STATISTICAL ANALYSIS PLAN

216152 (H08_01TP)

A PHASE 1/2A, OBSERVER-BLIND, RANDOMIZED, CONTROLLED, TWO-STAGE, MULTI-COUNTRY STUDY TO EVALUATE THE SAFETY, REACTOGENICITY, AND IMMUNE RESPONSE OF THE TRIVALENT VACCINE AGAINST INVASIVE NONTYPHOIDAL SALMONELLA (iNTS) AND TYPHOID FEVER IN HEALTHY EUROPEAN AND AFRICAN ADULTS

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STATISTICAL ANALYSIS PLAN SIGNATURE PAGE - AUTHORS

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STATISTICAL ANALYSIS PLAN SIGNATURE PAGE - APPROVAL

Upon review of this document, the undersigned approves this version of the Statistical Analysis Plan, authorizing that the content is acceptable for the reporting of this study.

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MODIFICATION HISTORY

Listed below are modifications made to the SAP after the signed approval(s).

Unique Identifier for this Version	Date of the Document Version	Author	Significant Changes from Previous Authorized Version
1.0	20JUL2022	PPD	Not Applicable – First Version
2.0	07DEC2023	PPD	Minor editorial and formatting revisions throughout the document Table 1 in Section 3 was updated to include additional visit intervals Added a new analysis set – Entered Set in Section 5 Table describing analysis sets on which data will be summarized was updated in Section 5 Data derivation rules were clarified in Section 7.2.4 and Section 7.2.6 Text related to COVID-19 summary tables was deleted Immunogenicity variables related to tertiary endpoints were clarified in Section 15 Reverse Cumulative Distribution Function curve for all components were added in Section 15 Model for calculation of unadjusted ratio was clarified in Section 15 Document with table shells was updated

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1. INTRODUCTION

This document describes the rules and conventions to be used in the presentation and analysis of safety and immunogenicity data at interim and final analyses for Protocol 216152 (H08_01TP). It describes the data to be summarized and analyzed, including specifics of the statistical analyses to be performed. This statistical analysis plan (SAP) is based on Original Protocol dated 27 April 2022, Protocol Amendment 1 dated 15 August 2022, and Protocol Amendment 2 dated 08 June 2023. In scope of this analysis are all primary and secondary objectives and part of tertiary CCI. The iSRC/SRT analyses will be described in a separate document.

2. STUDY OBJECTIVES

2.1. PRIMARY OBJECTIVE

To evaluate the safety and reactogenicity profile of GSK Vaccines Institute for Global Health (GVGH) invasive nontyphoidal Salmonella-typhoid conjugate vaccine (iNTS-TCV) in healthy European/African adults.

2.2. SECONDARY OBJECTIVES

- To evaluate the long-term safety profile of GVGH iNTS-TCV vaccine in healthy European/African adults
- To evaluate the immunogenicity profile of GVGH iNTS-TCV vaccine in healthy European adults
- To evaluate the seroresponse with the GVGH iNTS-TCV vaccine after each study intervention administration in healthy European adults
- To evaluate the immunogenicity profile of GVGH iNTS-TCV vaccine in healthy African adults
- To evaluate the seroresponse with the GVGH iNTS-TCV vaccine after each study intervention administration in healthy African adults

2.3. TERTIARY OBJECTIVES

CCI [redacted]

3. STUDY DESIGN

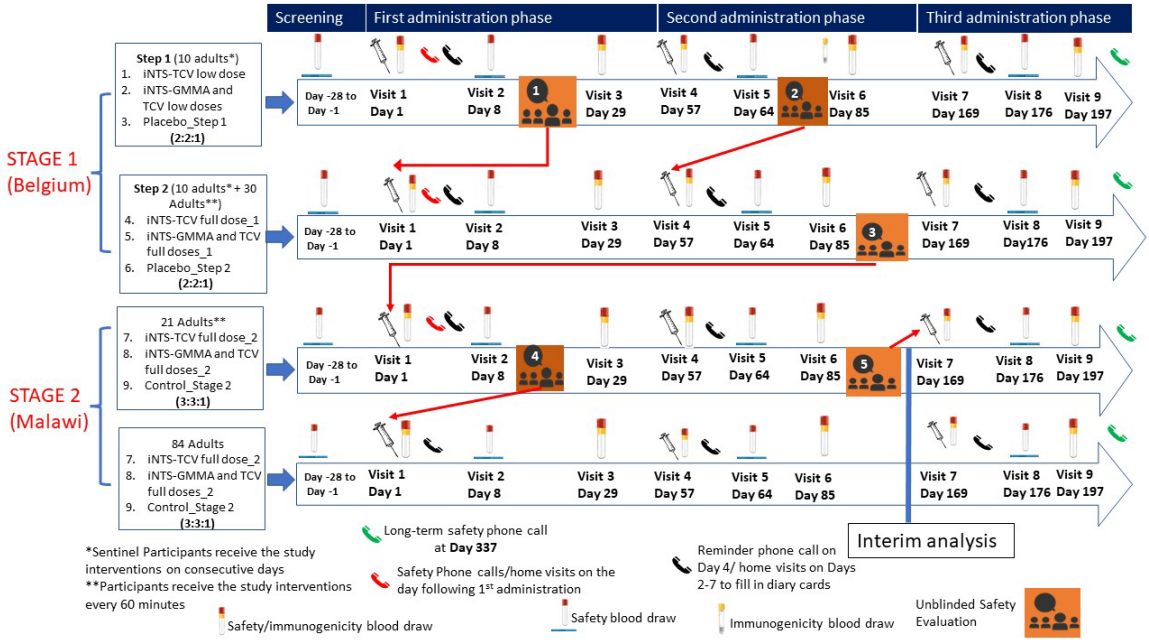
3.1. GENERAL DESCRIPTION

This is a Phase 1/2a, observer-blind, randomized, dose-escalation, controlled, multi-country, two-staged, and staggered study including 9 groups.

