STATISTICAL ANALYSIS PLAN

Protocol Title: **A Phase Ib, Multicenter, Randomized, Placebo-controlled, Observer-blinded, Dose escalation Study to Evaluate the Safety, Tolerability, and Immunogenicity of the rSm-p80 + GLA-SE (SchistoShield®) candidate vaccine in healthy adults in Burkina Faso and Madagascar**

Protocol Number: **IVI VASA 001**

Protocol Version: **4.0**

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Trial Registration: **US National Institutes of Health Clinical Trial Registry [NCT05762393] (http://www.clinicaltrials.gov)**

VERSION HISTORY

Version	Date	Description of Changes
1.0	22AUG2024	Initial version
2.0	16DEC2024	• Clarification of interim analysis • Changed Name of department

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List of abbreviations

Terminology	Definition
ABZ	Albendazole
ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Events of Special Interest
ATC	Anatomic Therapeutic Chemical Classification
BMI	Body Mass Index
CAA	Circulating Anodic Antigen
EDC	Electronic Data Capture
ELISpot	Enzyme-linked Immune Absorbent Spot
FAS	Full Analysis Set
GLM	Generalized Linear Model
GMT	Geometric Mean Titer
HD	High dose
IP	Investigational Product
IPD	Important Protocol Deviation
LD	Low dose
LLOQ	Lower Limit of Qualification
MD	Medium dose
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified Intention to Treat
PBMC	Peripheral Blood Mononuclear Cells
PD	Protocol Deviation
PPS	Per-Protocol Analysis Set
PT	Preferred Term
PZQ	Praziquantel
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SOC	System Organ Class
SUSAR	Suspected unexpected serious adverse event
TEAE	Treatment Emergent Adverse Event
UP	Unanticipated Problems

1. INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to provide more details about the statistical methodology and analyses to be implemented during the analysis of the data collected within the scope of the trial protocol titled *"A Phase 1b, multicenter, randomized, placebo-controlled, observer-blinded, Dose-escalation study to evaluate the safety, tolerability, and immunogenicity of the rSm-p80 + GLA-SE (SchistoShield®) candidate vaccine in healthy adults in Burkina Faso and Madagascar",* Protocol number: IVI VASA 001 Version 4.0 dated 06NOV2024. The scope of this SAP includes the interim analysis and final analysis that are planned and will be executed by the Data Science and Innovation department.

2. OBJECTIVES

2.1 Primary Objective

- To evaluate the safety and tolerability of 3 different dose formulations (low dose, medium dose, and high dose) of SchistoShield® vaccine given intramuscularly on D0, D28 and D56 to healthy participants 20 to 59 years of age in Burkina Faso and Madagascar

2.2 Secondary Objective

- To evaluate the immunogenicity of 3 different dose formulations (low dose, medium dose and high dose) of SchistoShield® vaccine, 28 days post-vaccination on D28, D56, and D84 as compared with the baseline and with those who received placebo

2.3 Exploratory Objective

- To describe the antigen-specific B- and T-cell responses, memory responses, and innate and adaptive immune signatures from samples collected at specified timepoints

3. STUDY OVERVIEW

3.1 Study Design

This is a phase 1b, multicenter, randomized, placebo-controlled, observer-blinded, dose-escalation study, assessing the safety, tolerability, and immunogenicity of a three-dose regimen, spaced four weeks apart, given intramuscularly in healthy adults (20-59 years old). Three different dose formulations of the investigational product with varying antigen contents will be investigated. A total of 120 eligible participants will be recruited in 3 sequential cohorts (A, B, and C) in Burkina Faso (N=60) and in Madagascar (N=60), as shown in Table 1, below. Cohort A will receive the low-dose antigen formulation (10µg) or placebo, Cohort B will receive the medium-dose antigen formulation (30µg) or placebo, and Cohort C will receive the high-dose antigen formulation (100µg) or placebo; all antigens with 5µg adjuvant (GLA-SE). In each cohort, volunteers will be randomized in a blinded manner into one of two arms, candidate vaccine or placebo, by a 3:1 ratio. A subset of five out of 20 subjects in each cohort will be sampled by convenience to enable us to further characterize the immune response using the peripheral blood mononuclear cells (PBMC).

To ensure that the study participants at enrollment do not have any active schistosomiasis or helminth infection and are schistosomiasis egg-negative, pre-screening activities including schistosomiasis treatment will be carried out in potential study participants prior to enrollment. Potential study participants will be identified in the catchment population and will be offered anti-helminth treatment using Praziquantel (PZQ) and Albendazole (ABZ) as per local guidelines at the study site. The pre-screening visit will be conducted 6-8 weeks before the screening visit. The last dose of PZQ/ABZ will be administered at least 5 weeks prior to the first dose of the investigational product.

