Protocol Amendment 2

Study ID: 216152

Official Title of Study: 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

NCT number: NCT05480800

Date of Document: 09-Jun-2023

TITLE PAGE

Protocol Title: 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

Protocol Number: 216152 (INTS-GMMA GVGH-002) (H08_01TP)

Amendment Number: 2

Product: GVGH iNTS-TCV Investigational Vaccine

Short Title: A study to evaluate safety, reactogenicity, and immune response of GVGH iNTS-TCV vaccine against invasive nontyphoidal Salmonella and Typhoid Fever

Study Phase: 1/2a (2 stages)

Sponsor Name: GlaxoSmithKline Biologicals SA

Legal Registered Address: Rue de l'Institut 89, Rixensart, 1330 Belgium

Site Details: Centre for Evaluation of Vaccination (CEV), University of Antwerp, Belgium
Principal Investigator: Kanchanamala Withanage

Malawi-Liverpool-Wellcome Trust Clinical Research Programme, Malawi
Principal Investigator: Melita Gordon

Regulatory Agency Identifier Number: 2021-005178-25

Date of Protocol: Final, 27 April 2022

Date of Protocol Amendment: Amendment 1 Final, 15 August 2022

Amendment 2 Final, 08 June 2023

Sponsor Signatory:

I have read this protocol in its entirety and agree to conduct the study accordingly:

Ashwani Kumar Arora **Head of Clinical Development and Regulatory Affairs**	**Date**

Refer to the Study Reference Manual for Medical Monitor's name and contact information.

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY

Document	Date	Substantial	Region
Amendment 2	08 June 2023	Yes	Global
Amendment 1	15 August 2022	Yes	Global
Original Protocol	27 April 2022	-	-

Amendment 2

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

The Protocol Amendment 1 has been amended to include requirements from Malawi site, and to update Stage 2 grading scale for hematology and biochemistry safety laboratory assessment, according to local ranges provided by the site.

Section # and Name	Description of Change	Brief Rationale
Throughout	Minor editorial and document formatting revisions	Minor, therefore, have not been summarized
Section 1.1 Synopsis, Section 3 Objective and Endpoints, Section 8.1.2 Laboratory Assays, Table 13 Tertiary Endpoints-Statistical Analyses	CCI [redacted]	
Table 1 Schedule of Assessments	Added that out-of-window vaccinations are not allowed	To provide clarity and avoid potential protocol deviations
Table 2 Interval between Visits	The intervals between a few visits were updated.	To provide flexibility and avoid protocol deviations arising due to out of window visits
Table 5 Study Holding Rules	Some of the events were reworded	To provide clarity
Section 7.3 Participant Discontinuation/Withdrawal from the Study Section 8.1.1 Biological Samples	Clarification added on taking immunogenicity sample and safety follow-up for participant discontinued due to AE	To avoid protocol deviations arising from taking immunogenicity samples from discontinued participants observed in Stage 1 due to lack of clarity in the current protocol.
Section 8.1.2 Laboratory assay	Clarified that Prothrombin time will not be done in Stage 2	Prothrombin time cannot be performed in the Malawi site.

Section # and Name	Description of Change	Brief Rationale
Section 8.2.1.1 Collection of Demographic Data, Medical/Vaccination History, and Physical Examination	Justification for collection of race (ethnic background) data was added	Collection of race (ethnic background) data is necessary to assess and monitor the diversity of the trial participants and the impact of race (ethnic background) on the trial endpoints
Section 9.7 Internal Safety Review Committee	Update in timing for iSRC #5 review	Updated to ensure data review #5 occurs before start of the 3rd doses administration in Stage 2 and to avoid protocol deviations (ie, having subjects receiving 3rd doses in Stage 2 outside the allowed time interval). All safety data collected 28 days after 2nd administrations of remaining 84 participants in Stage 2 will still be evaluated as described in Table 14 (blinded instream monitoring).
Appendix 2 Regulatory, Ethical, and Study Oversight Considerations	Clarification on Data protection, Data quality assurance, and Source documents	Additional requirement for GDPR compliance in accordance with the latest GSK protocol template
Appendix 7 Grading scales for hematology and biochemistry safety laboratory assessments	Updated Stage 2 grading scale	Updated to reflect ranges adjusted between DAIDS and local Malawi laboratory ranges.
Appendix 8 Protocol Amendment History	The summary of changes related to previous amendment (Amendment 1) moved to Appendix 8	In compliance with the template used for writing this protocol