The study will be conducted overall (both Stage 1 and Stage 2) with approximately 155 healthy adult participants (18 to 50 years of age). The healthy European adults will be randomly assigned to 1 of the groups indicated for Stage 1. The healthy African adults will be randomly assigned to 1 of the groups indicated for Stage 2. Each group will receive 2 of the 11 study interventions at each administration, except for the Control group in Stage 2 which will receive 4 study interventions (a different active comparator at each administration time point together with saline).

Each participant will receive 1 randomly selected intramuscular study intervention per arm on Day 1, Day 57, and Day 169.

Figure 1 Study Schema



Stage 1

Stage 1 (Europe) will follow a 2-step staggered design, leading in with low doses of all the study interventions, in a dose-escalation manner. The sentinel approach will be followed for the first 10 participants each in Step 1 and Step 2, in which only 1 participant will be treated daily. This will be

done in order to ensure maximum safety of the participants.

In Step 1, 10 healthy European adults, randomized in a 2:2:1 ratio, will receive:

- The low dose of the candidate iNTS-TCV vaccine and concomitant saline to be administered in different arms (Study Group 1), or
- Separate administration of low doses of iNTS-GMMA and TCV vaccines in different arms (Study Group 2), or
- Placebo and saline in different arms (Study Group 3).

The 10 sentinel participants in Step 1 will receive the first study intervention on consecutive days and a telephonic safety follow-up call will be performed on the next day. If the participants have any complaints, they will be invited to the study site for an evaluation of the possible adverse events (AEs) and holding rules, prior to administration of study intervention in the next participant. If the Investigator becomes aware of a holding rule being met, he/she must suspend administration of the study intervention and inform the Sponsor's delegate immediately who will in-turn inform the Sponsor.

The internal Safety Review Committee (iSRC) will review all safety data collected up to 7 days after the first study intervention in Step 1. Step 2 will only commence if there is a favorable safety assessment during this review.

In Step 2, 40 healthy European adults will be randomized in a 2:2:1 ratio. A staggered approach will be followed for the first 10 sentinel participants and these participants will be followed up with a safety follow-up call on the next day of administration of study intervention. If the participants have any complaints, they will be invited to the study site for an evaluation of the AEs and holding rules, prior to administration of study intervention in the next participant. If the Investigator becomes aware of a holding rule being met, he/she must suspend administration of the study intervention and inform the Sponsor's delegate immediately who will in-turn inform the Sponsor. The remainder of the 30 participants will receive the study intervention in a sequential (at least 60 minutes apart) manner. The participants in Step 2 will receive:

- The full dose of the candidate iNTS-TCV vaccine and concomitant saline to be administered in different arms (Study Group 4), or
- Separate administration of full doses of iNTS-GMMA and TCV vaccines in different arms (Study Group 5), or

Placebo and saline in different arms (Study Group 6).

For the trial to proceed to Stage 2, a favorable evaluation of all available safety data by the iSRC following the first and second study intervention administrations (up to 28 days after second administration) in Step 2 of Stage 1 will be required. In case a No-Go decision is made, the study will be terminated at the end of Stage 1 and there will be no further administration of the study intervention in Step 2.

Stage 2

In Stage 2 (Africa), a total of 105 healthy African adults, randomized in a 3:3:1 ratio, will receive:

- The full dose of the candidate iNTS-TCV vaccine and concomitant saline to be administered in different arms (Study Group 7), or
- Separate administration of full doses of iNTS-GMMA and TCV vaccines in different arms (Study Group 8), or
- MenACWY (Menveo) and saline for the first administration, TdaP (Boostrix) and saline for the second administration and Typhoid Vi polysaccharide vaccine (Typhim Vi) and saline for the third administration in different arms (Study Group 9). This is the Control_Stage 2 Group.

The first 21 participants in Stage 2 will initially be recruited with administration proceeding sequentially, at least 60 minutes apart. All safety data from these participants up to 7 days after the first administration of the study intervention will be reviewed by the iSRC and the recruitment of the remaining 84 participants in Stage 2 will only commence if there is a positive evaluation by the iSRC. The study interventions will be administered in parallel in the remaining 84 participants.

All 155 participants (Stage 1 and Stage 2) will be closely observed for a minimum of 60 minutes after each study intervention administration, before leaving the facilities. The Investigator will decide if the participant should be observed for more than 60 minutes after each study intervention administered, if required.

An internal GSK Safety Review Team (SRT) and iSRC will also be involved in the safety oversight for this study. For all planned safety data reviews refer to Table 14 and 15 of the study protocol.

The trial will be conducted in 2 sites, each with a different Principal Investigator. A total of 155 participants are planned to be randomized to achieve at least 133 evaluable participants. Each participant will be part of this trial for approximately 13 months (from the Screening starting 28 days before first study intervention administration and until 6 months after third study intervention administration).

Table 2 Intervals Between Study Visits

Interval	Planned visit interval	Allowed interval range
Screening (Day −28) → Visit 1 (Day 1)	Up to 28 days*	Up to 28 days*
Visit 1 (Day 1) → Visit 2 (Day 8)	7 days	7-10 days
Visit 1 (Day 1) → Reminder Phone Call 1 (Day 4)	3 days	1-3 days
Visit 1 (Day 1) → Visit 3 (Day 29)	28 days	28-33[#] days**
Visit 1 (Day 1) → Visit 4 (Day 57)	56 days	52-62 days**
Visit 4 (Day 57) → Visit 5 (Day 64)	7 days	7-10 days
Visit 4 (Day 57) → Reminder Phone Call 2 (Day 60)	3 days	1-3 days
Visit 4 (Day 57) → Visit 6 (Day 85)	28 days	28-33[#] days**
Visit 4 (Day 57) → Visit 7 (Day 169)	112 days	110-126 days**
Visit 4 (Day 57) → Visit 7 (Day 169)	112 days	110-140[$] days**
Visit 7 (Day 169) → Visit 8 (Day 176)	7 days	7-10 days
Visit 7 (Day 169) → Reminder Phone Call 3 (Day 172)	3 days	1-3 days
Visit 7 (Day 169) → Visit 9 (Day 197)	28 days	28-33[#] days**
Visit 7 (Day 169) → Visit 10 (Day 337)	168 days	154-182 days

*Screening evaluations may be completed up to 28 days before Visit 1 (Day 1). Site staff should allow enough time between the Screening Visit and Visit 1 to receive and review hematology/biochemical results. If screening laboratory tests are performed within 3 days of vaccination, it would not be necessary to repeat them pre-vaccination for the first study intervention administration.