Table 1: VASA phase 1b study plan in Burkina Faso and Madagascar

Country	Age group	Cohort	Arm	Treatment	Number of volunteers
Burkina Faso	20 - 59 years	Cohort A	Arm A1	SchistoShield® LD	15
			Arm A2	Placebo	5
		Cohort B	Arm B1	SchistoShield® MD	15
			Arm B2	Placebo	5
		Cohort C	Arm C1	SchistoShield® HD	15
			Arm C2	Placebo	5
Sample size					**60**
Madagascar	20 - 59 years	Cohort A	Arm A1	SchistoShield® LD	15
			Arm A2	Placebo	5
		Cohort B	Arm B1	SchistoShield® MD	15
			Arm B2	Placebo	5
		Cohort C	Arm C1	SchistoShield® HD	15
			Arm C2	Placebo	5
Sample size					**60**
Total Sample Size					**120**

LD: Low dose (10µg Ag/5µg GLA-SE Adjuvant); MD: Medium Dose (30µg Ag/5µg GLA-SE Adjuvant); HD: High Dose (100µg Ag/5µg GLA-SE Adjuvant)

3.2 Sample Size

A total of 120 participants will be enrolled in the study. The sample sizes in each study site are distributed by study cohorts and treatment arms. In each cohort, randomization will be performed in 3:1 allocation with 15 subjects in the rSm-p80 + GLA-SE arm and 5 subjects in the placebo arm.

- Cohort A with 20 participants (10µg Ag/5µg Adjuvant, 15 in rSm-p80 + GLA-SE group and 5 in placebo)
- Cohort B with 20 participants (30µg Ag/5µg Adjuvant, 15 in rSm-p80 + GLA-SE group and 5 in placebo)
- Cohort C with 20 participants (100µg Ag/5µg Adjuvant, 15 in rSm-p80 + GLA-SE group and 5 in placebo)

No formal power analysis is applicable to this study, as descriptive statistics will be used to summarize the data. A sample size of 30 participants who received a low, medium, or high antigen-dose formulation of the investigational product will provide 95% confidence that the true incidence of Serious Adverse Event (SAE) is <12%, if no SAE is observed in those dose cohorts. A sample size of 90 participants who received the candidate vaccine, irrespective of antigen-dose formulation, among all cohorts will provide 95% confidence that the true incidence of SAEs is <5% if no SAE is observed.

4. STUDY ENDPOINTS

4.1 Primary endpoints

- Proportion of participants with any Serious Adverse Events (SAEs)/ adverse events of special interest (AESI) from the time of the first study vaccination through the final study visit.
- Proportion of participants with immediate adverse events (reactogenicity events) within 60 minutes from the time of each study vaccination.
- Proportion of participants with solicited local and solicited systemic AEs as measured for 7 days (inclusive) following immunization with the three different dose formulations.
- Proportion of participants with unsolicited AEs from the time of vaccination until 28 days post immunization with the three different dose formulations.
- Proportion of participants with clinical safety laboratory adverse events measured at 7 days and 28 days after each study vaccination.

4.2 Secondary endpoints

- For Sm-p80 IgG antibodies, seroconversion rate at approximately 4 weeks (28 days) after each dose of study vaccination as compared to baseline.
- For Sm-p80 IgG antibodies, seroconversion rate at approximately 24 weeks after third dose of study vaccination as compared to baseline.
- Geometric Mean Titers (GMTs) of serum Sm-p80 IgG antibodies at approximately 4 weeks after each dose of study vaccination.
- Geometric Mean Titers (GMTs) of serum Sm-p80 IgG antibodies at approximately 24 weeks after third dose of study vaccination.

4.3 Exploratory endpoints

- For Sm-p80-specific cellular responses, enumeration of cytokine-secreting cells by IFNγ ELISpot (numbers of spot-forming cells) at specified time points.
- For Sm-p80 IgE antibodies, seroconversion rate at 4 weeks (28 days) after each dose of study vaccination as compared to baseline.
- Innate and adaptive immune signatures depicting the changes in a sub-set of immunized participants using PBMC’s collected at specified time points as measured by RNA seq and quantification of cytokines.
- T-cell cytokine and chemokine responses from whole blood and PBMC samples collected at specified time points in a subset of participants.
- Enumeration of antibody-secreting and memory B cells from PBMC samples collected at specified time points in a subset of participants.
- Enumeration of the ability of Sm-p80-specific antibodies from human participants to kill schistosome larvae in vitro (schistosomula-killing assay).

