment group divided by the sum of follow-up period expressed in years in the same treatment group, and multiplied by 100.

15 SAFETY AND TOLERABILITY

All safety and tolerability analyses will be conducted using Safety population.

Safety outcomes will include:

- Solicited AEs: local injection site pain, redness, and swelling, and general AEs including headache, fatigue, malaise, myalgia, gastrointestinal symptoms, and fever (defined as a temperature ≥37.5°C [99.5°F]).
- Unsolicited AEs
- All SAEs
- Vaccination-related SAEs
- AESI (pIMDs)
- Clinical laboratory assessments
- Vital signs
- Physical examination.

15.1 Adverse Events

AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 22.1 or higher. AE severity will be graded as Grade 1 (Mild), Grade 2 (Moderate), Grade 3 (Severe) or Grade 4 (Potentially Life-threatening) on the eCRF.

AE categories include:

- Solicited adverse events (AEs) through 7 days post each dose of study intervention
- Unsolicited AEs through 28 days post each dose of study intervention
- All serious adverse events (SAEs), adverse events of special interest (AESI) and pregnancies through end of study (Month 13/Day 390).
- Potential immune-mediated diseases (pIMDs) through end of study.

Only AEs within the reporting window will be included within the relevant category in summary tables. All AEs will be listed, regardless of if it was reported within the applicable reporting window. The most recent vaccination and the associated relative days (refer to Section 9.2) will be included within the listing.

Potential immune-mediated diseases (pIMDs) will be determined as in Section 9.6.7 of the protocol (Medical Dictionary for Regulatory Activities (MedDRA) Version 22.1 Preferred Term Codes for pIMDs).

Adverse events of special interest (AESIs) are adverse events that the sponsor wants to monitor carefully. The list in Appendix 3, which includes pIMDs, will be collected and reported as AESIs.

An AE overview table containing the frequency and percent of participants in each of the following categories (summarized by intervention group) and also the 95% CI (calculated for a single proportion using mid-p binomial option [refer to Appendix 5]):

- Unsolicited AEs.
- Related unsolicited AEs.
- Grade 1 unsolicited AEs.
- Grade 2 unsolicited AEs.
- Grade 3 or higher unsolicited AEs.
- Related, grade 3 or higher unsolicited AEs.
- Unsolicited AE leading to premature study discontinuation.
- AESI / Potential immune-mediated diseases (pIMDs)
- SAEs.
- SAE with outcome of death.

The AE overview analysis summary table will be repeated by subgroups (Section 7.2) and by study site.

Additionally, the following will be summarized by System Organ Class (SOC) and preferred term (PT), for each intervention group:

- Incidence of unsolicited AEs.
- Incidence of unsolicited AEs by highest grade.
- Incidence of related unsolicited AEs.
- Incidence of related unsolicited AEs by highest grade
- Incidence of SAEs.
- Incidence of unsolicited non-serious AEs.
- pIMDs (by PT only).

These tables will also by repeated to display results post first and post second vaccination. The most recent vaccination (refer to Section 9.2) will be used.

Summaries of SOC and PT will be sorted alphabetically by SOC and by decreasing frequency of PT in the M72/AS01$_E$ intervention group. If a participant has more than one unsolicited AE at a given level (eg, SOC and PT), the participant will only be counted once within that level.

Missing severities and relationship will not be regarded as 'worst case'.

15.2 Reactogenicity Data

Reactogenicity data is solicited AEs. The reactogenicity data collected from the paper diary after each dose and will be: injection area symptoms (pain at injection site, redness and swelling), and general AEs including headache, fatigue, malaise, myalgia, gastrointestinal symptoms, and fever.

On Day 1, participants are given a diary card and provided guidance on how to fill in the card. The paper diary will record reactogenicity data from Day 1 to Day 7 following vaccination. The analysis interval for reactogenicity data will be 'Any Day 1 to 7' which includes data from Day 1 to 7. The day of vaccination is considered as Day 1.