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1.0 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: 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

Short Title: A study to evaluate safety, reactogenicity, and immune response of GVGH iNTS-TCV vaccine against invasive nontyphoidal Salmonella and Typhoid Fever

Rationale:

GlaxoSmithKline Biologicals SA (GSK) Vaccines Institute for Global Health (GVGH), with the support of Combating Antibiotic Resistant Bacteria-X (CARB-X), is developing a new candidate trivalent vaccine (GVGH iNTS-typhoid conjugate vaccine [TCV]) against *Salmonella* Typhimurium (*S.* Typhimurium), *Salmonella* Enteritidis (*S.* Enteritidis), and *Salmonella* Typhi. GVGH iNTS-TCV is based on the previously developed GVGH monovalent TCV and bivalent *S.* Typhimurium and *S.* Enteritidis vaccine, using the generalized modules for membrane antigens (GMMA) -platform technology. The newly developed vaccine, GVGH iNTS-TCV vaccine, is new but its components are not new as the iNTS vaccine is already in development by GVGH while TCV is registered by Indian vaccine manufacturer Biological E in India and World Health Organization prequalified.

This candidate vaccine targets diseases of major importance for African populations. Until now, there is no vaccine for iNTS or TCV widely used in Africa. However, safety/effectiveness studies are ongoing in Africa to support TCV introduction, which is backed by the Global Alliance for Vaccines and Immunization.

The estimated death toll from these diseases combined was 90 000 deaths in sub-Saharan Africa in 2019.

The purpose of the current trial is to evaluate the safety, reactogenicity, and the immunogenicity of the primary response induced by this vaccine. The current clinical trial will evaluate the GVGH iNTS-TCV candidate vaccine for the first time in humans in European adults (Stage 1). Following Stage 1, the same vaccine will be evaluated in African adults as part of Stage 2 of the trial.

Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the safety and reactogenicity profile of GSK Vaccines Institute for Global Health (GVGH) invasive nontyphoidal Salmonella-typhoid conjugate vaccine (iNTS-TCV) vaccine in healthy European/African adults	• Number of participants in Europe/Stage 1 with solicited administration site and systemic events during 7 days after each study intervention administration (ie, on the day of study intervention administration and the 6 subsequent days) occurring at Day 1, Day 57, and Day 169, by study intervention group • Number of participants in Europe/Stage 1 with unsolicited adverse events (AEs) during 28 days after each study intervention administration (ie, on the day of study intervention administration and the 27 subsequent days) occurring at Day 1, Day 57, and Day 169, by study intervention group • Number of participants in Europe/Stage 1 with serious adverse events (SAEs) from first study intervention administration (Day 1) to 28 days after third study intervention administration (Day 197), by study intervention group • Number of participants in Europe/Stage 1 with AEs/SAEs leading to withdrawal from the study and/or withholding doses of study intervention, from first study intervention administration up to 28 days after third study intervention administration (Day 1 to Day 197), by study intervention group • Number of participants in Europe/Stage 1 with deviations from normal or baseline values for hematological, renal, and hepatic panels test results at 7 days after each study intervention administration (Day 8, Day 64, and Day 176) and at 28 days after each study intervention administration (Day 29, Day 85, and Day 197), by study intervention group • Number of participants in Africa/Stage 2 with solicited administration site and systemic events during 7 days after each study intervention administration (ie, on the day of study intervention administration and the 6 subsequent days) occurring at Day 1, Day 57, and Day 169, by study intervention group • Number of participants in Africa/Stage 2 with unsolicited AEs during 28 days after each study intervention administration (ie, on the day of study intervention administration and the 27 subsequent days) occurring at Day 1, Day 57, and Day 169, by study intervention group • Number of participants in Africa/Stage 2 with SAEs from first study intervention administration (Day 1) to 28 days after third study intervention administration (Day 197), by study intervention group • Number of participants in Africa/Stage 2 with AEs/SAEs leading to withdrawal from the study and/or withholding doses of study intervention, from first study intervention administration up to 28 days after third study intervention administration (Day 1 to Day 197), by study intervention group • Number of participants in Africa/Stage 2 with deviations from normal or baseline values for hematological, renal, and hepatic

