Statistical Analysis Plan

Study ID: 219449

Official Title of Study: A Phase 2 single-blind, randomized, controlled, single center study to assess the immunogenicity and safety of a 2-dose schedule with GVGH altSonflex1 2-3 vaccine in African infants (H06_02TP)

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TITLE PAGE

Protocol Title:	A Phase 2 single-blind, randomized, controlled, single center study to assess the immunogenicity and safety of a 2-dose schedule with GVGH altSonflex1 2-3 vaccine in African infants (H06_02TP)
Study Number:	219449
Compound Number:	GSK4001785A
Abbreviated Title:	SHIGELLA 4 GMMA GVGH-002 (H06_02TP)

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TABLE OF CONTENTS

PAGE

TITLE PAGE 1

VERSION HISTORY 5

1. INTRODUCTION 6
   - 1.1. Objectives, Estimands and Endpoints 6
   - 1.2. Study Design 13

2. STATISTICAL HYPOTHESES 14
   - 2.1. Multiplicity Adjustment 14

3. ANALYSIS SETS 14
   - 3.1. Criteria for eliminating data from Analysis Sets 15
     - 3.1.1. Elimination from the Enrolled Set 15
     - 3.1.2. Elimination from Exposed Set (ES) 15
     - 3.1.3. Elimination from Immunogenicity Set (IS) 16

4. STATISTICAL ANALYSES 19
   - 4.1. General Considerations 19
     - 4.1.1. General Methodology 19
     - 4.1.2. Baseline Definition 19
   - 4.2. Primary Endpoints Analyses 19
     - 4.2.1. Definition of estimands 19
     - 4.2.2. Main analytical approach 19
     - 4.2.3. Additional estimands 20
     - 4.2.4. Supportive primary endpoints 20
   - 4.3. Secondary Endpoint(s) Analyses 21
     - 4.3.1. Definition of estimands: 21
     - 4.3.2. Main analytical approach: 21
       - 4.3.2.1. Secondary safety estimands: 21
       - 4.3.2.2. Secondary immunogenicity estimands 23
       - 4.3.2.3. Additional estimands 23
     - 4.3.3. Supportive secondary safety endpoint(s) 24
   - 4.4. CCI [redacted] 24
     24
     25
     - 4.4.3. Additional Safety Assessments 25
       - 4.4.3.1. Vital Signs 25
   - 4.5. Other Analyses 25
   - 4.6. Interim Analyses 25
   - 4.7. Changes to Protocol Defined Analyses 26

5. SAMPLE SIZE DETERMINATION 26

6. SUPPORTING DOCUMENTATION 27
   - 6.1. Appendix 1 Study Population Analyses 27
     - 6.1.1. Participant Disposition 27
     - 6.1.2. Demographic and Baseline Characteristics 27
     - 6.1.3. Protocol Deviations 27

6.1.4. Prior and Concomitant Medications 28
6.1.5. Study Intervention Compliance 28
6.2. Appendix 2 Electronic Clinical Outcome Assessment (eCOA) Compliance 28
6.3. Appendix 3 Data Derivations Rule 28
6.3.1. Attributing events to vaccine doses 28
6.3.2. Laboratory data 29
6.3.3. Study Day and Reference Dates with Partial dates 30
6.3.4. Daily recording of solicited events 31
6.3.5. Unsolicited AEs 31
6.3.6. Multiple measurements at One Analysis Time Point 32
6.3.7. Data derivation 32
6.3.7.1. Age at first dose in months 32
6.3.7.2. Weight 32
6.3.7.3. Height 32
6.3.7.4. Temperature 32
6.3.7.5. Numerical serology results 33
6.3.7.6. Geometric mean titres (GMTs) and concentrations (GMCs) 33
6.3.7.7. Onset day 33
6.3.7.8. Duration of events 33
6.3.7.9. Counting rules for combining solicited and unsolicited AEs 33
6.3.7.10. Counting rules for occurrences of solicited AEs 34
6.3.8. Display of decimals 34
6.3.8.1. Percentages 34
6.3.8.2. Differences in percentages 34
6.3.8.3. Demographic/baseline characteristics statistics 35
6.3.8.4. Serological summary statistics 35
6.3.9. Trademarks 35

7. REFERENCES 36

LIST OF TABLES

PAGE

Table 1 Primary, secondary and part of tertiary objectives/endpoints 6

Table 2 Study Estimands 8

Table 3 Analysis sets 15

Table 4 List of elimination codes 16

Table 5 Changes to Protocol Defined Analysis Plan 26

Table 6 95% confidence intervals in participants with *at least* 4-fold increase receiving the altSonflex1-2-3 vaccine 26

Table 7 Grading scales for hematology and biochemistry safety laboratory assessments 29

VERSION HISTORY

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
SAP	17 Sep 2024	Amendment 1 (v1.0) 19 April 2024	Not Applicable	Original version

1. INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the planned analyses to be included in the clinical study report (CSR) for Study 219449. Details of the planned SRT assessment, as well as the final analyses, are provided.

1.1. Objectives, Estimands and Endpoints

Table 1 Primary, secondary and part of tertiary objectives/endpoints

Objectives	Endpoints
Primary	
To evaluate the immunogenicity profile of the altSonflex1-2-3 vaccine (Dose A, Dose B and Dose C) administered at 9 and 15 months of age using anti-LPS/OAg ELISA.	• Anti-serotype-specific *Shigella* LPS/OAg* serum IgG GMCs/GMTs, as measured by ELISA, before each study intervention administration (Day 1 and Day 169), and 28 days after each study intervention administration (Day 29 and Day 197), for each study intervention group.
To evaluate the seroresponse of the altSonflex1-2-3 vaccine (Dose A, Dose B and Dose C) administered at 9 and 15 months of age using anti-LPS/OAg ELISA.	• Number of infants with at least a 4-fold increase in anti-serotype-specific Shigella LPS/OAg* serum IgG, as measured by ELISA, at 28 days after each study intervention administration (Day 29 and Day 197), compared to baseline (Day 1), and at 28 days after dose 2 (Day 197) compared to pre-administration dose 2 (Day 169), for each study intervention group.
Secondary	
To evaluate the safety and reactogenicity of the altSonflex1-2-3 vaccine (Dose A, Dose B and Dose C) administered at 9 and 15 months of age.	• Number of infants with solicited administration-site events during the 7 days period (on the day of study intervention administration and the 6 subsequent days) after each study intervention administration (study intervention administration on Day 1 and Day 169). • Number of infants with solicited systemic events during the 7 days period (on the day of study intervention administration and the 6 subsequent days) after each study intervention administration (study intervention administration on Day 1 and Day 169). • Number of infants with unsolicited AEs during the 28 days period (on the day of study intervention administration and the 27 subsequent days) after each study intervention administration (study intervention administration on Day 1 and Day 169). • Number of infants with SAEs during their entire study participation period (from Day 1 to Day 197). • Number of infants with deviations from laboratory reference values or baseline values of hematological, renal, and hepatic panel test results, at 7 days after each study intervention administration (Day 8 and Day 176).
To evaluate the immunogenicity of co-administered *MR-VAC* administered at 9 and 15 months of age.	• Anti-measles IgG concentrations, as measured by ELISA, before the first *MR-VAC* (Day 1) and at 28 days after the second *MR-VAC* vaccination (Day 197). • Anti-rubella IgG concentrations, as measured by ELISA, before the first *MR-VAC* (Day 1) and at 28 days after the second *MR-VAC* vaccination (Day 197).