- Identification of immune signature markers identified by RNA Seq that are related to protective efficacy in animal passive transfer studies to identify markers that can be used for future down-selection of this other schistosome vaccine products.
- Determination of the changes in the circulating anodic antigen (CAA) levels before vaccination compared with the levels 4 weeks after the 3rd dose of vaccination.

5. HYPOTHESES AND/OR ESTIMATION

No formal statistical hypothesis is tested in this study.

6. DEFINITIONS

- **Seroconversion**: Seroconversion is defined as 4-fold rise in Sm-p80-specific total IgG antibodies after each investigational product administration compared to baseline (D0).
- **Seroconversion Rate**: Proportion of participants who had seroconversion.
- **Geometric Mean Titer (GMT)**: Methods of calculating the mean of antibody titer for a treatment group by multiplying all individual antibody titer values together and taking the nth root of product (where n is the number of available data points in the treatment group).

$$GMT = (Antibody\ titer_1^* \times Antibody\ titer_2^* \times Antibody\ titer_3^* \times \cdots \times Antibody\ titer_n^*)^{\frac{1}{n}}$$

n= Total number of individuals in the treatment group

*Serum Sm-p80 IgG or IgE antibodies

- **Randomization and/or study enrollment day**: Study enrollment day is Day 0 for participants who are satisfied with eligibility criteria and are enrolled. The enrollment number is '[Site Code]-[Cohort] and [Sequence Number], e.g., M-A01.
- **Derivation of study days**: calculated as (Date of Visit – Date of enrollment).
- **Age**: If the date of birth has not passed as of the date of informed consent, age = year of consent – year of birth – 1, or if the date of birth has passed as of the date of informed consent, age = year of consent – year of birth
- **BMI (kg/m^2)**: Weight (kg) / [Height (m)]^2
- **Day 0**: Day 0 is the time of 1st dose vaccination received after confirmed eligibility, enrollment and assigned enrollment number at Visit 2.
- **Study baseline**: For immunogenicity, baseline values are obtained from blood collected at enrollment/1st dose visit (Visit 2, that is, Day 0) before administration of Investigational Product (IP). For vital signs and physical examinations, baseline values are collected at Screening Visit (Visit 1, Day -28 to -1) and Enrollment/Vaccination Visit (Visit 2, Day 0) before the administration of IP. The values collected at Enrollment/Vaccination Visit before the administration of IP will be the baseline values if baseline values are collected on both screening and enrollment visit.
- **End of study**: A participant is considered to have completed the study if he or she has attended the planned final visit and the corresponding procedures of the visit. For participants who

discontinue the study before the planned final visit, the date of the final visit will be the date of their last visit.

- **Total duration of the study**: The expected total duration of the study spans from screening of first participants until last scheduled visit of the enrolled participant.
- **Adverse Event (AE)**: Any untoward medical occurrence which follows immunization, and which does not necessarily have a causal relationship with the administration of the vaccine. An AE may be any unfavorable or unintended sign, symptom, abnormal laboratory finding or disease.
- **Adverse Drug Reaction (ADR)**: All noxious and unintended responses to investigational product related to any dose of investigational product.
- **Immediate AE**: AEs that are observed in the first 60 minutes after the administration of the investigational product.
- **Solicited AEs**: Solicited AEs are predetermined events, identified in the Investigator's Brochure, which may reflect safety concerns related to the investigational product. AEs that will be solicited by the participant, recorded in the diary card and reviewed by a blinded observer during the 7 days after each dose for this study include:
  - Local reactions at the site of injection: Pain, tenderness, redness, swelling, pruritus, induration
  - Systemic reactions: Fever, headache, nausea, vomiting, myalgia, arthralgia, malaise, dizziness, fatigue