**Visits out of the allowed interval can lead to elimination from the Per Protocol Set for analysis of immunogenicity.

[$] Interval range will only be applicable for Stage 2 participants in Malawi.

[#]Under special circumstances, e.g., during coronavirus disease 2019 pandemic, the length of interval between visits for the collection of biological samples or for the vaccine administration may be extended to 38 days.

3.2. SCHEDULE OF EVENTS

Schedule of events can be found in Section 1.3, Table 1 of the protocol.

3.3. CHANGES TO ANALYSIS FROM PROTOCOL

Entered Set is defined in Section 5 to comprise of participants who provide informed consent for the

study.

4. PLANNED ANALYSES

4.1. INTERNAL SAFETY REVIEW COMMITTEE (iSRC)

This study will be overseen by an iSRC operating under a charter. Please refer to iSRC charter for details. An iSRC will be established to monitor the safety of participants throughout the trial and, more specifically, to recommend whether proceeding from low dose in Stage 1/Step 1 to the full dose in Stage 1/Step 2 is permissible, based on the accumulated safety data. They will also recommend proceeding the clinical testing of the vaccine in African participants in Stage 2 based on the post-primary safety results in Stage 1 (iSRC #3).

4.2. SAFETY REVIEW TEAM (SRT)

Instream blinded monitoring will also be performed by the internal GSK Safety Review Team (SRT). Refer the iSRC charter for details.

4.3. INTERIM ANALYSIS

A group-unblinded interim analysis will be performed for all immunogenicity data accumulated up to 28 days after second intervention (Day 85) administration in Stage 2. At this point, the statistical team at IQVIA will be unblinded for the analysis (i.e., will have access to individual participant treatment assignments). The remaining study personnel will stay blinded (i.e., will not have access to the individual participant treatment assignment) until Day 197. It is possible however, due to limited sample size, that indirect unblinding occurs for a few participants having as specific demographic characteristics or protocol deviations (e.g., participant with max height or weight, protocol deviations occurring only in a single group). Therefore, anyone having access to the analysis of Day 85 could become unblinded regarding those specific cases. The study will be considered as a single-blind from this point onwards. Results from immunogenicity analysis in Stage 2, and if applicable, in participants receiving the full dose in Stage 1/Step 2 will help with the design and approach in subsequent studies. No individual listings or data with the participants identifying information will be disseminated. The investigators and the participants will not have access to the treatment allocation up to study end (Day 337).

All analyses are descriptive and with the aim to characterize the safety and immunogenicity data and therefore no statistical adjustment for interim analysis is required.

Derivations and definitions for the interim analyses will be based on those required for the final analysis contained in this analysis plan, unless deviations are stated within the text.

Tables presenting summary statistics planned for final analysis to be generated at the time of interim analyses are listed in the document with table shells (see "Interim Analysis"). No unblinded individual participant listings or tables will be generated at the time of interim analyses.

Comparative analyses will be exploratory and should be interpreted with caution considering that there is no adjustment for multiplicity and that study is not powered for such comparisons.

4.4. FINAL ANALYSIS

All final, planned analyses identified in this SAP will be performed by IQVIA Biostatistics following sponsor authorization of this Statistical Analysis Plan, database lock, and unblinding of treatment.

After unblinding of the Sponsor personnel (partial observer-blind), an analysis on all data up to and including Day 197 (Visit 9) will be performed and individual listings will be generated.

A final CSR will be produced after the analysis after Visit 9 in Stage 2.

4.5. EXTENDED SAFETY FOLLOW-UP ANALYSIS

Data collected during the extended safety follow-up period will be analyzed after Day 337 and the analysis after Day 337 will be included in an integrated CSR to be written after.

5. ANALYSIS SETS

5.1. ENTERED SET

Participants who provided informed consent.

5.2. ENROLLED SET

Participants who provided informed consent and were randomized or received study intervention or underwent a post-screening procedure. The allocation in a group is based on the administered intervention.

Note: Participants who never passed screening even if rescreened (screening failures) and participants screened but never enrolled into the study (met eligibility but not needed for the study) are excluded from the Enrolled analysis set.

5.3. EXPOSED SET (ES)

All participants who received at least 1 dose of the study intervention. The allocation in a group is based on the administered intervention.

5.3.1. UNSOLICITED SAFETY SET

All participants who received at least 1 dose of the study intervention (ES) that report unsolicited adverse events (AEs)/report not having unsolicited AEs. The allocation in a group is based on the administered intervention.

Note: Participants will be considered to have reported no unsolicited AEs if they are in the study 28 days after vaccination without providing AEs.

5.3.2. SOLICITED SAFETY SET

All participants who received at least 1 dose of the study intervention (ES) who have solicited safety data for that intervention. The allocation in a group is based on the administered intervention.

5.4. FULL ANALYSIS SET (FAS)

All participants who received at least 1 dose of the study intervention and have post-dose immunogenicity data. The allocation in a group is based on the randomized intervention. The FAS for immunogenicity will be defined by time point.