Objectives	Endpoints
	• Number of infants achieving anti-measles IgG concentrations of ≥150 mIU/mL** and ≥200 mIU/mL**, as measured by ELISA, at 28 days after the second *MR-VAC* vaccination (Day 197). • Number of infants achieving anti-rubella IgG concentrations of ≥4 IU/mL** and ≥10 IU/mL**, as measured by ELISA, at 28 days after the second *MR-VAC* vaccination (Day 197). **This threshold is based on the vaccine correlate of protection and World Health Organization guidelines.

CCI [redacted]

**S. sonnei, S. flexneri 1b, S. flexneri 2a and S. flexneri 3a serotypes will be tested. Additional S. flexneri serotypes may be tested.*

***Length/height for age z score as described by WHO [WHO, 2021b].*

Linear growth faltering defined as a continuous variable (ΔLAZ) [Brander, 2019].

AE = Adverse event; ELISA = Enzyme-linked immunosorbent assay; GMC = Geometric mean concentration; GMT = Geometric mean titer; IgG = Immunoglobulin G; LAZ = length-for-age z-score; LPS = Lipopolysaccharide; OAg = O-antigen; SAE = Serious adverse event; SBA = Serum bactericidal assay.

Table 2 Study Estimands

Estimand	Attributes					Summary Measure
	Treatment	Population	Endpoint (Variable)	Intercurrent Events (ICEs)		
				Description	Handling Strategy	
Primary Estimands						
Immunogenicity						
Clinical question: The clinical question of interest is to evaluate the immunogenicity profile and seroresponse of 2 injections of the altSonflex1-2-3 vaccine (Dose A, Dose B and Dose C) administered at 9 and 15 months of age using anti-LPS/OAg ELISA, in all participants compliant with protocol criteria (evaluable participants). **Rationale for estimand:** The interest of the study lies in evaluating the effect of 2 injections of the altSonflex1-2-3 vaccine with different doses (Dose A, Dose B and Dose C) administered at 9 and 15 months of age, in compliance with the key protocol criteria (evaluable participants). The estimand addresses the objective of evaluating the immunogenicity response and seroresponse response in ideal conditions.						
Primary	2 injections (at Day 1 and 169) the altSonflex1-2-3 vaccine at 3 different doses (A, B and C) concomitantly with MR-VAC vaccine Control: Typhibev vaccine (at Day 1), Infanrix hexa vaccine (at Day 169) concomitantly with MR-VAC vaccine	Healthy infants 9 MOA at 1st study intervention administration	• Anti-serotype-specific *Shigella* LPS/OAg* serum IgG, as measured by ELISA, before each study intervention administration (Day 1 and Day 169), and 28 days after each study intervention administration (Day 29 and Day 197). • Participants with at least 4-fold increase compared to baseline (Day 1) and pre-administration (Day 169) of anti-serotype-specific Shigella LPS/OAg* total IgG as measured by ELISA.	• Study intervention discontinuation • Vaccination administration errors* • Noncompliance with the vaccination schedule • Blood draws occurring outside the Protocol- defined visit window • Intercurrent medical conditions impacting immunogenicity • Concomitant medications and vaccinations not foreseen by the study Protocol. • Study intervention administered differing from that assigned through randomization	data after the corresponding ICEs are considered not appropriate for assessing the vaccine effect, and data post ICE will not be considered for the analysis of the outcome measure	<u>For each timepoint, and for each serotype:</u> • Unadjusted GMTs/GMCs with 95% CI of anti-serotype-specific Shigella LPS/OAg* total IgG as measured by ELISA. • Geometric mean with 95% CI of within-participant ratio of each post-dose 1 titer (Day29, 169 and 197) versus pre-dose 1 titer (Day1) of anti-serotype-specific Shigella LPS/OAg* total IgG as measured by ELISA.

Estimand	Attributes					Summary Measure
	Treatment	Population	Endpoint (Variable)	Intercurrent Events (ICEs)		
				Description	Handling Strategy	
						• Geometric mean with 95% CI of within-participant ratio of post-dose 2 (Day 197) titer versus pre-dose titer (Day 169) of anti-serotype-specific Shigella LPS/OAg* total IgG as measured by ELISA. • Number and percentage of participants with at least 4-fold increase compared to baseline (Day 1) and pre-administration (Day 169), with exact 95% CI of anti-serotype-specific Shigella LPS/OAg* total IgG as measured by ELISA.
Secondary Estimands						
Safety						
Clinical question: The clinical question of interest is to evaluate the safety and the reactogenicity profile, in a clinical trial setting, of 2 injections of the altSonflex1-2-3 vaccine with different doses (Dose A, Dose B and Dose C) in healthy infants 9 MOA at 1st study intervention. **Rationale for estimand:** The interest of the study lies in assessing the safety and tolerability of 2 injections of the altSonflex1-2-3 vaccine with different doses (Dose A, Dose B and Dose C) assessing all outcomes regardless of any intercurrent events.						

Estimand	Attributes					Summary Measure
	Treatment	Population	Endpoint (Variable)	Intercurrent Events (ICEs)		
				Description	Handling Strategy	
Secondary Safety	2 injections (at Day 1 and 169) the altSonflex1-2-3 vaccine at 3 different doses (A, B and C) Concomitantly with MR-VAC vaccine **Control:** Typhibev vaccine (at Day 1), Infanrix hexa vaccine (at Day 169) Concomitantly with MR-VAC vaccine		• Occurrence of solicited administration site and systemic events during 7 days after each study intervention administration. • Occurrence of unsolicited AEs during 28 days after each study intervention administration • Occurrence of SAEs during their entire study participation period. • Occurrence of deviations from reference or baseline values for hematological, renal, and hepatic panels test results at 7 days after each study intervention administration	• Study intervention discontinuation. • Vaccination administration errors*** • Noncompliance with the vaccination schedule • Blood draws for safety occurring outside the Protocol- defined visit window. • Intercurrent medical conditions. • Concomitant medications and vaccinations Study intervention administered differing from that assigned through randomization	The data collected for the endpoints are used regardless of whether intercurrent events occur	For each study intervention group and endpoint: Number and percentage of participants (95% CI) having at least one instance, for each endpoint

Estimand	Attributes					Summary Measure
	Treatment	Population	Endpoint (Variable)	Intercurrent Events (ICEs)		
				Description	Handling Strategy	
Immunogenicity						
Clinical question: The clinical question of interest is to evaluate the immunogenicity of co-administered MR-VAC administered at 9 and 15 months of age. **Rationale for estimand:** The secondary immunogenicity estimands address the objective to evaluate the immunogenicity of co-administered MR-VAC administered at day 1 and day 169 in compliance with the key protocol criteria (evaluable participants).						
Secondary Immunogenicity	2 injections (at Day 1 and 169) the altSonflex1-2-3 vaccine at 3 different doses (A, B and C) concomitantly with MR-VAC vaccine **Control:** Typhibev vaccine (at Day 1), Infanrix hexa vaccine (at Day 169) concomitantly with MR-VAC vaccine		• Anti-measles IgG concentrations, as measured by ELISA, before the first MR-VAC (Day 1) and at 28 days after the second MR-VAC vaccination (Day 197). • Anti-rubella IgG concentrations, as measured by ELISA, before the first MR-VAC (Day 1) and at 28 days after the second MR-VAC vaccination (Day 197). • Infants achieving anti-measles IgG concentrations of ≥150 mIU/mL and ≥200 mIU/mL, as measured by ELISA, at 28 days after the second MR-VAC vaccination (Day 197). • Infants achieving anti-rubella IgG concentrations of ≥4 IU/mL and ≥10 IU/mL, as measured by ELISA, at 28 days after the second MR-VAC vaccination (Day 197).	• Study intervention discontinuation • Vaccination administration errors* • Noncompliance with the vaccination schedule • Blood draws occurring outside the Protocol- defined visit window • Intercurrent medical conditions impacting immunogenicity • Concomitant medications and vaccinations not foreseen by the study Protocol • Study intervention administered differing from that assigned through randomization	data after the corresponding ICEs are considered not appropriate for assessing the vaccine effect, and data post ICE will not be considered for the analysis of the outcome measure	• GMC of Anti-measles IgG and Anti-rubella IgG, as measured by ELISA, before the first MR-VAC (Day 1) and at 28 days after the second MR-VAC vaccination (Day 197). • GM of within participant ratios of Anti-measles IgG and Anti-rubella IgG concentrations, as measured by ELISA, at 28 days after the second MR-VAC vaccination (Day 197) over Day 1 • Number and percentage of Infants achieving anti-measles IgG concentrations of ≥150 mIU/mL and ≥200 mIU/mL, as measured by ELISA,