  If the reaction stops on Day 6 and reappears on Day 7, both reactions should be recorded as a single continuous one but non-consecutive events occurring within 7 days after vaccination are counted as separate events. If the reaction stops on Day 6 and reappears on Day 8, 2 separate reactions shall be recorded, and this episode should be reported as unsolicited AE in the subsequent visit. For the severity of solicited AE beyond 7 days post vaccination, the maximum severity during the interval from Day 7 until the stop date will be recorded.
- **Unsolicited AEs**: Unsolicited AEs are all other adverse events (those that do not fall under the categories of solicited adverse reactions) that are identified by site staff, the PI and the Study Medical Monitor. These unsolicited AEs will be documented in the participant's clinic records and entered in the study eCRFs. They will be recorded during the 4 weeks after each dose.
- **Adverse Event of Special Interest (AESI)**: Adverse Event of Special Interest (AESI) are AEs that are considered by the sponsor to be relevant for the monitoring of the safety profile of the investigational product.
- **Serious Adverse Event (SAE)**: An AE or suspected adverse reaction is considered "serious" if at any dose (including overdose):
  - Results in death
  - Is life-threatening[1]
  - Requires inpatient hospitalization or prolongation of existing hospitalization[2]
  - Results in persistent or significant disability/incapacity[3]

- Is a congenital anomaly/birth defect[4]
- Is an important medical event that may jeopardize the participant or may require intervention to prevent one of the other outcomes listed above

1. The term “life-threatening” refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
2. All medical events leading to hospitalizations will be recorded and reported as SAEs, with the exception of hospitalization planned before inclusion into the study or out-patient treatment with no hospitalization.
3. “Persistent or significant disability or incapacity” means that there is a substantial disruption of a person’s ability to carry out normal life functions.
4. Characteristic or abnormality existing at birth and found in the participant's offspring and not in the participant his/herself

- **Non-Serious Unanticipated Problems (UP)**: An UP that is not an Adverse Event (UP non-AE) is an unanticipated problem that does not fit the definition of an AE, but which may, in the opinion of the investigator, involve risk to the participant, affect others in the research study, or significantly impact the integrity of research data. Such events would be considered a non-serious UP. For example, accidental destruction of study records or samples.
- **Serious Unanticipated problems**: Serious Unanticipated problems include any incident, experience, or outcome that meets all the following criteria:
  - Unexpected in terms of nature, severity, or frequency of what is stated under adverse events in the protocol informed consent and Investigator’s Brochure.
  - Related or possibly related to vaccination.
  - Suggests that participants or others will be at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.
- **Suspected unexpected serious adverse event (SUSAR)**: Suspected unexpected serious adverse event (SUSAR) is defined as a serious adverse reaction whose nature or severity is not consistent with the applicable product information, Investigator’s Brochure or the summary of product characteristics of an authorized product.
- **Medical History**: Medical History includes all active conditions, and any other past conditions, as well as surgical procedure, that is considered to be clinically significant by the Investigator which occurring or detected in the participants within 60 days prior to the first study vaccination.
- **Prior Medication**: Prior Medication is defined as administered up to 60 days prior to the informed consent and stopped prior to first study vaccination on Day 0.
- **Concomitant Medication**: Concomitant Medication is defined as continuing or new treatment taken at or after first study vaccination.

7. ANALYSIS SETS

7.1 Safety Analysis Set

The safety analysis set (SAF) includes all participants who receive at least one dose of the rSm-p80 + GLA-SE formulation or Placebo. Participants for the safety analysis will be grouped in accordance with the dose of rSm-p80 + GLA-SE that they received. All primary safety endpoint analyses are based on SAF.

7.2 Full Analysis Set

The Full Analysis Set (FAS) is a modified intention to treat (mITT) analysis set that includes all participants who receive at least one dose of rSm-p80 + GLA-SE or Placebo and have at least one post baseline immunogenicity data available. The FAS will be used for the secondary and exploratory immunogenicity endpoints.

7.3 Per-Protocol Analysis Set

The per-protocol analysis set (PPS) is comprised of subsets of the FAS who receive all their planned study product administrations and who have no Study Medical Monitor-assessed important protocol deviations. Analyses on the PPS will be considered supportive of the corresponding immunogenicity analyses. Participants excluded from the PPS will be identified and documented prior to locking the study database. A sensitivity analysis using the PPS will be conducted for the secondary and exploratory immunogenicity endpoints.

8. DATA SCREENING AND ACCEPTANCE

8.1 Data Handling and Electronic Transfer of Data

All study data will be entered by site staff and stored on a cloud server using Viedoc™ electronic data capture (EDC) system. Study site staff will transcribe all data collected in source documents for recording into the eCRF. The EDC system incorporates identification of the data entry errors, range, and consistency checks during data entry. After all clinical data has been collected and cleaned through various quality control routine procedures, the database will be finalized. For this study, there will be one data freezing and one hard lock. Data Freezing will be performed after Visit 8 (Visit 2 (Day 0) + 84 days, 12 weeks) for interim analysis. Interim analysis will be performed by unblinded statistician who is not going to be involved in the rest of study activities. Other study team members will remain blinded to the vaccine allocation until final database lock. The hard lock will be performed after all participants complete all planned visits (Visit 9, Visit 2 (Day 0) +224 days, 32 weeks). Unblinding of study groups will be carried out after the completion of hard lock (final database lock) for final analysis.