Following second dose, on Day 29, participants are given a second diary card and provided guidance on how to fill in the card. The paper diary will record reactogenicity data from Day 29 to Day 35 following second dose of vaccination. The analysis interval for reactogenicity data will be 'Any Day 29 to 35' which includes data from Day 29 to Day 35.

The diary card is used to record duration and intensity (Grade 1 to 4) and largest diameter in mm of the red and swollen area of solicited injection area symptoms and general body symptoms AEs for 7 days following each dose of vaccination.

Reactogenicity data will be presented for the Safety population unless otherwise noted. The number of participants who returned the diary card after each dose, inducing the reason for not returning the diary card will be summarized. Participants reporting any symptoms (for both injection area symptoms and general body symptoms) on each day after vaccination above, will be summarized.

The following additional summaries will be presented for the Safety population:

15.2.1 Injection Area Symptoms

Injection area symptoms will be summarized as proportion of participants reporting each injection area symptom. For each injection area symptom, the derivation of whether or not the specific symptom occurred on each day and 'Any Day 1 to 7' will be made. Same analyses will be repeated for Day 29 to Day 35, therefore post second vaccination.

For the 'Any Day 1 to 7' summary tables, the derivation of the proportion is calculated as n1/(n1+n2) where

- n1: Any Day 1 to 7 participant reports the symptom as 'mild', 'moderate' or 'severe' on any Day 1 to 7.
- n2: Participant reports the symptom as 'none' on all 7 days or as a combination of 'none' and missing on all 7 days.

Participants that report the symptom as missing on all 7 days are not included in the proportion calculations. For redness and swelling, 'mild', 'moderate', and 'severe' categories are based on the largest diameter of the redness or swelling reported in mm: Mild = 25 to < 50mm; Moderate ≥ 50 to < 100 mm; Severe ≥ 100 mm (refer to the 'Site Reactions to Injections and Infusions' table in Appendix 3 of the study protocol which is based on the Modified from Division of AIDS Table for Grading the Intensity (severity) of Adult and Pediatric Adverse Events Version 2.1, July 2017). An "any" category will also be included to present the number of participants reporting any non-zero measurements 95% CI based on the conditional binomial Clopper-Pearson method with mid-p correction (refer to Appendix 5) will also be provided.

The maximum severity (highest grading) of each local reaction within 7 days of vaccination will be derived as follows:

- =, if values are missing for all Day 1 to Day 7.
- = 0, if the participant reports all reactions as 'None' or a combination of missing and none for all Day 1 to Day 7.
- =, highest grade (maximum severity) within 7 days of vaccination, if the answer is not 'None' for at least 1 day.

Duration and Onset Day of Injection Area Symptom:

- For participants experiencing any injection area symptom, the following will be derived after each vaccination:
  - the onset day (first day of the injection area symptom reported via diary relative to the vaccination),
  - duration of event = sum of days post vaccination when the symptom was reported. Resolution of the event is the last day in which the event is recorded on the diary or the date the event ends if it is unresolved during the participant diary-recording period.

The following summary results will be generated for injection area symptoms within 7 days after each vaccination:

- number and percentage of participants with injection area symptom (any severity) and by severity grade.
- number and percentage of participants with any injection are symptom within 7 days after vaccination.
- number and percentage of participants by injection area symptom onset day.
- number and percentage of participants by injection area symptom duration (number of days).

- for each injection area symptom: mean, median, Q1-Q3, and min-max for symptom duration.

The following summary will be generated for injection area symptoms within 7 days after any vaccination:

- number and percentage of participants with injection area symptom (any severity) and by severity grade.
- number and percentage of participants with any injection are symptom.

15.2.2 General Body Symptoms

For each general body symptom event recorded on the diary, the following summaries and analyses will be presented similar to injection area symptoms:

- Each general body symptom on each day (up to Day 7) after vaccination.
- Each general body symptom event on 'Any Day 1 to 7' after vaccination.
- Maximum severity of each general body symptom event on 'Any Day 1 to 7' after vaccination.
- Onset day of each general body system after each vaccination.
- Duration of each general body symptom after vaccination (defined as sum of days symptom was present).
- Any general body symptom event (including fever) on 'Any Day 1 to 7' after vaccination.