Estimand	Attributes					Summary Measure
	Treatment	Population	Endpoint (Variable)	Intercurrent Events (ICEs)		
				Description	Handling Strategy	
						at 28 days after the second MR-VAC vaccination (Day 197). • Number and percentage of Infants achieving anti-rubella IgG concentrations of ≥4 IU/mL and ≥10 IU/mL, as measured by ELISA, at 28 days after the second MR-VAC vaccination (Day 197).

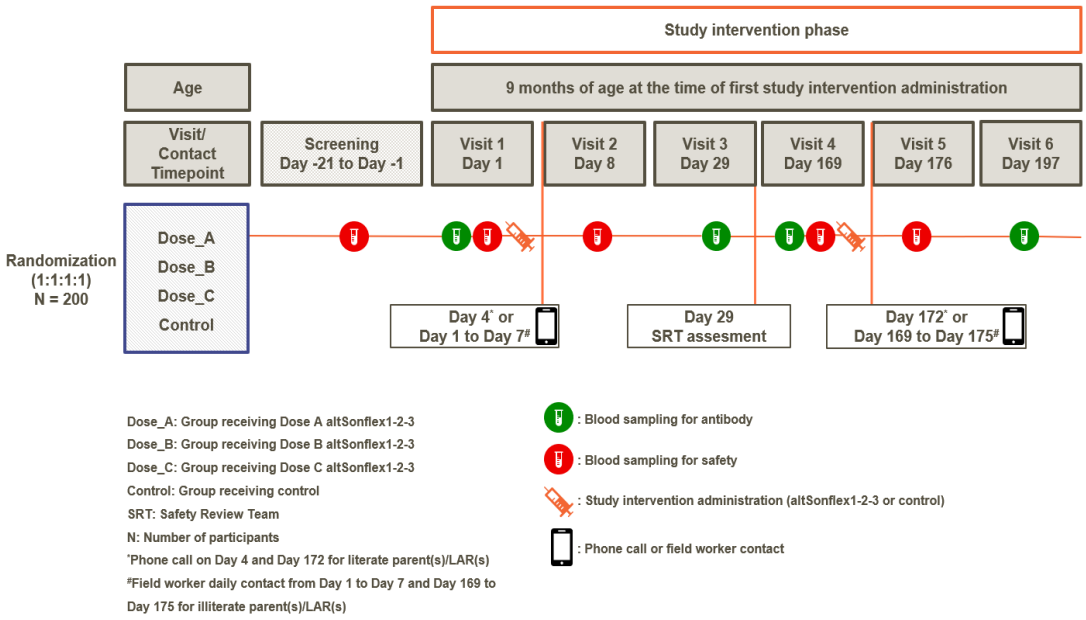
Abbreviations: AE = adverse event; CI = confidence interval; ELISA = ; Enzyme-linked Immunosorbent Assay; ICEs = intercurrent events; GMC = geometric mean concentration; GM= geometric mean fold rise; GVGH = GSK Vaccine Institute for Global Health; IgG = Immunoglobulin GMOA = months of age; SAE = serious adverse event; MOA = months of age.

*_S. sonnei_, _S. flexneri_ 1b, _S. flexneri_ 2a and _S. flexneri_ 3a serotypes will be tested. _Additional S. flexneri serotypes may be tested._

*** Vaccination administration errors, such as administration of a vaccine following storage outside the appropriate temperature range, a vaccine after expiry date, a vaccine following improper reconstitution, or a lower or higher dose than allowed by the study protocol

1.2. Study Design

Overview of Study Design and Key Features



Design Features

- **Type of study**: self-contained.
- **Experimental design:** Phase II, randomized (ratio 1:1:1:1), open-label, single centre study with 4 parallel groups.
- **Study groups:**
  - **Dose_A group**: Participants receiving 2 doses of altSonflex1-2-3's Dose_A in a sequential manner.
  - **Dose_B group**: Participants receiving 2 doses of altSonflex1-2-3's Dose_B in a sequential manner.
  - **Dose_C group**: Participants receiving 2 doses of altSonflex1-2-3's Dose_C in a sequential manner.
  - **Control group**: Participants receiving the Typhibev vaccine and Infanrix Hexa vaccine in a sequential manner.
- **Duration of the study**: ~7 months.
- **Control**: active comparator, i.e., sequential administration of licensed Typhibev vaccine and Infanrix Hexa vaccine.
- **Blinding**: open-label.
- **Vaccination schedule:**
  - **Dose_A, Dose_B and Dose_C Groups:** Participants will be receiving the 1st dose at visit 1 (Day 1) and the 2nd dose at visit 4 (Day169).
  - **Control group:** Participants will be receiving the Typhibev vaccine at Visit 1 (Day 1) and subsequently the Infanrix Hexa vaccine at Visit 4 (Day 169).
  - All Participants will also receive an EPI vaccination with MR-VAC concomitantly to study interventions

<table>
<tr><th colspan="2">Overview of Study Design and Key Features</th></tr>
<tr><td>Study intervention</td><td>
<table>
<tr><th>Study Groups</th><th>Number of Participants</th><th>Age (Min-Max)</th><th>Study Interventions*</th></tr>
<tr><td>Dose_A</td><td>~50</td><td>9 months</td><td>Dose_A of altsonflex 1-2-3</td></tr>
<tr><td>Dose_B</td><td>~50</td><td>9 months</td><td>Dose_B of altsonflex 1-2-3</td></tr>
<tr><td>Dose_C</td><td>~50</td><td>9 months</td><td>Dose_C of altsonflex 1-2-3</td></tr>
<tr><td rowspan="2">Control</td><td rowspan="2">~50</td><td rowspan="2">9 Months</td><td>Typhibev vaccine</td></tr>
<tr><td>Infanrix Hexa vaccine</td></tr>
</table>
*All Participants will also receive an EPI vaccination with MR-VAC concomitantly to study interventions.
</td></tr>
<tr><td>Interim Analysis</td><td>No interim analysis is planned in this study, but an SRT assessment will be performed to review all safety data collected up to 28 days after the first vaccination in infants to evaluate any trends in safety and potential safety signals after the first vaccination.

The SRT safety review for this study is planned for the first 200 participants who are dosed and have provided all safety data within 28 days after administration of the first study intervention administration (on the day of study intervention administration and the 27 subsequent days).</td></tr>
</table>

2. STATISTICAL HYPOTHESES

This is a Phase 2 study aimed to descriptively evaluate immunogenicity (primary, secondary and tertiary objectives) and safety (secondary objective) profiles of the study intervention therefore, no statistical hypothesis testing will be performed for this clinical study.