8.2 Handling of Missing and Incomplete Data

The missing data will not be imputed or replaced for the analysis, and the analysis will be based on the reported values.

8.3 Multiple Comparison/Multiplicity

No adjustment for multiplicity will be made for this study as it is not applicable.

8.4 Distributional Characteristics

Sm-p80 IgG antibodies titer and Sm-p80 IgE antibodies will be logarithmically transformed prior to statistical analyses for better approximate normality. The base of the logarithm will be provided for each immunogenicity data by laboratory.

9. STATISTICAL METHODS OF ANALYSIS

9.1 General Principles

This is a phase Ib, randomized, placebo-controlled, observer-blinded, dose-escalation study to evaluate the safety, tolerability, and immunogenicity of the rSm-p80 + GLA-SE (SchistoShield®) candidate vaccine in healthy adults in Burkina Faso and Madagascar.

The primary objective of the study is to evaluate tolerability and safety of rSm-p80+GLA-SE administered intramuscularly in healthy adults.

Unless otherwise specified, standard descriptive statistics will be computed for all endpoints and other observed values. The standard descriptive statistics for continuous variables include number of observations analyzed, mean, standard deviation, median, minimum, and maximum. The standard descriptive statistics for categorical variables include frequency distribution with the number and percentage of participants included in each category.

The binary outcome measures of safety and immunogenicity will be summarized with frequency, proportion and associated 95% confidence interval. The continuous outcome measures of immunogenicity will be summarized with geometric mean and associated 95% confidence interval. Immunogenicity titers that are below the lower limit of qualification (LLOQ) will be set to half the LLOQ in the analysis.

Statistical significance will be compared using generalized linear models (GLMs) to assess any treatment effect among two treatment groups within Cohort. An appropriate link function depending on the given distribution assumptions of dependent or response variable will be used to construct the analysis of variance model. If the lower limit of the estimated confidence interval for seroconversion rate from the model is less than 0, it will be replaced with 0, and if the upper limit is greater than 100, it will be considered as 100. And comparison of two treatment groups will be performed using two-sample t-test or Wilcoxon rank-sum test for continuous variables, and Chi-square test or Fisher's exact test for categorical variables. All statistical tests will be conducted at the 5% (two-sided) level of significance unless otherwise specified.

All reported p-values greater than or equal to 0.0001 will be rounded to four decimal points and p-values less than 0.0001 will be displayed as '<0.0001'. The mean and standard deviation, percentages and 95% confidence interval will be rounded to two decimal points. All analyses will be done using SAS Version 9.4.

9.2 Interim Analysis

Interim analysis without group information for safety endpoints and with the group information for immunogenicity endpoints will be conducted independently at each site after the completion of the Visit 8 (Visit 2 (Day 0) + Day 84, Week 12) of last participant (4 weeks post 3rd vaccination dose).

9.3 Final Analysis

The final analysis will be performed after all participants complete all planned visits and all safety and immunogenicity data are cleaned and locked. Immunogenicity and safety data up to 8-month follow-up will be included in the final analysis.

9.4 Subject Accountability

Summaries of Participants Disposition will be based on all participants who provide informed consent in the study. A flow diagram of participant disposition (CONSORT flow diagram) will illustrate the progress of participants through the study duration from initial screening for eligibility to the completion of the final outcome assessment. The numbers and percentage by study cohort and treatment group will be given for participants in the SAF, FAS, PPS, and reasons for study discontinuation.

9.5 Important Protocol Deviations

Major protocol deviations (PD) are defined as those jeopardize the safety or rights of the participant or the scientific integrity of the study which is applicable to cases listed below.

- Violation of inclusion and exclusion criteria
- Vaccination with the wrong vaccine as defined in the protocol
- Vaccination not following the immunization schedule defined in the protocol
- Visit outside window for the immunogenicity assessment after discussion with the study medical monitor
- Missed samples for immunogenicity
- Missing SAE report
- Unblind-observer involved in the study subject evaluation

Major PD categories are defined by the study team before the first participant visit and updated during the PD reviews throughout the study prior to database lock. If a snapshot is being taken during the study rather than a database lock at the end of the study, categories should be updated during the PD reviews throughout the study prior to database lock. With categorized Major PDs, the study team defines Important Protocol Deviation (IPD) for PP analysis set. These definitions of IPD categories, sub-category codes, and descriptions will be used during the course of the study. The final IPD list is used to produce the Summary of IPDs table and the List of Subjects with IPDs.