The Full Analysis Set will be used as second-line analysis for secondary and tertiary endpoints if the percentage of vaccinated participants (in any study group at any time point) with serological results excluded from the Per-protocol Set for analysis of immunogenicity is 10% or more.

5.5. PER-PROTOCOL SET (PPS)

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, without prohibited concomitant medication/vaccination and without protocol deviation leading to exclusion. The PPS for immunogenicity will be defined by time point.

The protocol deviations leading to exclusion of the participants are described in Section 11.2. Three Per-protocol Sets for analysis of immunogenicity will be derived:

5.5.1. PER-PROTOCOL SET FOR ANALYSIS OF IMMUNOGENICITY AT DAY 29

The analysis set will contain all participants included in the Per-protocol Set, with no protocol deviations leading to exclusion until Day 29 and with at least 1 valid immunogenicity data available at Day 29.

5.5.2. PER-PROTOCOL SET FOR ANALYSIS OF IMMUNOGENICITY AT DAY 85

The analysis set will contain all participants included in the Per-protocol Set, with at least 1 immunogenicity data available at Day 85 without any protocol deviations that could lead to exclusion.

5.5.3. PER-PROTOCOL SET FOR ANALYSIS OF IMMUNOGENICITY AT DAY 197

The analysis set will contain all participants included in the Per-protocol Set with at least 1 immunogenicity data available at Day 197 without any protocol deviations that could lead to exclusion.

Analyses will be performed on specific sets as per the table below.

Analysis	**Entered Set**	**Enrolled Set**	**Exposed Set**	**Un-solicited Safety Set**	**Solicited Safety Set**	**Full Analysis Set****	**Per-protocol (PP) Set**		
							PP Set Day 29	**PP Set Day 85**	**PP Set Day 197**
Participant Disposition	✓								
Baseline Assessments		✓	✓				✓	✓	✓
Concomitant Medications			✓						
Exposure			✓						
Immunogenicity Analysis						✓	✓	✓	✓
Protocol Deviations			✓						
Solicited Adverse Events					✓				
Unsolicited Adverse Events				✓					
Solicited and Unsolicited Adverse Events			✓						
Other Safety (lab, vitals)			✓						

** Analysis in this set will be performed if the percentage of vaccinated participants with serological results excluded from the Per-protocol Set for analysis of immunogenicity is 10% or more

6. GENERAL CONSIDERATIONS

The safety summaries, data listings and figures as well as the statistical analysis of the variables will be the responsibility of the study biostatistician at IQVIA.

6.1. SUMMARY STATISTICS

For qualitative variables, the population size (N for sample size and n for available data) and the percentage (of available data) for each class of the variable will be presented. Quantitative variables will be summarized using descriptive statistics, including N (with data available), mean, standard deviation (SD), median, Q1, Q3, minimum, and/or maximum values. Geometric mean will be included for immunogenicity parameters together with 95% confidence interval (CI), where applicable.

The exact two-sided 95% CIs for a proportion within a group will be calculated using the Clopper-Pearson exact method. The geometric mean antibody concentrations (GMCs) and titers (GMTs) calculations will be performed by taking the anti-log of the mean of the log10 titer transformations. Confidence interval for geometric means will be derived by raising 10 to the confidence interval associated with mean of log10 values i.e., CI of geometric mean = 10^(CI for the mean of log10 values). All participants with valid data will be considered. Participants whose antibody titers are below the cut-off of the assay will be given an arbitrary value of half the cut-off for the purpose of GMC/GMT calculation.

6.2. TREATMENT SUMMARIZATION

In general, data will be presented for each treatment group:

Country/Stage	Treatment
Europe/Stage 1	iNTS-TCV Low
	iNTS-GMMA + TCV Low
	Placebo
	iNTS-TCV Full
	iNTS-GMMA + TCV Full
Africa/Stage 2	iNTS-TCV Full
	iNTS-GMMA + TCV Full
	Control

Data for All Stage 1, All Stage 2 and All Study Participants combined will also be presented when appropriate.

6.3. PRECISION

Safety data (vital signs, laboratory parameters) and immunogenicity data will be reported to the same precision as the source data.

For the reporting of descriptive statistics, the mean, median, Q1, Q3, standard deviation, standard error and confidence intervals will be presented to one digit more precision than the source data. The minimum and maximum will be presented to the same precision as the source data. P-values, if any, shall be reported to four decimal places or as <0.0001.

Geometric mean concentrations (GMC)/titers (GMT), geometric mean ratios (GMR) and their confidence limits will always be shown with 2 decimal places.

6.4. REFERENCE START DATE AND STUDY DAY

Study Day will be calculated from the reference start date and will be used to show start/stop day of assessments and events.

Reference start date is defined as the day of the first dose of study vaccination, (Day 1 is the day of the first dose of study treatment) and will appear in every listing where an assessment date or event date appears.

- If the date of the event is on or after the reference date, then:

Study Day = (date of event – reference date) + 1.

- If the date of the event is prior to the reference date, then:

Study Day = (date of event – reference date).

In the situation where the event date is partial or missing, Study Day, and any corresponding durations will appear partial or missing in the listings. Refer to Section 7.1.1 for rules applicable on partially completed dates when used in calculations.

6.4.1. 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 CRF using the contents of the flag indicating if the event occurred before

or after vaccination. If 'after vaccination' is selected or if the selection is missing , the relative dose for the event will be the one administered on the start day of the event. If 'before vaccination' is selected, the relative dose for the event will be the dose prior to this one. Where applicable, the event will be classified as "pre-treatment".

6.5. BASELINE

Baseline is defined as the last scheduled measurement taken prior to vaccination and will correspond to:

- Day 1 pre-dose for seroresponse calculation (4-fold for Anti-serotype specific IgG and ≥CCI [redacted] ≥CCI [redacted] for Anti-S. Typhi Vi Ag IgG antibody concentrations and GMR)
- Each vaccination pre-dose for immunogenicity within-participant GMR assessments, hematology, biochemistry and vital signs.