2.1. Multiplicity Adjustment

No multiplicity adjustment will be performed for any of the endpoints.

3. ANALYSIS SETS

The following analysis sets will be used for this study:

Table 3 Analysis sets

Analysis set	Definition/Criteria	Analyses evaluated
Enrolled	All participants who entered the study (who were randomized or received study intervention or underwent a post-screening study procedure). Note: participants who never passed screening (screening failures) and participants screened but who never enrolled into the study (met eligibility criteria but were not needed) are excluded from the Enrolled Set.	Study population
Exposed (ES)	All participants who received at least 1 dose of the study intervention. The allocation in a group is based on the administered intervention.	Safety (secondary objective)
Immunogenicity Set (IS)	All eligible participants who received all doses as per protocol, had immunogenicity results post-dose, complied with dosing/blood draw intervals, without intercurrent conditions that may interfere with immunogenicity and without prohibited concomitant medication/vaccination. The IS for immunogenicity will be defined by time point.	Immunogenicity analyses (primary objective)

AEs = Adverse events.

3.1. Criteria for eliminating data from Analysis Sets

Elimination codes will be used to identify participants to be eliminated from analysis. Details are provided below for each set.

3.1.1. Elimination from the Enrolled Set

The following codes are used to eliminate participants from the Enrolled Set:

Code	Category and subcategory	Visit (timepoints) where the code is applicable
700	Screening failure	All
800	Fraudulent data	All
900	Invalid Informed Consent	All

3.1.2. Elimination from Exposed Set (ES)

All the elimination codes used for the Enrolled Set are applicable. Additionally, the following code is used to eliminate participants from the Exposed Set:

- 1030 (Study intervention not administered at all).

For the analysis of solicited adverse events (AEs), only participants with available solicited safety data will be included in the set.

3.1.3. Elimination from Immunogenicity Set (IS)

A participant will be excluded from the populations for analysis under the following conditions:

- For codes 700,800, 900, 1030, 1050 and 2020: participants will be eliminated for all visits.
- For codes 1070, 1080, 1090: participants will be eliminated from a specific visit (at which the condition is met).
- For codes 1040,2010, 2040, 2050, 2080: participants will be eliminated from a specific visit (at which the condition is met) onwards.
- For codes 2090, 2100, 2120: participants will be eliminated at the specific visit at which the condition is met.

Table 4 List of elimination codes

Code	Condition under which the code is used	Visit /Contact(timepoints) where the code is checked	Visit from when it is applicable	Applicable for analysis set/endpoint
800	Screening failure	All	All	Enrolled, ES and IS for analysis of immunogenicity
800	Fraudulent data	All	All	Enrolled, ES and IS for analysis of immunogenicity
900	Invalid informed consent	All	All	Enrolled, ES and IS for analysis of immunogenicity
1030	Study intervention not administered at all;	All	All	ES and IS for analysis of immunogenicity
1040	Planned administration/administration of a vaccine not foreseen by the Protocol in the period starting 21 days before the first dose and ending after the last dose of study intervention(s) administration* with the exception of COVID-19 vaccines and EPI vaccines. The recommended time intervals for administration of these vaccines are at least 7 days before or 7 days after (at least 14 days before or 14 days after in case of live vaccines) each dose of study intervention administration	All visits	From the specific visit the condition is met	IS for analysis of immunogenicity
1050	Randomization failure: Participant not randomized in the correct group.	Visit 1	All	IS for analysis of immunogenicity

Code	Condition under which the code is used	Visit /Contact(timepoints) where the code is checked	Visit from when it is applicable	Applicable for analysis set/endpoint
1070	Vaccine administration not according to protocol Incomplete vaccination course Participant was vaccinated with the correct vaccine but containing a lower volume Wrong replacement or study vaccine administered (not compatible with the vaccine regimen associated to the treatment number) Route of the study vaccine is not intramuscular Side of administration wrong. Wrong reconstitution of administered vaccine	Vaccination visit(s) 1 and 4	From the specific visit (1 or 4) the condition is met as applicable.	IS for analysis of immunogenicity
1080	Vaccine temperature deviation Vaccine administered despite a GMP no-go temperature deviation	Vaccination visit(s) 1 and 4.	From the specific visit (1 or 4) the condition is met.	IS for analysis of immunogenicity
1090	Expired vaccine administered	Vaccination visit(s) 1 and 4.	From the specific visit (1 or 4) the condition is met.	IS for analysis of immunogenicity
2010	Protocol violation linked to inclusion/exclusion criteria All inclusion/exclusion criteria defined in the protocol to be checked.	Visit 1,4	From the specific visit (1 or 4) the condition is met.	IS for analysis of immunogenicity
2040	• Planned administration/administration of a product not foreseen by the Protocol in the period starting 21 days before the first dose and ending after the last dose of study intervention(s) administration*. • Administration of long-acting immune-modifying drugs at any time during the study period. • Administration of immunoglobulins and/or any blood products or plasma derivatives, or bone marrow transplantation, from birth or planned administration during the study period. • Chronic administration of immune-modifying drugs (defined as more than 14 days consecutive days in total) and/or planned use of long-acting immune-modifying treatments	All visits	From the specific visit (1,2,3* or 4) the condition is met	IS for analysis of immunogenicity

Code	Condition under which the code is used	Visit /Contact(timepoints) where the code is checked	Visit from when it is applicable	Applicable for analysis set/endpoint
	at any time up to the end of the study. • Up to 3 months prior to the study intervention administration: For corticosteroids, this will mean prednisone equivalent ≥0.5 mg/kg/day with maximum of 20 mg/day for pediatric participants. Inhaled and topical steroids are allowed. • Up to 3 months prior to study intervention administration: long-acting immune modifying drugs including among others immunotherapy (e.g., TNF inhibitors), monoclonal antibodies, antitumoral medication.			
2050	Intercurrent medical condition: Participants may be eliminated from the IS for immunogenicity if, during the study, they incur a condition that has the capability of altering their immune response (intercurrent medical condition) or are confirmed to have an alteration of their initial immune status.	All visits	From the specific visit (1,2,3,4,5 or 6) the condition is met	IS for analysis of immunogenicity
2080	Participants did not comply with vaccination schedule group number of days between dose 1 and dose 2 is outside [158-178] days	Visit 4	Visit 6	IS for analysis of immunogenicity
2090	Participants did not comply with blood sample schedule: • Number of days between vaccination1 (visit1) and blood sample (visit 3) is outside [28-33] days • Number of days between vaccination (visit 4) and blood sample (visit 6) is outside [28-33] days	Visit 4, Visit 6,	At the specific visit (4 or 6) the condition is met	IS for analysis of immunogenicity
2100	Serological results not available at the post-dose time point for all antigens tested at that particular time point.	Visit 3, 4 and 6	At the specific visit (3,4 or 6) the condition is met	IS for analysis of immunogenicity
2120	Obvious incoherence/abnormality or error in laboratory data Unreliable released data as a result of confirmed sample mismatch or confirmed inappropriate sample handling at lab	Visit 3, 4 and 6	At the specific visit (3,4 or 6) the condition is met	IS for analysis of immunogenicity

ES = exposed set; **GMP** = Good Manufacturing Practices; **HI** = hemagglutination inhibition; **IS** = Immunogenicity set

4. STATISTICAL ANALYSES

4.1. General Considerations

4.1.1. General Methodology

Unless otherwise specified, continuous data will be summarized using descriptive statistics: N, mean, standard deviation (SD), median, minimum, and maximum. Categorical data will be summarized as the number and percentage of participants in each category.