Grading for fever is as follows: Mild = 38.0 to < 38.6°; Moderate ≥ 38.6 to < 39.3°C; Severe ≥ 39.3 to < 40.04°C; Life-threatening ≥ 40°C (refer to the 'Site Reactions to Injections and Infusions' table in Appendix 3 of the study protocol which is based on the Modified from Division of AIDS Table for Grading the Intensity (severity) of Adult and Pediatric Adverse Events Version 2.1, July 2017).

The derivation of these variables is similar to the derivation of the variables for injection area symptoms.

The following summary results will be generated for injection area symptoms within 7 days after each vaccination:

- number and percentage of participants with general body symptom event (any severity) and by severity grade.

- number and percentage of participants with any general body symptom event within 7 days after vaccination.
- number and percentage of participants by general body symptom event onset day.
- number and percentage of participants by general body symptom event duration (number of days).
- for each general body symptom: mean, median, Q1-Q3, and min-max for symptom duration.

The following summary will be generated for general body symptom events within 7 days after any vaccination:

- number and percentage of participants with general body symptom event (any severity) and by severity grade.
- number and percentage of participants with any general body symptom event.

15.2.3 Use of Medication

The use of medication will be recorded on the Diary Card for 7 days after each vaccination.

The following variable will be derived:

- Use of medication on 'Any Day 1 to 7' after each vaccination

A listing for the diary card data, including the derived variable mentioned above will be displayed for the Safety population. Same analyses will be repeated for Day 29 to Day 35, therefore post second vaccination.

15.3 Diary Card Completion

The number of participants who returned the diary card, including the reason for not returning the diary card will also be summarized. For any given day, the diary will be considered as complete if all expected data (the 3 injection area symptoms, the 5 general body symptom events, and the use of medication for the 7 days) are available (i.e. a non-missing response is available). If any of the items in the diary is missing on a specific day, the diary is considered as incomplete.

The following diary compliance variables will be derived as follows and presented by intervention group:

- Compliance per day: the numerator is the number of participants who completed the diary on a given day (Day 1 to Day 7) and the denominator is the total number of participants who receive the applicable vaccination.

- Compliance at least x days for x = 1, 2, ….7: the numerator is the number of participants who completed the diary on any x days and the denominator is the total number of participants who received the applicable vaccination.

Same analyses will be repeated for Day 29 to Day 35, therefore post second vaccination.

15.4 Clinical Laboratory Assessments

Descriptive statistics (based on Systeme Internationale [SI] units) for chemistry and hematology parameters, as well as the change from baseline (only applicable to Day 29), will be summarized by intervention group at baseline and Day 29. Change from baseline will be calculated for each participant at the specified time point as the value at the specified time point minus the baseline value. If multiple values are obtained prior to first vaccine dose, the last non-missing values collected prior to the first dose will be used for the baseline.

The number and percentage of participants with low, normal, and high results at baseline and Day 29 will be summarized by intervention groups.

The laboratory values will be graded using the criteria specified in Section 9.8 of the protocol. Shift tables will be presented to show the number of participants with each toxicity grade (1, 2, 3, or 4) at baseline versus Day 29 and the worst post-baseline grade (including any unscheduled visits). For those laboratory parameters for which high toxicity grades are specified for both low and high values, shifts in toxicity will be presented for high and low toxicities separately. The percentages will be based on the number of participants with both a baseline and post-baseline (at the specified visit) assessment of the specific laboratory parameter. Percentages for each lab test will be based on the number of participants with both a baseline and a post-baseline evaluation of the particular laboratory test. A listing will be provided which provides all results for a given laboratory test for participants who have at least one 2-grade increase from baseline.