If a participant is missing the planned individual vaccination pre-dose result, change from baseline will not be calculated for within-participant GMR, hematology and biochemistry.

6.6. COMMON CALCULATIONS

For quantitative safety measurements (e.g., vital signs, laboratory parameters), change from baseline will be calculated as:

- Observed Value (after baseline) – Baseline Value (exceptions might apply as per protocol grading scale table, e.g., creatinine in Stage 2).

For immunogenicity measurements, change from baseline will be calculated as:

- Test Value (after baseline)/Baseline Value.

6.7. SOFTWARE VERSIONS

All derivations, statistical analyses, summaries, graphs and listings will be generated using SAS version 9.4 or higher (SAS Institute, Inc., Cary, North Carolina).

7. STATISTICAL CONSIDERATIONS

7.1. MISSING DATA

Missing immunogenicity data will be handled as described in Section 15. Following imputation will be

used for statistical calculations (and not for participant listings):

7.1.1. DATES

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 15
- A missing day and month will be replaced by June 30th

The following exceptions apply:

- Adverse event start dates with missing day:
  - If the event starts in the same month as at least one 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 vaccination' is selected or if the selection is missing, the imputed start date will match the first (or only) study dose given during that month. If 'before vaccination' is selected, the imputed date will be one day before the first (or only) study dose given during that month.
- Adverse event start dates with missing day and month:
  - If the event starts in the same year as at least one 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 vaccination' is selected, the imputed start date will match the first (or only) study dose given during that year. If 'before vaccination' is selected, the imputed date will be one day before the first (or only) study dose given during that year.

All other cases of incomplete AE or concomitant medication/vaccination start date will follow the standard rules as outlined in Section 6.4.

7.1.2. LABORATORY DATA

Missing laboratory results will not be replaced.

7.1.3. ADVERSE EVENTS

Solicited Adverse Events:

Daily recording of solicited adverse events: for diary cards indicating the presence or absence of solicited adverse events, for studies 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 adverse 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) adverse events.

- When a specific solicited adverse event is marked as having not occurred following a specific vaccination (i.e., SDTM FA.FAOCCUR=N for the specified post-vaccination period for the adverse event in question), all daily measurements will be presented as missing.

- When a specific solicited adverse event is marked as having occurred following a specific vaccination (i.e. SDTM FA.FAOCCUR=Y for the specified post-vaccination period for the adverse 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 adverse event summary tables.

- When the occurrence of a specific solicited adverse event is not present (i.e. SDTM FA.FAOCCUR is neither Y nor N for the specified post-vaccination period for the symptom in question) but the group of solicited adverse events (administration site or systemic) is marked as having occurred (i.e. SDTM FA.FAOCCUR=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 adverse event summary tables.

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

Solicited adverse 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
Grade 1	All participants with at least one occurrence of the adverse event at grade 1, between Day X and Day Y
Grade 2	All participants with at least one occurrence of the adverse event at grade 2 between Day X and Day Y
Grade 3	All participants with at least one occurrence of the adverse event at grade 3 between Day X and Day Y

Unsolicited adverse events

Unsolicited adverse event summaries 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' in all statistical listings.

7.2. DATA DERIVATION

7.2.1. BODY MASS INDEX

BMI (kg/m^2) = weight (kg)/height (m^2)

7.2.2. AGE AT VACCINATION IN YEARS

When age at vaccination is to be displayed in years, it will be calculated as the number of complete calendar years between the date of birth and the date of vaccination, divided by 365.25. For example:

DOB = 10SEP1983, Date of vaccination = 09SEP2018 -> Age = 34.998 years

DOB = 10SEP1983, Date of vaccination = 10SEP2018 -> Age = 35.001 years

7.2.3. ONSET DAY

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

7.2.4. 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, i.e., an event that starts on 03MAR2018 and ends on 12MAR2018 has a duration of 10 days.

The duration of solicited events will be calculated as the difference between the dates when the first and last symptom reported at grade 1 or higher were observed plus one day (also including days after Day 7 if event is still ongoing).

7.2.5. COUNTING RULES FOR COMBINING SOLICITED AND UNSOLICITED ADVERSE EVENTS

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

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

7.2.6. COUNTING RULES FOR OCCURRENCES OF SOLICITED ADVERSE EVENTS

When the occurrences of solicited adverse events 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.

For a given participant and the analysis of solicited symptoms within 7 days post-vaccination, missing or non-evaluable measurements will not be replaced. Therefore, the analysis of the solicited adverse events will include only vaccinated participants for doses with documented safety data (i.e., diary card completed). A diary card is considered complete when it has data recorded for all 7 days post vaccination. More specifically the following rules will be used:

- Participants who documented the absence of a solicited symptom after one dose will be considered not having that symptom after that dose.
- Participants who documented the presence of a solicited symptom and fully or partially recorded daily measurement over the solicited period will be included in the summaries at that dose and classified according to their maximum observed daily recording over the solicited period.
- Participants who documented the presence of a solicited symptom after one dose without having recorded any daily measurement will be assigned the value 'UNKNOWN'.
- Doses without diary cards returned will be excluded.