Objectives	Endpoints
	panel test results at 7 days after each study intervention administration (Day 8, Day 64, and Day 176) and at 28 days after each study intervention administration (Day 29, Day 85, and Day 197), by study intervention group
Secondary	
• To evaluate the long-term safety profile of GVGH iNTS-TCV vaccine in healthy European/African adults	• Number of participants with any SAE from 28 days after third study intervention administration (Day 197) up to Day 337, per study intervention group in Stage 1/Stage 2. • Number of participants with AEs/SAEs leading to withdrawal from the study, from 28 days after third study intervention administration (Day 197) up to Day 337, by study intervention group in Stage 1/Stage 2.
• To evaluate the immunogenicity profile of GVGH iNTS-TCV vaccine in healthy European adults	• Anti-serotype specific immunoglobulin (Ig) G* geometric mean concentrations (GMCs), in participants in Europe/Stage 1, as determined by enzyme-linked immunosorbent assay (ELISA), before each study intervention administration (Day 1, Day 57, and Day 169) and 28 days after each study intervention administration (Day 29, Day 85 and Day 197), for each study intervention group and between groups ratios • Anti-serotype specific IgG* within-participant geometric mean ratios (GMRs), in participants in Europe/Stage 1, as determined by ELISA at 28 days after each study intervention administration compared to each study intervention administration baseline (Day 29 versus Day 1, Day 85 versus Day 57 and Day 197 versus Day 169) * 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.
• To evaluate seroresponse with the GVGH iNTS-TCV vaccine after each study intervention administration in healthy European adults	• Number of participants in Europe/Stage 1 achieving, for each Ag, at least a 4-fold** rise in Anti-serotype specific IgG* antibody concentration 28 days after each study intervention administration (Day 29, Day 85, and Day 197) compared to first study intervention administration baseline (Day 1), as measured by ELISA, by study intervention group • Number of participants in Europe/Stage 1 with Anti-*S*. Typhi Vi Ag IgG antibody concentrations equivalent to ≥4.3 µg/mL***, before each study intervention administration (Day 1, Day 57, and Day 169) and 28 days after each study intervention administration (Day 29, Day 85, and Day 197), as measured by ELISA, by study intervention group * Anti-*S*. Typhi Vi Ag total IgG, Anti-*S*. Typhimurium O Ag total IgG, Anti-*S*. Enteritidis O Ag total IgG will be tested ** 4-fold is considered clinically meaningful measure of seroconversion in the absence of an established correlate of protection. *** 4.3 µg/mL threshold is clinically meaningful as accepted by World Health Organization (WHO) as immunological protection threshold for Vi containing typhoid vaccines and has been used in previous studies for registration of these vaccines