A summary table will provide the number and percentage of participants having aspartate aminotransferase (AST), alanine aminotransferase (ALT) > 3, 5, 10 x upper limit of normal (ULN) or Total Bilirubin (TBL) > 1.5, 2 x ULN and any other criteria specified in Table 14-1 at any time post-baseline regardless of their baseline value. For a combined criterion to be fulfilled, all conditions must be fulfilled on the same lab measurement. Participants meeting either criteria based on any combination of post-baseline laboratory results, irrespective of their temporal association, as well as participants meeting the criteria at the same time point, will be listed. All laboratory results for the parameters included in the criteria will be presented by visit for all participants who meet the criteria.

Table 14-1: Criterion-based hepatic events

Parameter	Criterion
ALT	> 3 x ULN; > 5 x ULN; > 10xULN
AST	> 3 x ULN; > 5 x ULN; > 10xULN
ALT or AST	> 3 x ULN; > 5 x ULN; > 10xULN
TBL	> 1.5 x ULN; > 2 x ULN
(ALT or AST) & TBL	ALT or AST > 3 x ULN & TBL > 2 x ULN
	ALT or AST > 5 x ULN & TBL > 2 x ULN
	ALT or AST > 8 x ULN &TBL > 2 x ULN

Parameter	Criterion
	ALT or AST > 10 x ULN & TBL > 2 x ULN ALT or AST > 3 x ULN & TBL > 2.0 x ULN (potential Hy's Law)

AST = Aspartate aminotransferase; ALT = Alanine aminotransferase; TBL = Total bilirubin.

Detailed participant listings of all laboratory data collected during the study will be provided. Laboratory values outside normal limits will be identified in the participant data listings. A column will display any applicable toxicity grading of the laboratory value.

15.5 Vital Signs and Weight

Vital signs, including blood pressure, pulse rate, respiratory rate and body temperature, will be collected at Screening and Day 1 (pre vaccination), as well as on Day 29 (prior to second dose administration).

The results (including change from baseline at Day 29 and number and percentage of participants with potentially clinically significant results for vital signs will be summarized at baseline and Day 29 by intervention group.

The following will be considered potentially clinically significant criteria for pulse rate, blood pressure, and temperature:

Table 14-2:Criterion-based vital signs

Parameter	Criterion
Pulse rate	≥ 120 bpm and increase of ≥ 15 bpm and ≥ 30 bpm, ≤ 50 bpm and decrease of ≥ 15 bpm and ≥ 30 bpm
Systolic blood pressure	≥ 180 mmHg and increase of ≥ 20 mmHg and ≥ 40 mmHg, ≤ 90 mmHg and decrease of ≥ 20 mmHg and ≥ 40 mmHg
Diastolic blood pressure	≥ 105 mmHg and increase of ≥ 15 mmHg and ≥ 30 mmHg, ≤ 50 mmHg and decrease of ≥ 15 mmHg and ≥ 30 mmHg
Body Temperature	> 38.0°C or < 36.0°C
Weight	± 7% change from baseline weight

15.6 Physical Examination

Physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal and neurological systems, as well as assessment of height and weight, body temperature, and resting vital signs (blood pressure, pulse and respiratory rate).

As part of the history/physical at each visit, a TB symptom/sign checklist from RSA TB guidelines will be used. This will include TB contact history. The TB symptom/sign checklist in the eCRF includes:

- Cough for longer than 2 weeks
- Fever for longer than 2 weeks
- Fatigue for longer than 2 weeks
- Night sweats for longer than 2 weeks
- Loss of weight or insufficient weight gain or growth
- Other.

If TB is suspected, potential participants would be managed according to standard of care.

Findings from physical examinations will be presented in listings for the randomized population. Focused physical examination will be summarized descriptively by intervention group and visit.

15.7 COVID-19

The following information related to COVID-19 will be collected in the eCRF and will be summarized by visit for the Safety population overall and by study site:

- number and percentage of participants with COVID-19 diagnosis
- number and percentage of participants who experienced an episode of illness with one or more of the following signs/symptoms: fever, chills, muscle pain, joint pain, headache, fatigue, cough, sore throat, nasal congestion, nausea, vomiting, diarrhea, shortness of breath, loss of sense of smell, and/or loss of sense of taste.
- number and percentage of participants with close contact (being within 6 feet for a cumulative total of 15 minutes or more over a 24-hour period) with a person/persons who has/have been diagnosed with COVID-19.