Protocol Deviations will be summarized as the number of subjects, percentage, and the number of events by treatment group for the enrolled participants. A listing of protocol deviations will also be provided.

9.6 Demographic and Baseline Characteristics

Demographic characteristics and other baseline data of participants enrolled and randomized will be tabulated by study cohort and treatment group for the participants in all analysis sets listed above. Continuous variables (i.e., age, height and weight) and categorical variables (i.e., sex) will be summarized by standard descriptive statistics.

9.7 Safety Analysis

The Safety Analysis Set (SAF) will be used for safety analysis. In interim analysis using data till Visit 8 (one month post 3rd vaccination), the total number of all events without arm information will be presented. After final Database lock, it will be presented with the arm information.

9.7.1 Adverse Events

The primary endpoint analyses are safety analyses of treatment-emergent adverse events (TEAEs). TEAEs are defined for this study as any following AEs/AESIs/SAEs that occur from the time of the first study vaccination of rSm-p80+GLA-SE or placebo:

- SAEs and AESIs from the time of the first study vaccination through the final study visit
- Immediate AEs (Reactogenicity Events) within 60 minutes from the time of each study vaccination
- Solicited AEs (injection site and systemic reactogenicity events) from the time of each study vacc ination through 7 days (inclusive) after each study vaccination
- Unsolicited AEs from the time of each study vaccination through 4 weeks (28 days) after each stu dy vaccination
- Clinical safety laboratory AEs (significant laboratory abnormality) at 1 week (7 days) and 4 weeks (28 days) after each study vaccination.

All TEAEs/ADRs will be summarized by frequency, percentage and associated 95% confidence interval by study cohort and treatment group. The frequencies will also be presented separately by dose regimen and will be depicted by system organ class (SOC) and preferred term (PT). Additional frequencies will be presented with respect to maximum severity and relationship to investigational product. Multiple occurrences of the same TEAEs related to the same vaccine dose in a single subject will be counted only once following a worst-case approach with respect to severity and relationship to investigational product. However, for the solicited AE, if the reaction stops on Day 6 and reappears 24 hours after then it will be considered separate event and for the unsolicited AE. All of these primary endpoint analyses will be conducted on the participants in the Safety Analysis Set (SAF). Number of AEs/ADRs and proportion of participants with safety endpoints will be analyzed within each cohort and treatment group.

9.7.1.1 Immediate Reactions

The MedDRA version 26.1 (or the latest version) will be used to code immediate reactions to SOC and PT. Number and proportion of participants with immediate reactogenicity (immediate reactions within 60 minutes after vaccination) will be presented for each treatment group, and the number of immediate

reactions will be summarized for severity and IP relatedness by cohort and treatment group.

9.7.1.2 Solicited Adverse Events

The MedDRA version 26.1 (or the latest version) will be used to code solicited adverse events to SOC and PT. The number and proportion of participants with solicited adverse events within 7 days after each dose of vaccination will be presented for each cohort and treatment group, and the number of solicited adverse events will be summarized for severity and IP relatedness of the adverse events by each cohort and treatment group.

9.7.1.3 Unsolicited Adverse Event

The MedDRA version 26.1 (or the latest version) will be used to code unsolicited adverse events to SOC and PT. The number and proportion of participants with unsolicited adverse events within 28 days after the administration of the investigational product will be presented for each cohort and treatment group, and the number of unsolicited adverse events will be summarized for severity and IP relatedness of the adverse events by cohort and treatment group.

9.7.1.4 Serious Adverse Event

The MedDRA version 26.1 (or the latest version) will be used to code SAEs to SOC and PT. The number of SAEs and the number of participants who had experienced SAEs will be presented by cohort and treatment group. A listing of SAEs will be provided.

9.7.2 Laboratory Test Results

Clinical laboratory response variables will be descriptively summarized in accordance with time points. The normal ranges by each result will be used to present the number and proportion of abnormal lab results.

9.7.3 Vital Signs

A box plot and summary statistics such as mean, standard deviation, median, minimum, and maximum for vital signs consisting of systolic blood pressure (mmHg), diastolic blood pressure (mmHg), heart rate (beat/minute), respiratory rate (breaths/minute), and body temperature (°C) changes over time will be provided by cohort and treatment group.