Objectives	Endpoints
• To evaluate the immunogenicity profile of GVGH iNTS-TCV vaccine in healthy African adults	• Anti-serotype specific IgG* GMC, in participants in Africa/Stage 2, as determined by ELISA, before each study intervention administration (Day 1, Day 57, and Day 169) and 28 days after each study intervention administration (Day 29, Day 85, and Day 197), for each study intervention group and between-groups ratios • Anti-serotype specific IgG* within-participant GMRs, in participants in Africa/Stage 2, as determined by ELISA at 28 days after each study intervention administration compared to each study intervention administration baseline (Day 29 versus Day 1, Day 85 versus Day 57, and Day 197 versus Day 169) * Anti-*S.* Typhi Vi Ag total IgG, Anti-*S.* Typhimurium O Ag total IgG, Anti-*S.* Enteritidis O Ag total IgG will be tested.
• To evaluate seroresponse with the GVGH iNTS-TCV vaccine after each study intervention administration in healthy African adults	• Number of participants in Africa/Stage 2 achieving, for each Ag, at least a 4-fold** rise in Anti-serotype specific IgG* antibody concentration 28 days after each study intervention administration (Day 29, Day 85, and Day 197) compared to first study intervention administration baseline (Day 1), as measured by ELISA, by study intervention group • Number of participants in Africa/Stage 2 with Anti-*S.* Typhi Vi Ag IgG* antibody concentrations equivalent to ≥4.3 µg/mL***, before each study intervention administration (Day 1, Day 57, and Day 169) and 28 days after each study intervention administration (Day 29, Day 85, and Day 197), as measured by ELISA, by study intervention group * Anti-*S.* Typhi Vi Ag total IgG, Anti-*S.* Typhimurium O Ag total IgG, Anti-*S.* Enteritidis O Ag total IgG will be tested ** 4-fold is considered clinically meaningful measure of seroconversion in the absence of an established correlate of protection. *** 4.3 µg/mL threshold is clinically meaningful as accepted by WHO as immunological protection threshold for Vi containing typhoid vaccines and has been used in previous studies for registration of these vaccines
Tertiary	
CCI [redacted]	

Objectives	Endpoints
CCI	[redacted]

Overall Design:

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_Stage 2 group 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.

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 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, or
- Separate administration of low doses of iNTS-GMMA and TCV vaccines in different arms, or
- Placebo and saline in different arms.

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, or
- Separate administration of full doses of iNTS-GMMA and TCV vaccines in different arms, or
- Placebo and saline in different arms.

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, or
- Separate administration of full doses of iNTS-GMMA and TCV vaccines in different arms, 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. 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. 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 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. 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.

Number of Investigators and Study Centers:

The trial will be conducted in 2 sites, each with a different Principal Investigator.

Number of Participants:

A total of 155 participants are planned to be randomized to achieve at least 133 evaluable participants.

Treatment Groups and Duration:

The treatment groups in Stage 1 are:

- iNTS-TCV low dose: the low dose of the candidate iNTS-TCV vaccine and concomitant saline to be administered in different arms,
- iNTS-GMMA and TCV low doses: separate administration of low doses of iNTS-GMMA and TCV vaccines in different arms,
- Placebo: placebo and saline in different arms,
- iNTS-TCV full dose: the full dose of the candidate iNTS-TCV vaccine and concomitant saline to be administered in different arms,
- iNTS-GMMA and TCV full doses: separate administration of full doses of iNTS-GMMA and TCV vaccines in different arms.

The treatment groups in Stage 2 are:

- iNTS-TCV full dose: the full dose of the candidate iNTS-TCV vaccine and concomitant saline to be administered in different arms,
- iNTS-GMMA and TCV full doses: separate administration of full doses of iNTS-GMMA and TCV vaccines in different arms,
- Control: MenACWY (Menveo) and saline for the first administration, TdaP (Boostrix) and saline for the second administration and Typhim Vi and saline for the third administration in different arms.

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).

Statistical Methods:

A total of 155 participants are planned to be randomized to achieve at least 133 evaluable participants. The following analysis sets are being included in the study:

- Enrolled Set: Participants who were randomized or received study intervention or underwent a post-screening procedure. The allocation in a group is based on the administered intervention.
- 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.
- 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.
- Per Protocol Set (PPS): All eligible participants who received all doses as per protocol, have 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 PPS for immunogenicity will be defined by time point.

- Unsolicited Safety Set: All participants who received at least 1 dose of the study intervention (ES) that report unsolicited AEs/report not having unsolicited AEs. The allocation in a group is based on the administered intervention.
- Solicited Safety Set: All participants who received at least 1 dose of the study intervention (ES) who have solicited safety data. The allocation in a group is based on the administered intervention.