Findings for COVID-19 will be presented in a listing for the randomized population.

16 OTHER RELEVANT DATA ANALYSES/SUMMARIES

16.1 Medical History

Medical history will be coded using MedDRA version 22.1 or higher. Medical history will be summarized by SOC and PT by intervention group for the Safety population and listed for the randomized population. Summaries of SOC and PT will be sorted alphabetically by SOC and by descending frequency of PT in the M72/AS01$_E$ group. If a participant has more than one medical history even at a given level (eg, SOC and PT), the participant will only be counted once within that level. Summary tables will be generated overall and by study site. A listing of medical history will also be presented.

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

16.2 Concomitant Medications

Concomitant medications will be coded using the World Health Organization (WHO) Drug Global March 2019 or later version. A concomitant medication is defined as a medication with a stop date on or after the first dose date, thus a medication that is ongoing at the time of a participant's vaccination is considered concomitant. Partial and missing dates for concomitant medications will be imputed using the guidance in Appendix 4. The recorded partial/missing dates will be displayed in the listings and study days will not be presented for these cases.

Medications will be summarized by Anatomical Therapeutic Chemical (ATC) level 3 and preferred name by intervention group for the Safety population. Summaries of ATC level 3 and preferred name will be sorted alphabetically by ATC level 3 and by decreasing frequency of preferred name in the M72/AS01$_E$ group. If a participant has more than one medication at a given level (eg, ATC level 3 and preferred name), the participant will only be counted once at that level. Separate summaries for prior and concomitant medications will be provided overall and by study site. Prior and concomitant medications will be included in by-participant data listings.

17 REFERENCES

1. QIAGEN, QuantiFERON®-TB Gold Plus (QFT®-Plus) Package Insert, July 2018.

2. Horton H, Thomas EP, Stucky JA, Frank I, Moodie Z, Huang Y, Chiu Y, McElrath MJ and De Rosa SC. Optimization and validation of an 8-color intracellular cytokine staining (ICS) assay to quantify antigen-specific T cells induced by vaccination. Journal of Immunological Methods. 2007:23;39-54.

3. Food and Drug Administration (FDA) 2020. FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Pandemic Guidance for Industry, Investigators, and Institutional Review Boards.

18 APPENDICES

Appendix 1 Schedule of Assessments

Procedure	Screen	Intervention and Follow-up Period							
		Visit 1 Day 1	Visit 2 Day 8	Visit 3 Day 29	Visit 4 Day 36	Visit 5 Day 57	Visit 6 Day 210	Visit 7 Day 390	Discon Visit
Visit window	-30 to Day 0	±0	Day 8 to 12	Day 29 to 35	Day 36 to 42	Day 57 to 63	±28days	±28days	
Informed consent/assent	X								
Inclusion and exclusion criteria-verify eligibility	X	X							
Full medical history/full physical examination (PE), height	X								
Record Body weight, and pregnancy status	X	X	X	X	X	X	X	X	X
Focused medical history/focused PE		X	X	X	X	X	X	X	X
Vital signs	X	X		X					
βHCG serum pregnancy test (5mL)	X	X		X		X	X	X	X
Randomization		X							
Hepatitis B and C screening (3 mL)	X								
Urine pregnancy test (prior to study intervention administration)		X		X					
Safety laboratory assessments (7 mL)	X	X		X					X
Urinalysis by dipstick (glucose, protein, blood), and microscopy	X								
HIV antibody assessment (10 mL)	X								
HIV viral load assessment (3 mL)	X	X				X	X	X	X
$CD4^+$ cell count (3 mL)	X	X				X	X	X	X
QFT assay (4 mL)	X							X	X
Sputum Xpert MTB/RIF assay	X								
Sputum Xpert MTB/RIF assay ONLY if TB is suspected		X	X	X	X	X	X	X	X
Study Intervention Administration		X		X					
30- minute post admin. observation		X		X					
Diary card training and distribution		X		X					
Diary card: return, review, transcribe			X		X				
Memory aid training and distribution (unsol. AEs/ conmeds)			X		X				
Memory aid: return, review, transcribe				X		X			
Record AE (at screening until Day 1)	X								
Record solicited AEs		X	X	X	X				
Record unsolicited AEs		X	X	X	X	X			X
Record all SAEs and AESIs	X	X	X	X	X	X	X	X	X
Record concomitant medications		X	X	X	X	X	X	X	X