95% confidence interval (CI) for proportion will be based on exact Clopper-Pearson CI [Clopper, 1934].

4.1.2. Baseline Definition

For all safety endpoints measured on laboratory parameters, the baseline value will be the latest pre-dose assessment with a non-missing value; in particular:

- Visit 2 (Day 8) has Visit 1 (Day 1) as baseline.
- Visit 5 (Day 176) has Visit 4 (Day 169) as baseline.

Unless otherwise stated, if baseline data is missing no derivation will be performed. In this case, baseline, and baseline-derived values (e.g., change from baseline) will be set to missing.

4.2. Primary Endpoints Analyses

4.2.1. Definition of estimands

For the definition of the primary estimands, see Table 1 and Table 2.

4.2.2. Main analytical approach

The analysis on primary objective will be based on the ***IS***.

- For each study group, for each sampling timepoint, and for each serotype, the following statistics will be computed:
  - Unadjusted GMTs/GMCs with 95% CI of anti-serotype-specific *Shigella* LPS/OAg* total IgG as measured by ELISA **and represented graphically**.
  - Geometric mean with 95% CI of within-participant ratio of each post-dose 1 titer (Day 29, 169 and 197) versus pre-dose 1 titer (Day1) of anti-serotype-specific Shigella LPS/OAg* total IgG as measured by ELISA **and represented graphically**.

- Geometric mean with 95% CI of within-participant ratio of post-dose 2 (Day 197) titer versus pre-dose titer (Day 169) of anti-serotype-specific Shigella LPS/OAg* total IgG as measured by ELISA **and represented graphically**.
- Number and percentage of participants with at least 4-fold increase compared to baseline (Day 1) and pre-administration (Day 169), with exact 95% CI as measured by ELISA.

The distribution of antibody concentrations for each serotype will be displayed using reverse cumulative distribution curves and box plots (all groups and available timepoints will be presented in the same graph).

**S. sonnei*, *S. flexneri* 1b, *S. flexneri* 2a, and *S. flexneri* 3a serotypes will be tested.

4.2.3. Additional estimands

If, in any investigational vaccine group at any timepoint, the percentage of participants excluded from the ***IS*** is 10% or more of the ***ES***, a supplementary analysis based on the ***ES*** for immunogenicity will be performed to complement the ***IS*** analysis.

The handling strategy will be the following: The data collected for the endpoints are used regardless of whether intercurrent events occur.

All analyses described in the Section 4.2.2 should be reproduced.

4.2.4. Supportive primary endpoints

For each study group, for each sampling timepoint, and for S. sonnei serotype only, the following statistics will be computed based on IS:

- Number and percentage of participants achieving an ELISA level ≥1:800 TAU titers equivalent against S. sonnei LPS with exact 95% CI.
- Number and percentage of participants achieving an ELISA level ≥1:1600 TAU titers equivalent against S. sonnei LPS with exact 95% CI.

If, in any investigational vaccine group at any timepoint, the percentage of participants excluded from the IS is 10% or more of the ES, a supplementary analysis based on the ES for immunogenicity will be performed to complement the IS analysis.

Cohen's equivalent threshold (1:800 titres) and double of Cohen's equivalent threshold (1:1600 titres) [Cohen, 1988] will be used for statistical analysis. Individual sera ran in GVGH ELISA, reference ELISA (WRAIR ELISA) and Cohen's ELISA, to establish commutability of results as obtained by the three methodologies, and especially to establish the antibody level corresponding to the median titre reported in convalescent sera [Cohen, 1988] and the double of this (1:800 and 1:1600 in Cohen's ELISA, respectively). Analysis of results obtained in the three labs performed by NIBSC estimated equivalent of 800 and 1600 titres in Tel Aviv Assay (TAU) as per table below.

TAU titre	Estimated GVGH EU (95% CI)	Estimated WRAIR titre (95% CI)
800	161 (124 – 211)	1053 (703 – 1577)
1600	396 (315 – 497)	2550 (1811 – 3590)

It has been decided for analyses purposes to consider as equivalent for each threshold the Lower Limit of the 95% CI of the point estimate. (i.e. 124 EU/mL and 315 EU/mL for GVGH ELISA and 703 titres and 1811 titres for reference ELISA, for 800 and 1600 TAU titres respectively). The decision to consider the LL of 95% CI and not the point estimate was made in order to maximise the probability of excluding participants above threshold at baseline.

4.3. Secondary Endpoint(s) Analyses

4.3.1. Definition of estimands:

For the definition of the secondary estimands, see Table 1 and Table 2.

4.3.2. Main analytical approach:

4.3.2.1. Secondary safety estimands:

The analyses of the secondary safety estimands will be descriptive analyses of safety data based on the Exposed Set as follows:

- The number and percentage of participants with at least 1 administration-site solicited event or unsolicited AE, with at least 1 systemic solicited event (fever) or unsolicited AE and with any AE during the 7-day (i.e., the day of vaccination and 6 subsequent days) or 28-day (i.e., the day of vaccination and 27 subsequent days) follow-up period will be tabulated with exact 95% CI by group after each vaccine dose and overall. The same computations will be done for Grade 3 AEs and for AEs resulting in a medically attended visit.
- The number and percentage with exact 95%CI of doses associated with at least 1 administration-site solicited event or unsolicited AE, with at least 1 solicited systemic event(fever) and unsolicited AE, and with any AE will be tabulated with exact 95%CI for the overall vaccination course. The same calculations will be performed for symptoms rated as Grade 3 and resulting in a medically attended visit.
- The number and percentage of participants reporting each individual solicited administration-site and systemic event (any Grade and Grade 3 and resulting in medically attended visit) during the 7-day (i.e., the day of vaccination and 6 subsequent days) solicited follow-up period will be tabulated with exact 95%CI. The number and percentage of doses associated with each individual solicited administration-site and systemic event will be tabulated with exact 95%CI for the overall vaccination course.

- The number and percentages of participants reporting each individual solicited administration-site event by maximum intensity during the 7 days follow-up period will be tabulated with exact 95%CI.
- The number and percentage of doses associated with each individual solicited administration-site event will be tabulated with exact 95%CI for the overall study intervention administration course. The same tabulation will be performed for events rated as Grade 3 and resulting in medically attended visit.
- The number and percentages of participants reporting the solicited systemic event (fever) by maximum intensity during the 7 days follow-up period will be tabulated.
- The number and percentage of doses associated with the solicited systemic event (fever) will be tabulated with exact 95%CI for the overall study intervention administration course. The same tabulation will be performed for events rated as Grade 3 and according to relationship to study intervention administration.
- Occurrence of fever will be reported as number and percentages of participants reporting temperature ≥38°C in 0.5°C cumulative increments during the 7-day (i.e., the day of vaccination and 6 subsequent days) follow-up period. This will be tabulated with exact 95%CI for each group after each dose. The same tabulation will be performed according to relationship to study intervention administration.
- The percentage of participants with each solicited administration site event and solicited systemic event (any grade and Grade 3) will be **represented graphically** for each group after each dose.
- The percentage of participants with at least one reported unsolicited AE during the 28-day (i.e., the day of vaccination and 27 subsequent days) follow-up period after each vaccination with its exact 95% CI will be tabulated by group and by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) and Preferred Term (PT). The same tabulation will be performed for Grade 3 unsolicited AEs and for unsolicited AEs according to relationship to vaccination, for Grade 3 causally related unsolicited AEs and for unsolicited AEs resulting in a medically attended visit.
- The number and percentage of doses associated with at least 1 reported unsolicited AE within 28 days after each study intervention administration with its exact 95% CI will be tabulated by group and by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) and Preferred Term (PT) for the overall study intervention administration course. The same tabulation will be performed for Grade 3 unsolicited AEs for any causally related unsolicited AEs, for Grade 3 causally related unsolicited AEs and for unsolicited AEs resulting in a medically attended visit.
- The number and percentage of participants reporting SAEs and AEs/SAEs leading to withdrawal from the study or discontinuation from further vaccinations during the participant period participation with its exact 95% CI will be tabulated by group and by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) and Preferred Term (PT). The detailed listings will also be produced.