9.7.4 Physical Examination

The shift tables of changes from baseline will be provided. Changes will be defined as the worst case during the trial the change is recorded as ‘clinically significant’. The shift table will include the number and percentage of changes by treatment group. Clinically significant results will be presented in listing for subjects.

9.7.5 Prior/Concomitant Medication

The number and percentage of participants taking concomitant medication will be summarized. The summaries will show ATC level 1 and ATC level 2 by cohort and treatment group. The number and

percentage of participants taking prior medication will be summarized in a similar fashion to concomitant medication. A listing of prior/concomitant medication will also be provided. Coding of the concomitant medications using ATC will be added in the final analysis.

9.7.6 Medical History

Medical history will be summarized by SOC and PT. Summaries will show the number and percentage of participants by cohort and treatment group. A listing of medical history will also be provided. Medical coding of the medical histories using MedDRA version 26.1 (or the lasted version) will be added in the final analysis.

9.7.7 Pregnancy

A listing of participants who are confirmed to be pregnant at each planned visit will be presented.

9.7.8 Circulating Anodic Antigen

The shift tables of changes from each vaccination to Visit 8 (4 weeks post 3rd vaccination) will be provided. The shift table will include the number and percentage of changes by cohort and treatment group using FAS and PPS.

9.8 Immunogenicity Analysis

The FAS and PPS will be used for immunogenicity analysis.

9.8.1 Analysis of Secondary Endpoint

The secondary endpoint analyses are immunogenicity analyses of anti-Sm-p80 IgG antibody levels measured at 4 weeks (28 days) after each dose of study vaccination and at 24 weeks (168 days) after the third dose of study vaccination. These analyses will be summarized descriptively by cohort and treatment group using seroconversion rates and associated 95% confidence interval. The GMT and 95% confidence interval of Sm-p80 IgG response at 4 weeks (28 days) after each dose of study vaccination and at 24 weeks (168 days) after the third dose of study vaccination will be summarized descriptively by study cohort and treatment group.

9.8.2 Analysis of Exploratory Endpoint

Antigen-specific cellular immune responses by IFNγ ELISpot, innate and adaptive immune signatures, and T and B cell response will be analyzed descriptively by cohort and treatment group using the geometric mean and associated 95% confidence intervals. Exploratory endpoint analysis will be conducted on sub-group.

9.9 Sub-Group Analysis

The subgroup analysis will be carried out to assess the difference/consistency of immunogenicity and safety across subgroups. The potential difference in safety and immunogenicity by age groups (20 to <45 years old, ≥45 years old), and gender (female, male) will be assessed, if needed.

10. CHANGES FROM PROTOCOL-SPECIFIED ANALYSES

Protocol	Changes from Protocol
There is no description of adverse drug reactions (ADR) in the protocol.	In addition, analysis of ADR is described.

11. APPENDICES

11.1 Appendix I. Grading Scale of Adverse Event

1) Injection site reactogenicity grading

Local (Injection Site) Reaction	Mild (Grade 1)	Moderate (Grade2)	Severe (Grade 3)
Pain — experienced without touching the injection site (spontaneous discomfort)	Subject is aware of pain, but it does not interfere with daily activity and no pain medication is taken	Subject is aware of pain; there is interference with daily activity, or it requires use of pain medication	Subject is aware of pain and it prevents daily activity
Tenderness — hurts only when injection site is touched, or the arm is moved	The area immediately surrounding the injection site hurts only when touched or with arm motion, and it does not interfere with daily activity	The area immediately surrounding the injection site hurts when touched or with arm motion, and it interferes with daily activity	The area immediately surrounding the injection site hurts when touched or with arm motion, and it prevents daily activity
Pruritus (itching)	Does not interfere with daily activity	Interferes with daily activity	Prevents daily activity
Swelling*	Does not interfere with daily activity	Interferes with daily activity	Prevents daily activity

2) Injection site reactogenicity measurement

Local (Injection Site) Reaction	Small (Grade 1)	Medium (Grade 2)	Large (Grade 3)
Erythema (Redness)*	2.5 — 5 cm	5.1 — 10 cm	> 10 cm
Induration (Hardness)/Swelling*	2.5 — 5 cm	5.1 — 10 cm	> 10 cm