Procedure	Screen	Intervention and Follow-up Period							
		Visit 1 Day 1	Visit 2 Day 8	Visit 3 Day 29	Visit 4 Day 36	Visit 5 Day 57	Visit 6 Day 210	Visit 7 Day 390	Discon Visit
M72-specific IgG antibody (serum) (10mL)		X		X		X	X	X	X
M72-specific $CD4^+$ and $CD8^+$ T cells (17 mL)		X		X		X	X	X	X
Exploratory PBMC and plasma for CoP & CoR (34 mL)		X			X		X	X	X
Exploratory CoP & CoR serum(10 mL) innate and adaptive		X			X		X	X	X
Exploratory CoP & CoR transcriptomics (2.5 mL)		X			X		X	X	X

X indicates procedure to be performed and mL indicates blood volume collected (volumes listed are approximate)
Unsol. AE= unsolicited adverse event, conmed= concomitant medication
QFT= QuantiFERON®-TB Gold Plus assay (note that participants with an indeterminate result will not be eligible).
A discontinuation (discon) visit will be scheduled for participants who discontinue or withdraw, whenever possible. Any AEs will be collected.
As part of history/physical at each visit, a TB symptom/sign checklist and history of TB household contact will be included.
A single self-expectorated sputum sample will be collected for Xpert MTB/RIF assay from all participants at screening visit, and in participants with suspected TB at the other visits. No sputum induction is required. Sputum Xpert MTB/RIF assay will not be done in participants who are unable to produce sputum.
CoP and CoR= correlate of protection and correlate of risk
Note that all blood samples collected on Days 1 and 29 will be collected prior to study intervention administration.
Laboratory test results of samples collected at screening visit will be utilized to determine eligibility.
Laboratory test results of blood samples collected on Day 1 will be used to establish baseline pre-vaccination values (and not to determine eligibility), and blood samples collected at Day 29 will be used to establish baseline values prior to the administration of the second dose (and not to determine eligibility for second dose administration).
All blood volumes are approximate. Total amount of whole blood to be collected is approximately 423 mL (assuming all samples are collected at each visit and not at discon visit). Maximum amount of whole blood to be collected at any given visit is approximately 91.5 mL.

Appendix 2 Study Visit Intervals

Study Visits	Length of Interval (per protocol SoA)
Screening	Day -30 to 0
Day 1	NA
Day 8	Day 8 to 12
Day 29	Day 29 to 35
Day 36	Day 36 to 40
Day 57	Day 57 to 63
Day 210	± 28 days
Day 360	± 28 days

NA = not applicable

Appendix 3 Adverse Events of Special Interest (AESI)