- The number and percentage of participants reporting at least one report of causally related SAE leading to withdrawal from the study during the participant period participation will be tabulated. The detailed listings will also be produced.
- The same tabulation will be presented for fatal SAEs.

For each group and for haematological, renal, and hepatic panel test results at 7 days after each vaccination:

- The number and percentage of participants having results below or above the laboratory reference ranges versus baseline (Day 1 and Day 169) values will be tabulated.
- The number and percentage of participants with abnormal results by Grade values versus baseline (Day 1 and Day 169) Grade values will be tabulated.

The verbatim reports of unsolicited symptoms will be reviewed by a physician and the signs and symptoms will be coded according to the MedDRA Dictionary for AE Terminology.

All the analyses above will also be part of the SRT assessment.

4.3.2.2. Secondary immunogenicity estimands

The analyses of the secondary immunogenicity estimand will be descriptive based on the IS.

For each study group, for the sampling timepoint before the first vaccination and 28 days after the second MR-VAC vaccination, the following statistics will be computed for the anti-measles and anti-rubella antigens, as measured by ELISA:

- Unadjusted GMCs with 95% CI of anti-measles and anti-rubella antibodies.
- Percentage of participants with measles seroresponse of ≥150 mIU/mL and ≥200 mIU/mL, with exact 95% CI.
- Percentage of participants with rubella seroresponse of ≥4 mIU/mL and ≥10 mIU/mL, with exact 95% CI.

For all the above, within-participant GMRs will be computed for GMC with 95% CI versus baseline (Day 1).

4.3.2.3. Additional estimands

- **For immunogenicity secondary estimands:**

Please refer to Section 4.2.3

4.3.3. Supportive secondary safety endpoint(s)

- **For safety secondary endpoint** the following additional statistics will be provide:
  - The number of days with solicited events reported during the 7-day follow-up period (i.e., the day of vaccination and 6 subsequent days) will be tabulated for each individual solicited event using descriptive statistics (mean, minimum, Q1, median, Q3, maximum). The same computations will be done for Grade 3 solicited events.
  - The number of days with solicited events ongoing beyond the 7-day follow-ups will be done for Grade 3 solicited events.
  - Compliance in completing solicited events information will be provided by day after each vaccination for each group.

CCI

[redacted]

CCI



4.4.3. Additional Safety Assessments

4.4.3.1. Vital Signs

Axillary temperature, pulse rate, respiratory rate, and blood pressure will be recorded (before blood collection for laboratory tests) before and 60 minutes after vaccination.

Vital signs will be summarized by vaccine group using descriptive statistics at all timepoint(s) the information is collected on Exposed Set.

This analysis will be part also from SRT assessment.

4.5. Other Analyses

Not applicable

4.6. Interim Analyses

No interim analysis is planned for this study, but an unblinded early aggregated safety data review will be performed by Safety review team (SRT) as defined in the protocol. The goal of this is to allow for a cautious approach to the second study intervention administration and to guarantee early potential safety signal detection during the study. The safety review for this study is planned for the first 200 participants who are dosed and have provided all safety data within 28 days after administration of the first study intervention administration (on the day of study intervention administration and the 27 subsequent days).

4.7. Changes to Protocol Defined Analyses

Changes from the originally planned statistical analysis specified in the protocol are detailed in Table 5.

Table 5 Changes to Protocol Defined Analysis Plan

Protocol Defined Analysis	SAP Defined Analysis	Rationale for Changes
• Per protocol set (PPS)	• Immunogenicity Set (IS)	• The per protocol set has been renamed as immunogenicity set to align with new requirements from Estimands framework
• Randomized set	• Removed from the analysis set	• No added value for this analysis the enrolled set is sufficient.

5. SAMPLE SIZE DETERMINATION

Approximately 200 participants will be randomized to achieve 176 evaluable participants, assuming a drop-out rate of 12% in each intervention group. Participants who withdraw from the clinical study after being randomized will not be replaced. Sample size is not driven by statistical hypotheses, rather it is determined to support an adequate immunogenicity and safety assessment of the primary study intervention group.

Statistical considerations for the immunogenicity are based on the percentage of participants with at least 4-fold increase in anti-serotype-specific *Shigella* LPS/OAg serum IgG among the 4 serotypes. Table 6 shows the associated precision in terms of 95% CI for different scenarios of number/percentage of participants with at least 4-fold increase assuming 44 evaluable participants in each group.

Table 6 95% confidence intervals in participants with *at least* 4-fold increase receiving the altSonflex1-2-3 vaccine.

Number of participants with 4-fold increase	Percentage of participants with 4-fold increase (%)	95% confidence interval (%)
22	50.0	34.6-65.4
24	54.5	38.8-69.6
26	59.1	43.2-73.7
28	63.6	47.8-77.6
30	68.2	52.4-81.4
33	75	59.7-86.8
35	79.5	64.7-90.2
37	84.1	69.9-93.4
39	88.6	75.4-96.2
42	95.5	84.5-99.4

Estimated with PASS 2019, v19.0.1 Two-Sided Confidence Intervals for One Proportion with Exact Formula (Clopper-Pearson).

Non-evaluable participant is an individual who entered in the study but has been excluded from analysis due to protocol deviation.

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 Study Population Analyses

6.1.1. Participant Disposition

A summary of the number and percentage of participants who completed the study as well as those who prematurely withdrew from the study will be provided. Reasons for study withdrawal will be summarized.

A summary of the number and percentage of participants who attended scheduled study visits will be provided.

Summary tables that include subject eliminations from analysis sets will be provided for:

- Exposed Set to Immunogenicity Set.

In case the Enrolled Set is different from the Exposed Set, an additional summary table from Enrolled Set to Exposed Set will be added.

6.1.2. Demographic and Baseline Characteristics

Demographic characteristics (age at first study intervention administration in months or years, sex, race) will be summarized by treatment group and overall using descriptive statistics:

- Frequency tables will be generated for categorical variable such as sex and race.
- Mean, median, standard deviation (SD) and range will be provided for continuous data such as age, height/length, weight.

The analysis population will be the Enrolled Set, Exposed Set and Immunogenicity Set.

Medical history will be tabulated by SOC and PT. The summary will be performed by study intervention group using descriptive statistics, as described in Section 4.1.1.

All analyses based on ES above will be part of SRT assessment.

6.1.3. Protocol Deviations

Important protocol deviations will be summarized.

Protocol deviations will be tracked by the study team throughout the conduct of the study. These protocol deviations will be reviewed to identify those considered as important as follows:

- Data will be reviewed prior to freezing the database to ensure all important deviations (where possible without knowing the study intervention details) are captured and categorised in the protocol deviations dataset.
- This dataset will be the basis for the summaries of important protocol deviations.