The following table describes the rules in detail to be followed in various possible scenarios:

Solicited Symptom	**Occurred?**	**Daily Measurement Record (D1-D7) Missing?**	**Grade of non-missing values**	**Maximum Grade for Summary Tables**	**Contribute to 'Any' row in Summary Tables**
All administration site/systemic AEs	No (as per CRF)	Fully Missing	NA	NA	No
All administration site/ systemic AEs (except Temperature)	Yes (as per CRF)	Fully Missing	NA	UNKNOWN	Yes
	Yes (as per CRF)	Partially Missing	All 0s	UNKNOWN	Yes

Solicited Symptom	Occurred?	Daily Measurement Record (D1-D7) Missing?	Grade of non-missing values	Maximum Grade for Summary Tables	Contribute to 'Any' row in Summary Tables
	Yes (as per CRF)	Partially Missing	At least one grade ≠ 0	Maximum grade of non-missing values	Yes
Temperature	Missing (computed variable if value >=38.0°C)	Fully Missing	NA	UNKNOWN	Yes
	Missing (computed variable if value >=38.0°C)	Partially Missing	All values <38.0°C	UNKNOWN	Yes
	Yes (computed variable if value >=38.0°C)	Partially Missing	At least one value ≥38.0°C	Maximum grade of non-missing values	Yes

7.2.7. GEOMETRIC MEAN CONCENTRATIONS (GMCS)/TITERS (GMTS)

Geometric Mean Concentration (GMC)/Titer (GMT) calculations are performed by taking the inverse logarithm of the mean of the log10 titer transformations. Antibody titers below the cut-off of the assay will be given an arbitrary value of half the cut-off of the assay for the purpose of GMT calculation. The cut-off value will be defined by the laboratory before the analysis.

8. OUTPUT PRESENTATIONS

The templates provided with this SAP describe the presentations for this study and therefore the format and content of the summary tables, figures and listings to be provided by IQVIA Biostatistics.

Some minor modifications may be necessary to the planned design of tables, figures, and listings to accommodate data collected during the actual study conduct.

9. DISPOSITION AND WITHDRAWALS

All participants who provide informed consent will be accounted for in this study. Participant disposition will be tabulated for each stage, each study treatment, and for all participants combined per stage and overall (using the Entered Set) with the number of participants who did not meet eligibility criteria, randomly assigned to treatment, completed Day X (for each scheduled visit), completed the study, prematurely discontinued, and the reason for early discontinuation. A listing will

present dates of completion or early withdrawal and the reason for early discontinuation, if applicable, for each participant.

Listings of treatment discontinuation, participant visits, inclusion/exclusion criteria responses, study protocol deviations, treatment randomization and study treatment administration will be provided.

10. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Individual participant demographics and baseline characteristics (medical history and results from viral serology, HLA-B27 screening result and urine pregnancy tests) will be presented in listings.

Demographic characteristics such as age at first vaccination, sex, race (ethnic background), height, weight, and body mass index (BMI) will be summarized and tabulated for each treatment, each stage and for all participants overall. Descriptive statistics (mean, median and standard deviation) will be presented for age, height, weight, and BMI. Frequency counts and percentages will be presented for sex, race, and step.

No statistical testing will be carried out for demographic or other baseline characteristics.

11. PROTOCOL DEVIATIONS

11.1. DEVIATIONS RELATED TO STUDY CONDUCT

A deviation from a protocol occurs when Investigator site staff or a study participant does not adhere to the Protocol's stipulated requirements, whether inadvertently or planned. Protocol deviations will be listed and will include a classification of minor or major, as determined by study team.

Important protocol deviations will be reviewed by the study team to identify deviations which have the potential to affect the immunogenicity results.

11.2. DEVIATIONS RELATED TO IMMUNOGENICITY ANALYSIS

Changes to the procedures or events, which may impact the quality of the immunogenicity data, will be considered important protocol deviations and will be described within the clinical study report. These changes or events will include any circumstances that will alter the evaluation of the immunogenicity results. Examples include, but may not be limited to, sample processing errors that lead to inaccurate immunogenicity results, and/or inaccurate dosing.

Participants may be eliminated from the per-protocol set for analysis of immunogenicity if, during the study, they incur a condition that has the capability of altering their immune response or are confirmed to have an alteration of their initial immune status. Participants may also be eliminated

from the per-protocol set as described in Section 7.2 and Section 9.3 of the protocol. Such scenarios will be discussed by the study team and decision to exclude a participant and/or data from the Per-protocol analysis set (Day 29, Day 85 and Day 197) will be taken on a case-by-case basis.

Other deviations (not a comprehensive list) leading to elimination from the per-protocol set are:

- invalid informed consent
- fraudulent data
- randomization code broken
- dose volume insufficient
- vaccination not according to protocol
- vaccine dose storage conditions (temperature deviation)
- vaccine administered out of expiry date
- violation of inclusion/exclusion criteria
- interval between doses
- interval between post vaccination blood sampling and previous dose
- two doses not in the same treatment group
- concomitant infection related to study vaccine or not related to study vaccine that may alter the immune response
- serology result at post vaccination dose 2 not available for all assays (blood sample not available or result not available)

Protocol Deviation Management Plan (PDMP) describes the complete list of elimination codes that could lead to exclusion from the per-protocol set.

12. MEDICAL HISTORY

Medical History coded using MedDRA Version 26.0 or higher will be listed for the exposed set.

13. MEDICATIONS

Medication usage coded using the WHO Drug Dictionary Version GlobalC3Mar22 or higher will be listed for the exposed set.

'Prior' medications are medications which started and stopped prior to the first dose of study treatment.

'Concomitant' medications are medications which were taken during the treatment period, or

specifically:

- started after the first dose of study treatment or
- started prior to the first dose of study medication and were continued after the first dose of study treatment

The percentage of participants using concomitant medications (any medication, any antipyretic and any antipyretic taken prophylactically, respectively) during the 28-day follow-up period will be summarized by group after each vaccination and overall.

14. STUDY MEDICATION EXPOSURE

Exposure to study treatment as the number of doses administered will be presented for each treatment, each stage and all participants overall.

15. IMMUNOGENICITY ANALYSIS

The immunogenicity analysis will be based on the Per-protocol Set for analysis of immunogenicity. If, in any study group at any time point, the percentage of vaccinated participants with serological results excluded from the Per-protocol Set for analysis of immunogenicity is 10% or more, a second-line analysis based on the Full Analysis Set will be performed.