Neuroinflammatory disorders	Musculoskeletal disorders	Skin disorders
• Cranial nerve neuropathy, including paralysis and paresis (e.g. Bell's palsy). • Optic neuritis. • Multiple sclerosis. • Transverse myelitis. • Guillain-Barré syndrome, including Miller Fisher syndrome and other variants. • Acute disseminated encephalomyelitis, including site specific variants e.g.: non-infectious encephalitis, encephalomyelitis, myelitis, myeloradiculoneuritis. • Myasthenia gravis, including Lambert-Eaton myasthenic syndrome. • Demyelinating peripheral neuropathies including: - Chronic inflammatory demyelinating polyneuropathy, - Multifocal motor neuropathy - Polyneuropathies associated with monoclonal gammopathy. • Narcolepsy.	• Systemic lupus erythematosus and associated conditions • Systemic scleroderma (Systemic sclerosis), including: - Diffuse Scleroderma - CREST syndrome • Idiopathic inflammatory myopathies, including: - Dermatomyositis - Polymyositis • Anti-synthetase syndrome. • Rheumatoid Arthritis and associated conditions including: - Juvenile Idiopathic Arthritis - Still's disease. • Polymyalgia rheumatica. • Spondyloarthropathies, including: - Ankylosing Spondylitis, - Reactive Arthritis (Reiter's Syndrome), - Undifferentiated Spondyloarthritis, - Psoriatic Arthritis, - Enteropathic arthritis. • Relapsing Polychondritis. • Mixed Connective Tissue disorder. • Gout.	• Psoriasis. • Vitiligo. • Erythema nodosum. • Autoimmune bullous skin diseases (including pemphigus, pemphigoid and dermatitis herpetiformis). • Lichen planus. • Sweet's syndrome. • Localised Scleroderma (Morphoea).

Vasculitis	Blood disorders	Others
• Large vessels vasculitis including: - Giant Cell Arteritis (Temporal Arteritis), - Takayasu's Arteritis. • Medium sized and/or small vessels vasculitis including: - Polyarteritis nodosa, - Kawasaki's disease, - Microscopic Polyangiitis, - Wegener's Granulomatosis (granulomatosis with polyangiitis), - Churg–Strauss syndrome (allergic granulomatous angiitis or eosinophilic granulomatosis with polyangiitis), - Buerger's disease (thromboangiitis obliterans), - Necrotizing vasculitis (cutaneous or systemic), - anti-neutrophil cytoplasmic antibody (ANCA) positive vasculitis (type unspecified), - Henoch-Schonlein purpura (IgA vasculitis), - Behcet's syndrome, - Leukocytoclastic vasculitis.	• Autoimmune hemolytic anemia. • Autoimmune thrombocytopenia. • Antiphospholipid syndrome. • Pernicious anemia. • Autoimmune aplastic anemia. • Autoimmune neutropenia. • Autoimmune pancytopenia.	• Autoimmune glomerulonephritis including: - IgA nephropathy, - Glomerulonephritis rapidly progressive, - Membranous glomerulonephritis, - Membranoproliferative glomerulonephritis, - Mesangioproliferative glomerulonephritis. - Tubulointerstitial nephritis and uveitis syndrome. • Ocular autoimmune diseases including: - Autoimmune uveitis - Autoimmune retinitis. • Autoimmune myocarditis. • Sarcoidosis. • Stevens-Johnson syndrome. • Sjögren's syndrome. • Alopecia areata. • Idiopathic pulmonary fibrosis. • Goodpasture syndrome. • Raynaud's phenomenon.
Liver disorders	**Gastrointestinal disorders**	**Endocrine disorders**
• Autoimmune hepatitis. • Primary biliary cirrhosis. • Primary sclerosing cholangitis. • Autoimmune cholangitis.	• Inflammatory Bowel disease, including: - Crohn's disease, - Ulcerative colitis, - Microscopic colitis, - Ulcerative proctitis. • Celiac disease. • Autoimmune pancreatitis.	• Autoimmune thyroiditis (Hashimoto thyroiditis). • Grave's or Basedow's disease. • Diabetes mellitus type I. • Addison's disease. • Polyglandular autoimmune syndrome. • Autoimmune hypophysitis.

Appendix 4 Prior and Concomitant Medications Date Imputation

Imputation Rules for Partial Dates (D = day, M = month, Y = year)			
Parameter	**Missing**	**Additional Conditions**	**Imputation**
Start Date	D only	M and Y same as M and Y of date of vaccination	Date of vaccination
		M and/or Y not the same as date of vaccination	First day of month
	M and D	Y same as Y of date of vaccination	Date of vaccination
		Y not the same as date of vaccination	Jan 01 of Y
	M, D, and Y	Non-date completely missing	Day prior to date of vaccination
Stop Date	D only	M and Y same as M and Y of date of discontinuation/completion of study	Date of discontinuation/ completion of study
		M and/or Y not the same as date of discontinuation/completion of study	Last day of month
	M and D	Y same as Y of date of discontinuation/completion of study	Date of discontinuation/ completion of study
		Y not the same as date of discontinuation/completion of study	Dec 31 of Y
	M, D, and Y	None – date completely missing and NOT ongoing	Date of discontinuation/ completion of study