Protocol deviations which result in exclusion from the analysis set will also be summarized.

- Data will be reviewed prior to freezing the database to ensure all deviations leading to analysis population exclusions are captured and categorized in the protocol deviations ADaM dataset.

6.1.4. Prior and Concomitant Medications

Concomitant medications/vaccinations will be coded using both the GSK Drug and WHO Drug dictionaries.

Summary of participants taking a concomitant medication/vaccination within 28 days following each dose and overall will be performed on Exposed Set by GSK Drug dictionary only.

All collected concomitant medications and vaccinations will be listed. In addition, concomitant medication will be summarized by any antipyretic, any antibiotic or any medication.

Analyses described above will be also part of SRT assessment.

6.1.5. Study Intervention Compliance

The number and percentage of participants receiving the first (i.e., only the first) and the second doses will be summarized by study intervention on the Exposed set.

6.2. Appendix 2 Electronic Clinical Outcome Assessment (eCOA) Compliance

Not applicable.

6.3. Appendix 3 Data Derivations Rule

6.3.1. Attributing events to vaccine doses

The dose relative to an event is the most recent study dose given to a participant prior to the start of a given event. For example, if the start date of an adverse event is between Dose 1 and Dose 2, the relative dose will be Dose 1.

If an event starts on the same day as a study dose, the relative dose will be derived from the additional information provided in the case report form (CRF) using the contents of the flag indicating if the event occurred before or after study dose. If ‘after study dose’ is selected, the relative dose for the event will be the one administered on the start day of the event. If ‘before study dose’ is selected, the relative dose for the event will be the dose prior to this one.

6.3.2. Laboratory data

Missing laboratory results (including immunological data) will not be replaced.

Haematology/chemistry laboratory data requiring grading as indicated in the table below may have more decimals than expected or may require conversion to the unit associated to the grade leading to more decimals than expected (eg. Calcium results may be 7.91).

In order to determine the grading, the following rule will be used:

1. In case a conversion is needed, the original results will be used for the conversion without a previous rounding.
2. The result expressed in the expected unit will be rounded to the number of decimals used for the grading (eg. 1 decimal will be used for Calcium and therefore 7.91 will be rounded to 7.9 and grade as 2).
3. For grading defined from normal range such as liver function, the original results will be divided by ULN before applying rounding to the number of decimals used for the grading.

Table 7 Grading scales for hematology and biochemistry safety laboratory assessments

Laboratory test	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially life-threatening (Grade 4)
Creatinine – µmol/L	≥40.7 – 48.1	>48.1 – 66.6	>66.6 – <129.5	≥129.5
Liver function tests – ALT, AST	≥1.25 – <2.5 x ULN	2.5 – <5.0 x ULN	5.0 – <10.0 x ULN	≥10.0 x ULN
Hemoglobin (female) – g/dL	9.5 – <10.2	8.5 – <9.5	6.5 – <8.5	<6.5
Hemoglobin (male) – g/dL	9.5 – <10.1	8.5 – <9.5	6.5 – <8.5	<6.5
WBC decrease (female) – cell/mm^3	2000 – <6480	1500 – <2000	1000 – <1500	<1000
WBC decrease (male) – cell/mm^3	2000 – <5980	1500 – <2000	1000 – <1500	<1000
Platelets decreased (female) – cell/mm^3	100 000 – <214 000	50 000 – <100 000	25 000 – <50 000	<25 000
Platelets decrease (male) – cell/mm^3	100 000 – <206 000	50 000 – <100 000	25 000 – <50 000	<25 000
Neutrophils decrease (female) – cell/mm^3	800 – <1270	600 – <800	400 – <600	<400
Neutrophils decrease (male) – cell/mm^3	800 – <1190	600 – <800	400 – <600	<400

ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; ULN = Upper limit of normal; WBC = White blood cell.

The grading scale has been adapted from the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events and adjusted considering local normal ranges provided by the site U.S. Department of Health and Human Services [DAIDS, 2017]. Parameters not included in the DAIDS grading scales will not be graded; their assessment will be based on laboratory normal ranges and medical judgment.

6.3.3. Study Day and Reference Dates with Partial dates

Partial dates will be displayed as captured in participant listing displays.

When partially completed dates (i.e., with missing day or month) are used in calculations, the following standard rules will be applied:

- A missing day will be replaced by 1.
- A missing day and month will be replaced by 01 January.

The following exceptions apply:

- Birth dates:
  - A missing day will be replaced by 15.
  - A missing month will be replaced by 30 June.
- AE start dates with missing day:
  - If the event starts in the same month as at least 1 of the study doses, the contents of AE.AESTRTPT (the flag indicating if the event occurred before or after study intervention administration) will be used to complete the date. If 'After Study Intervention' is selected or missing, the imputed start date will match the first (or only) study dose given during that month. If 'Before Study Intervention' is selected, the imputed date will be 1 day before the first (or only) study dose given during that month.
- AE start dates with missing day and month:
  - If the event starts in the same year as at least 1 of the study doses, the contents of AE.AESTRTPT (the flag indicating if the event occurred before or after vaccination) will be used to complete the date. If 'After Study Intervention' is selected, the imputed start date will match the first (or only) study dose given during that year. If 'Before Study Intervention' is selected, the imputed date will be 1 day before the first (or only) study dose given during that year.
- AE end dates with missing day:
  - If the event ends in the same month and year as the end of study date (if it exists) then the imputed end date will match the end of study date
  - Otherwise, day will be imputed to the last day of the month.
- AE end dates with missing day and missing month:
  - If the event ends in the same year as the end of study date (if it exists) then the imputed end date will match the end of study date
  - Otherwise, day and month will be imputed to the last day and month of the year, i.e., 31 December.

All other cases of incomplete AE or concomitant medication/vaccination start date will follow the standard rules above.

6.3.4. Daily recording of solicited events

This study is using paper diaries which have questions in the CRF indicating the presence or absence of solicited events, the following rules are applicable:

- Denominators for the summary of administration site (or systemic) solicited events will be calculated using the number of participants who respond “Yes” or “No” to the question concerning the occurrence of administration site (or systemic) events.
- When a specific solicited event is marked as having not occurred following a specific study dose (i.e. SDTM CE.CEOCCUR=N for the specified post-dose period for the event in question), all daily measurements will be imputed as Grade 0.
- When a specific solicited event is marked as having occurred following a specific study dose (i.e. SDTM CE.CEOCCUR=Y for the specified post-dose period for the event in question), any missing daily recordings will be given imputed values to allow them to contribute to the ‘Any’ rows but not to specific grade rows of the solicited event summary tables.
- When the occurrence of a specific solicited event is not present (i.e. SDTM CE.CEOCCUR is neither Y nor N for the specified post-dose period for the event in question) but the group of solicited events (administration site) is marked as having occurred (i.e. SDTM CE.CEOCCUR=Y), all missing daily recordings will be given imputed values to allow them to contribute to the ‘Any’ rows but not to specific grade rows of the solicited event summary tables.
- When the occurrence of fever is not present (i.e. SDTM CE.CEOCCUR is neither Y nor N for the specified post-dose period for the event in question), missing daily recordings will be given imputed values to allow them to contribute to the ‘Any’ rows and "Unknown” grade category.