*Will not be used as halting criteria

3) Subjective Systemic Reactogenicity Grading

Systemic (Subjective)	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Chills	No interference with daily activity	Some interference with daily activity	Significant interference, prevents daily activity
Myalgia (Body Aches/Muscular Pain)*	No interference with daily activity	Some interference with daily activity	Significant interference, prevents daily activity
Arthralgia (Joint Pain)*	No interference with daily activity	Some interference with daily activity	Significant interference, prevents daily activity
Nausea	No interference with daily activity	Some interference with daily activity	Significant interference, prevents daily activity
Vomiting	No interference with daily activity	Some interference with daily activity	Significant interference, prevents daily activity
Headache	No interference with daily activity	Some interference with daily activity	Significant interference, prevents daily activity
Dizziness	No interference with daily activity	Some interference with daily activity	Significant interference, prevents daily activity
Malaise	No interference with daily activity	Some interference with daily activity	Significant interference, prevents daily activity
Fatigue	No interference with daily activity	Some interference with daily activity	Significant interference, prevents daily activity

*Not at injection site

4) Quantitative Systemic Reactogenicity Grading

Systemic (Quantitative)	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Fever*	37.5 – 38.5°C	38.6 – 39.2°C	39.3 – 39.9°C

*A fever can be considered not related to the study product if an alternative etiology can be documented.

11.2 Appendix II. Adverse Events of Special Interest

Body System	Adverse Events of Special Interest
Gastrointestinal disorders	• Celiac disease (gluten-sensitive enteropathy) • Inflammatory bowel disease (Crohn's disease, ulcerative colitis or proctitis)
Liver disorders	• Autoimmune cholangitis • Autoimmune hepatitis • Primary biliary cirrhosis • Primary sclerosing cholangitis
Metabolic diseases	• Primary adrenal insufficiency (Addison's disease) • Chronic lymphocytic thyroiditis (Hashimoto's disease) • Diabetes mellitus type I • Graves' or Basedow's disease
Musculoskeletal disorders	• Antisynthetase syndrome • Dermatomyositis • Juvenile chronic arthritis/juvenile idiopathic arthritis (including juvenile Still's disease [macrophage activating syndrome]) • Mixed connective tissue disorder • Polymyalgia rheumatica • Polymyositis • Relapsing polychondritis • Rheumatoid arthritis • Scleroderma, including diffuse systemic form and CREST syndrome • Spondyloarthritis, including ankylosing spondylitis, reactive arthritis (Reiter's Syndrome) and undifferentiated spondyloarthritis • Systemic lupus erythematosus • Systemic sclerosis
Neuroinflammatory disorders	• Acute disseminated encephalomyelitis, including site specific variants (e.g., noninfectious encephalitis, encephalomyelitis, myelitis, myeloradiculomyelitis) • Possibly immune-mediated cranial nerve disorders (e.g., Bell's palsy) • Guillain-Barré syndrome, including Miller Fisher syndrome and other variants • Immune-mediated peripheral neuropathies and plexopathies, including chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy and polyneuropathies associated with monoclonal gammopathy • Multiple sclerosis • Optic neuritis • Transverse myelitis • Myasthenia gravis, including Lambert-Eaton myasthenic syndrome (LEMS) • Skin disorders • Alopecia areata

Body System	Adverse Events of Special Interest
	• Autoimmune bullous skin diseases, including pemphigus, pemphigoid and dermatitis • Herpetiformis • Cutaneous lupus erythematosus • Erythema nodosum • Localized scleroderma (morphea) • Lichen planus • Psoriasis • Acute febrile neutrophilic dermatosis (Sweet's syndrome) • Vitiligo
Vasculitides	• Large artery vasculitis: Takayasu's arteritis and giant cell arteritis (temporal arteritis) • Small and medium-sized artery vasculitis: • Polyarteritis nodosa • Mucocutaneous lymph node syndrome (Kawasaki disease) • Microscopic polyangiitis • Granulomatosis with polyangiitis (Wegener's granulomatosis) • Eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome) • Thromboangiitis obliterans (Buerger's disease) • Necrotizing vasculitis (systemic necrotizing vasculitis) • Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis • IgA vasculitis (Henoch-Schonlein purpura) • Behcet's syndrome • Leukocytoclastic vasculitis (hypersensitivity vasculitis)
Others	• Antiphospholipid syndrome • Autoimmune hemolytic anemia • Autoimmune glomerulonephritis (including IgA nephropathy, glomerulonephritis rapidly progressive, membranous glomerulonephritis, membranoproliferative glomerulonephritis, and mesangioproliferative glomerulonephritis) • Autoimmune myocarditis/cardiomyopathy • Autoimmune thrombocytopenia • Goodpasture syndrome • Idiopathic pulmonary fibrosis • Pernicious anemia • Raynaud's phenomenon • Sarcoidosis • Sjögren's syndrome • Stevens-Johnson syndrome • Uveitis