Appendix 5 SAS Code

The following SAS code will be implemented to **compile CI's based on the mid-p method**:

```
proc freq data=<dataset> order=freq;
   tables category / binomial (CL=MIDP);
     weight Count;
run;
```

The following SAS code will be implemented to **compile CI's based on the Miettinen and Nurminen method without stratification**:

```
proc freq data=<dataset>;
   tables treatment*rate / nocol nopct missing riskdiff (CL=mn);
run;
```

The following SAS code will be implemented **for mixed models:**

```
proc mixed data=<dataset> method=reml;
   class usubjid treatment timepoint;
   model responsevariable = treatment timepoint /solution noint ddfm=kr;
      repeated timepoint /subject=usubjid type=un;
      lsmeans treatment|timepoint / pdiff cl;
run;
```

Appendix 6 Data Considerations for the Anti-M72 Antibody Data

Other data considerations for the anti-M72 antibody data are included below. These considerations might be updated once the actual data is received.

- For a given participant and a given immunogenicity measurement, missing or non-evaluable measurements will not be replaced. Therefore, an analysis will exclude participants with missing or non-evaluable measurements.
- 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) as indicated below.

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):

Rawres	**Numeric Result**
'NEG' or '-' or '(-)'	cut-off/2
'POS' or '+' or '(+)'	cut-off
'< value' and value ≤ cut-off	cut-off/2
'< value' and value > cut-off	value
'> value' and value < cut-off	cut-off/2
'> value' and value ≥ cut-off	value
'≤ value' or '≥ value' and value < cut-off	cut-off/2
'≤ value' or '≥ value' and value ≥ cut-off	value
value < cut-off	cut-off/2
value ≥ cut-off	rawres
otherwise the numeric result is left blank.	

Appendix 7 Data Considerations for Determining Responder Status for ICS Data

1. Compare the positive and negative cell count values of the active antigens to the positive and negative cell count values of the negative control (DMSO) at each visit per participant, T cell type, stimulation antigen and the relevant derived cytokine subset (Positive (Gamma [G],2)), using a one-sided Fisher's Exact test.
2. Since many tests will be conducted simultaneously for multiple T cell subsets and multiple peptide pools, a multiplicity adjustment will be made using PROC MULTTEST (Holm Method). The p-values will be adjusted across T cells, and antigens, therefore, by visit-level per participant.
3. If the adjusted p-value is less than or equal to $\alpha = 0.00005$, this will be regarded as a positive response.
4. Due to possible positive baseline results seen in previous similar trials, the final responder status will be determine taking baseline (Day 1, pre-vaccination) into account as follows:

Baseline	Post-baseline	Responder Status
Negative	Negative	Negative
Negative	Positive	Positive
Positive	Negative	Negative
Positive	Positive	Determine status by means of the odds ratio and the Breslow-day test

5. Derive the odds ratio for baseline and each post-baseline visit using the positive and negative counts of the active antigen and negative control value. If the negative control positive count is 0, 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. Calculate the difference in the log of the odds ratio at each post-baseline visit and baseline as: Difference in logs odds ratio = log (odds ratio at post-baseline visit) – log(odds ratio at baseline).
6. Perform the Breslow-Day for testing homogeneity of odds ratios and obtain the associated p-value.
7. Using the odds ratio and the Breslow-Day test p-value determine the responder status for cases where both baseline and post-baseline are positive as follows:

Breslow-Day test p-value	Difference in log odds ratio	Responder Status
≥ 0.05	< 0	Negative
≥ 0.05	> 0	Negative
< 0.05	< 0	Negative
< 0.05	> 0	Positive

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