The following table shows how participants contribute to each category for a specific solicited event over the Day X to Day Y post-dose period:

Solicited event category	Participants included in the calculation of the numerator
Any	All participants with at least one occurrence of the adverse event at grade 1, grade 2, or grade 3 between Day X and Day Y or with the adverse event marked as present and at least one missing daily recording between Day X and Day Y
At least grade 1	All participants with at least one occurrence of the adverse event at grade 1, grade 2, or grade 3 between Day X and Day Y
At least grade 2	All participants with at least one occurrence of the adverse event at grade 2 or grade 3 between Day X and Day Y
At least grade 3	All participants with at least one occurrence of the adverse event at grade 3 between Day X and Day Y

6.3.5. Unsolicited AEs

Unsolicited adverse event summaries are excluding solicited AE continuing beyond the solicited period and are including serious adverse events unless specified otherwise.

Missing severity, relationship with study vaccine, and outcome of unsolicited adverse events will not be replaced and will appear as ‘UNKNOWN’ when displayed in a statistical output.

6.3.6. Multiple measurements at One Analysis Time Point

For laboratory tests on a study day, if multiple assessments are taken from the same type of laboratory:

- Before the vaccination the last value will be used.
- Post vaccination last value will be used.

6.3.7. Data derivation

6.3.7.1. Age at first dose in months

When age at first dose is to be displayed in months, it will be calculated as the difference in days of Date of first dose and date of birth (DOB), divided by 30.4375.

6.3.7.2. Weight

Weight will be presented in kilograms. Weights reported in pounds will be converted as follows:

Weight in kilograms = Weight in pounds / 2.2

6.3.7.3. Height

Height will be presented in centimeters. Heights reported in feet and inches will be converted as follows:

Height in centimeters = Height in inches x 2.54

6.3.7.4. Temperature

Temperatures will be presented in degrees Celsius (°C). Temperatures reported in degrees Fahrenheit (°F) will be converted as follows:

Temperature (Celsius) = ((Temperature (Fahrenheit) - 32) x 5)/9

6.3.7.5. Numerical serology results

Numerical serology results will be derived from the content of IS.ISORRES in the SDTM dataset. For assays with a specific cut-off, the following derivation rules apply:

IS.ISORRES	Derived value
"NEG", "-", or "(-)"	cut-off/2
"POS", "+", or "(+)"	cut-off
"< value" and value is <= assay cut-off	cut-off/2
"< value" and value is > assay cut-off	value
"> value" and value is < assay cut-off	cut-off/2
"> value" and value is >= assay cut-off	value
"value" and value is < cut-off	cut-off/2
"value" and value is >= cut-off	value
All other cases	missing

6.3.7.6. Geometric mean titres (GMTs) and concentrations (GMCs)

Geometric Mean Titre (GMT) or Concentration (GMC) calculations are performed by taking the inverse logarithm of the mean of the log titre or concentration transformations.

Non quantifiable antibody titres or concentrations will be converted as described in Section 6.3.7.5 for the purpose of GMT/GMC calculation.

Cut-off values are defined by the laboratory before the analysis.

6.3.7.7. Onset day

The onset day for an event (e.g. AE, concomitant medication/vaccination) is the number of days between the last study dose and the start date of the event. This is 1 for an event occurring on the same day as a study dose (and reported as starting after study dose).

6.3.7.8. Duration of events

The duration of an event with a start and end date will be the number of days between the start and end dates plus one day, e.g., an event that starts on 03MAR2025 and ends on 12MAR2025 has a duration of 10 days.

6.3.7.9. Counting rules for combining solicited and unsolicited AEs

For output combining solicited and unsolicited adverse events, all serious unsolicited adverse events will be considered systemic events since the administration site flag is not included in the expedited adverse event CRF pages. Unsolicited adverse events with missing administration site flag will also be considered systemic.

Multiple events with the same preferred term which start on the same day are counted as only one occurrence.

6.3.7.10. Counting rules for occurrences of solicited AEs

When the occurrences of solicited AEs are summarized, each event recorded as having occurred during a specific period will be counted as only one occurrence regardless of the number of days on which it occurs.

Solicited administration site AEs will be summarized according to the following grading categories:

Event	Intensity Grade	Parameter
Pain at administration-site	0	None
	1	Mild: Minor reaction to touch
	2	Moderate: Cries/protests on touch
	3	Severe: Cries when limb is moved/spontaneously painful
Redness at administration-site		Greatest surface diameter in mm
Swelling at administration-site		Greatest surface diameter in mm
Temperature*		Temperature in °C (with 1 decimal)

*Fever is defined as temperature ≥38.0°C. The preferred location for measuring temperature will be the axilla for all participants.

The maximum intensity of local injection-site redness/swelling will be scored as follows:

Redness/Swelling			
Grade 0 **Absent**	**Grade 1** **Mild**	**Grade 2** **Moderate**	**Grade 3** **Severe**
<1 mm	≥1 – ≤25 mm	>25 – ≤50 mm	>50 mm

The maximum intensity of fever will be scored as follows:

Fever			
Grade 0 **Absent**	**Grade 1** **Mild**	**Grade 2** **Moderate**	**Grade 3** **Severe**
<38.0°C	38.0°C – <39.0°C	≥39.0°C – ≤40.0°C	>40.0°C

6.3.8. Display of decimals

6.3.8.1. Percentages

Percentages and their corresponding confidence limits will be displayed with one decimal except for 100% in which case no decimal will be displayed.

6.3.8.2. Differences in percentages

Differences in percentages and their corresponding confidence limits will be displayed with one more decimal than the maximum number used to display the individual percentages, for example the difference between two percentages displayed with one decimal will be displayed with two decimals.

6.3.8.3. Demographic/baseline characteristics statistics

The mean, median, and standard deviation for continuous baseline characteristics (age, pre-vaccination body temperature) will be presented with one decimal.

The minimum and maximum values and quartile values (if required) will be presented with the same number of decimals as the observed values.

The maximum and minimum of transformed body temperatures will be displayed with one decimal.

6.3.8.4. Serological summary statistics

The number of decimals used when displaying GMTs/GMCs and their CIs is assay specific based on the magnitude of the assay result post-dose and the clinically relevant assay threshold. The same number of decimals will be used for a given assay regardless of the timepoint presented.

GMTs/GMCs fold increase from pre-dose follows the same principle. Namely when the lowest clinically relevant threshold is 2-fold, 2 decimals are displayed while when the lowest clinically relevant threshold is 4-fold, 1 decimal is displayed.

GMT or GMC group ratios and CIs will be displayed with 2 decimals regardless of the actual values.

6.3.9. Trademarks

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Typhibev

7. REFERENCES

Brander RL, Pavlinac PB, Walson JL, et al. Determinants of linear growth faltering among children with moderate-to-severe diarrhea in the Global Enteric Multicenter Study. BMC Med. 2019;17(1):214.

Clopper CJ, Pearson E. The Use of Confidence or Fiducial Limits Illustrated in the case of the Binomial. *Biometrika.* 1934;26:404-13.

Cohen D, Green MS, Block C, et al. Serum antibodies to lipopolysaccharide and natural immunity to shigellosis in an Israeli military population. J Infect Dis. 1988;157:1068-71

U.S. Department of Health and Human Services. Division of AIDS (DAIDS) Table for grading the severity of adult and pediatric adverse events. Corrected Version 2.1; 2017. Updated 04 May 2018. Accessed 07 March 2024. https://rsc.niaid.nih.gov/clinical-research-sites/grading-severity-adult-pediatric-adverse-events-corrected-version-two-one.

World Health Organization (WHO). Length height for age. Updated December 2021b. Accessed 21 March 2024. https://www.who.int/tools/child-growth-standards/standards/length-height-for-age.