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

The following derivation rules will apply in the context of LLOQ values:

- If baseline value is below LLOQ
  - 4-fold is defined as 4 times the LLOQ cut-off value
  - GMR is defined as within-participant GMR against LLOQ/2
- If baseline value is above or equal to LLOQ
  - 4-fold is defined as 4 times the baseline value
  - within-participant GMR is defined as within-participant GMR against the baseline value.

The following immunogenicity variables will be assessed:

Assay Type	Sampling Time Points	Component	Method	Unit of Measure	Number of Participants
Humoral Immunity (Antibody determination)	Stage 1: Days 1, 29, 57, 85, 169 and 197	Anti-S. Typhi Vi Ag total IgG	ELISA	EU/mL[#]	50 (Stage 1) 105 (Stage 2)
		Anti-S. Typhimurium O Ag total IgG		EU/mL	
	Stage 2: Days 1, 29, 57, 85, 169 and 197	Anti-S. Enteritidis O Ag total IgG		EU/mL	
	CCI [redacted]				

CCI [redacted]

The IgG against Vi antigen will be determined using GVGH ELISA and the results will be presented in EU/mL unit, which may be further converted to µg/mL, based on correlation with concentration of the standard calibrated against the international standard/another standard already calibrated.

A listing of collection dates and times for the immunogenicity variables will be presented for participants within each treatment group. For each component, the concentration/titer will be listed and summarized by treatment groups across all scheduled timepoints during entire study for each stage. Antibody concentrations/titers for all components will be investigated using Reverse Cumulative Distribution Curves based on the Per-protocol analysis set.

For each study group, each stage, at each timepoint that blood samples are collected for humoral immune response and for each component as measure by ELISA and CCI [redacted]

- Geometric mean concentrations/titers and their 95% CI will be calculated.
- Within-participant geometric mean ratio (geometric mean at 28 days after each study intervention to each study intervention administration baseline, ie, Day 29 versus Day 1, Day 85 versus Day 57 and Day 197 versus Day 169 and to Day 1 baseline) with their 95% CI will be tabulated.
- Percentage of participants with >=4 fold-increase from Day 1 baseline with their exact 95% CI will be calculated.
- Unadjusted between-group ratio of GMC with 95% CI between iNTS-TCV groups and iNTS-GMMA and TCV groups will be computed for each anti-serotype specific IgG[1]*, visit, and administration. The unadjusted ratios for each visit will be calculated using results from the corresponding visit as the dependent variable and the treatment group as independent variable. No other covariates will be included in the model.

For each study group, each stage, at each timepoint for S. Typhi Vi component as measured by ELISA:

- The number and percentage of participants with Anti-S. Typhi Vi Ag IgG antibody concentrations ≥CCI [redacted] and their 95% exact CI will be calculated.
- The number and percentage of participants with Anti-S. Typhi Vi Ag IgG antibody

[1] * Anti- Salmonella Typhi (S. Typhi) Vi antigen (Ag) total IgG, Anti Salmonella Typhimurium (S. Typhimurium) O Ag total IgG, Anti Salmonella Enteritidis (S. Enteritidis) O Ag total IgG will be tested.

concentrations ≥CCI [redacted] and their 95% exact CI will be calculated.

The above tabulations may be performed by LLOQ status at baseline (above or equal to cut-off versus below the cut-off) for all 3 components, data permitting.

Only for S. Typhi Vi component the above tabulations may be performed by Anti-S. Typhi Vi Ag IgG antibody concentrations status at baseline as measured by ELISA (>=CCI [redacted] and <CCI [redacted], >=CCI [redacted] and <CCI [redacted]), data permitting.

Linear mixed model with repeated measures (MMRM) will be used to perform pairwise comparison between full doses of iNTS-TCV and iNTS-GMMA + TCV at Day 29, Day 57, Day 85, Day 169 and Day 197. The model will use fixed effects for center, treatment, time point, treatment*time point, center*treatment, baseline immunogenicity value as covariate, and a repeated time point effect within a participant under an unstructured covariance matrix. Variance between the groups will not be considered equal unless the assumption leads to convergence issues. Additional covariance structures and suitable transformation (e.g., log) may be explored to attain convergence and meet model assumptions, respectively. This analysis will be performed for full doses of iNTS-TCV and iNTS-GMMA + TCV from both the stages.

```
proc mixed data=indsn;    by parameter;
   class subjid center trta avisit;
   model aval=center trta avisit trta*avisit center*trta baseline/ddfm=satterth;
   repeated avisit/subject=subjid type=un group=trta;
   lsmeans trta*avisitn/pdiff cl alpha=0.05;
 run;
```

In this analysis, immunogenicity data from full dose group in Europe will be pooled with those from full dose group in Africa if p-value associated to parameter for center*treatment interaction from MMRM model ≥0.10 (i.e., suggesting that impact of treatment on immunogenicity endpoint does not depend on center). In that case, GMC, GMRs, and ratio of GMC will be calculated for entire full dose group (i.e., Europe + Africa) adjusted by center from the above MMRM model without the center*treatment interaction term.

In case center*treatment interaction term is significant (i.e., p-value<0.1) the following analyses will be performed: 1) main analysis including center*treatment interaction term and GMC ratio separately for Europe and Africa will be produced from model with center*treatment interaction term, 2) sensitivity analysis excluding center*treatment interaction and GMC ratio for pooled Europe and Africa will be produced from model without center*treatment interaction term.

The following Table summarizes the statistical analyses:

Starting Model	P-value for Center*Treatment Interaction	Main Analysis Model	Sensitivity Analysis
center, treatment, center*treatment time point, treatment*time point, baseline immunogenicity value as covariate	≥0.1 drop center*treatment from the model	Starting model without center*treatment term	No sensitivity analysis
	<0.1	Same as the starting model. Output GMC ratio from model with interaction, separately from Europe and Africa	Starting model without center*treatment term

In other words, analysis pooling Europe and Africa data adjusting treatment effect for center variable will be performed in all cases, however in case center*treatment interaction parameter is statistically significant at 0.1 level, it will be considered as sensitivity analysis.

A sensitivity analysis may also be performed pooling Europe and Africa and adjusting treatment effect for race variable if there is evidence of different races at the two centers.

CCI [redacted]

16. SAFETY OUTCOMES

There will be no statistical comparisons between the treatment groups for safety data, unless otherwise specified with the relevant section.

16.1. ADVERSE EVENTS

The analysis of solicited adverse event will be performed in the Solicited Safety Set. The percentage of participants with at least 1 administration site AE (solicited and unsolicited), with at least 1 systemic AE (solicited and unsolicited) and with any AE during the 7-day or the 28-day follow-up period, for each stage, will be tabulated with exact 95% CI after each vaccination and overall. The same calculations will be performed for symptoms rated as grade 3 (severe). This combined analysis of solicited and unsolicited AEs will be performed on the Exposed Set as requested for public disclosure. Solicited

events and unsolicited AEs will be coded by MedDRA.

The percentage of doses followed by at least 1 administration site AE and by at least 1 systemic AE will be tabulated, overall vaccination course, with exact 95% CI. The same computations will be done for Grade 3 AEs, any unsolicited AEs considered related to vaccination, any Grade 3 unsolicited AEs considered related to vaccination and any AEs resulting in a medically attended visit.

The percentage of participants/doses reporting each individual solicited administration site and systemic AE during the 7-day follow-up period will be tabulated with exact 95% CI as follows:

- Over the 3 doses, the percentage of participants with the symptom and its exact 95% CI.
- Over the 3 doses, the percentage of doses with the symptom and its exact 95% CI.
- At each study dose (visit), the percentage of participants with the symptom and its exact 95% CI.

Occurrence of fever within 7 days post vaccination will be reported per grade, per 0.5°C cumulative increments classes as from ≥38°C as well as the occurrence of fever >40°C/104°F.

Solicited events ongoing after the observation period reported by maximum intensity will be left out of summary tables and only reported in solicited AE listings. Any solicited event with onset day greater than solicited period (i.e., 7 days) will be reported as unsolicited AE and will be included in unsolicited summary tables and listings.

The analysis of unsolicited adverse event will be performed in the Unsolicited Safety Set. The verbatim reports of unsolicited symptoms will be reviewed by a physician and the signs and symptoms will be coded per the Medical Dictionary for Regulatory Activities (MedDRA), Version 26.0 or higher. Every verbatim term will be matched with the appropriate preferred term (PT). The percentage of participants with unsolicited AEs within 28 days after any doses with its exact 95% CI will be tabulated by group, stage and by MedDRA preferred term. Similar tabulation will be done for Grade 3 unsolicited AEs, for unsolicited AEs that resulted in a medically attended visit, for Grade 3 and causally related unsolicited AEs and for unsolicited AEs causally related to vaccination. These tabulations will include System Organ Class (SOC) and SOC/PT analyses.

The number of participants who experienced at least 1 SAE within 28 days after any dose, from dose 1 until 28 days post last dose (Day 197) and from Day 198 until Day 337 will be reported by treatment.

16.1.1. ADVERSE EVENTS LEADING TO DISCONTINUATION FROM STUDY OR FROM TREATMENT

Adverse events leading to permanent discontinuation from study and leading to discontinuation of study vaccine but continued further study procedures (safety or immunogenicity) will be identified by using the variable pertaining to outcome the Adverse Events page of the (e)CRF, and listed, separately. AEs leading to discontinuation from treatment will be listed.

16.1.2. SERIOUS ADVERSE EVENTS

Serious adverse events (SAEs) are those events recorded as "Serious" on the Adverse Events page of the (e)CRF, and will be listed.

16.1.3. DERIVATION

Adverse Event	Intensity grade	Parameter
Redness/swelling at administration site (greatest surface diameter in mm)	0	<20 mm.
	1 (Mild)	≥20 to ≤50 mm.
	2 (Moderate)	>50 to ≤100 mm.
	3 (Severe)	>100 mm.
Temperature[a]	0	<38.0°C.
	1 (Mild)	≥38.0°C to <39°C.
	2 (Moderate)	≥39.0°C to ≤40.0°C.
	3 (Severe)	>40.0°C.

[a]Fever is defined as temperature ≥38.0°C/100.4°F

16.2. SAFETY LABORATORY EVALUATIONS

Laboratory results will be included in the reporting of this study for Hematology and Biochemistry. A list of laboratory assessments to be included in the outputs is included in Table 9 of the protocol.

For each group and for each haematology and biochemistry parameter:

- The percentage of participants having hematology and biochemistry results below/within/ above the local laboratory ranges versus baseline will be tabulated by treatment, timepoint and stage.
- The percentage of participants with hematology and biochemistry results by grade versus baseline will be tabulated by treatment, timepoint and stage.

16.2.1. GRADING FOR LABORATORY DATA

Grades will be based on local laboratory ranges and derived from Food and Drug Administration [FDA] Guidance to Industry "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials" in Stage 1 and from the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events in Stage 2 (refer to Table 19 and Table 20 in protocol). Laboratory parameters not included in the grading scale will not be graded.

16.3. VITAL SIGNS

The following Vital Signs measurements will be reported for this study:

- Resting systolic and diastolic blood Pressure (mmHg)
- Resting heart rate (bpm)
- Respiratory rate (breaths per minute)
- Temperature (°C)

Observed vital signs data will be summarized by treatment and time point.

16.4. COVID-19

Data collected on the COVID-19 infection assessment page from the eCRF will be presented in listings.

17. DATA NOT SUMMARIZED OR PRESENTED

The other variables not summarized or presented are:

- Comments

These variables will not be summarized or presented, but will be available in the clinical study database, SDTM and/or ADaM datasets.

18. REFERENCES

Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of binomial. Biometrika. 1934;26:404-413