The analysis on primary objective will be based on the Solicited, Unsolicited, and Exposed Sets. The analysis on secondary and tertiary objectives will be based on the PPS for immunogenicity. If, in any study group and at any time point, the percentage of vaccinated participants with serological results excluded from the PPS for analysis of immunogenicity is 10% or more, a second-line analysis based on the FAS for immunogenicity will be performed to complement the PPS analysis.

A group-unblinded interim analysis for immunogenicity will be performed 28 days after the second administration in all study participants in Stage 2 to support the preparation for future studies. The final analysis will be performed after all data from Stage 1 and Stage 2 are available. All analyses before unblinding the study team will be conducted on data as clean as possible.

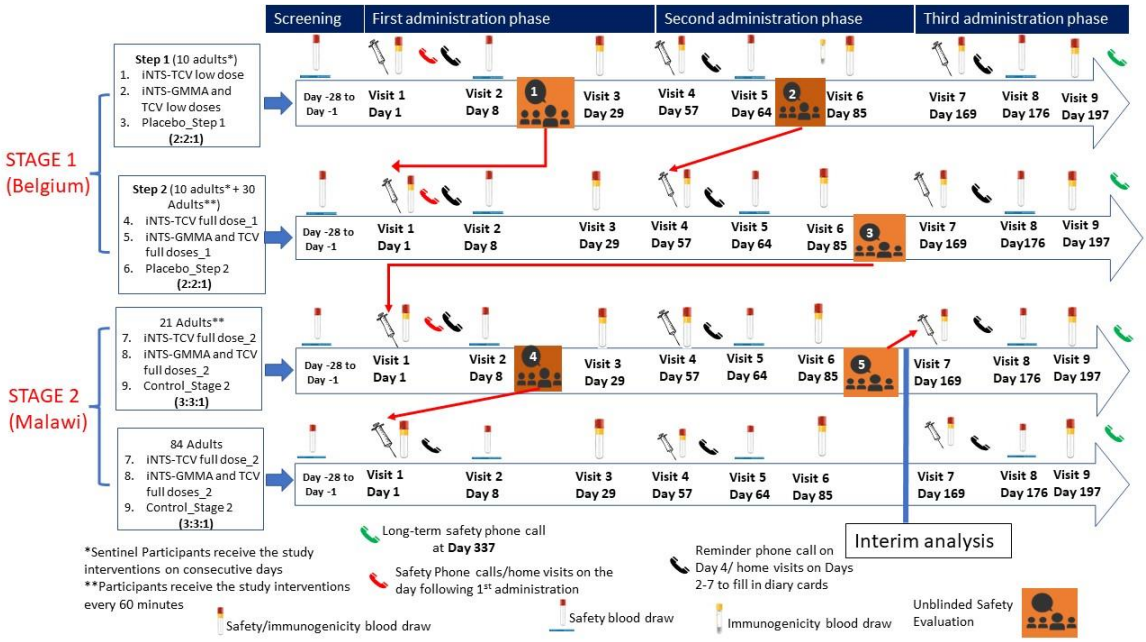
Data Monitoring Committee: Yes

An internal GSK SRT and an iSRC will be involved in the trial.

The SRT is a GSK Central Committee responsible for ongoing assessment of the benefit/risk balance of the product. In addition, a separate iSRC will be established to monitor safety and to specifically recommend continuation of subsequent steps of the study based on the safety results. The iSRC, which will be comprised of study-independent GSK members and an external expert in clinical development, will review unblinded data at predefined time points during the study. Ad hoc safety evaluations by the iSRC may be called at any time if there are any suspected safety concerns.

1.2 Schema

Figure 1 Study Schema



1.3 Schedule of Activities

Table 1 Schedule of Activities

Epoch	**Screening**	**First study intervention administration**						**Second study intervention administration**					**Third study intervention administration**					
Type of contact	**Screening Visit**	**Visit 1 (First adm, A1)**	**Sentinel Safety phone contact**	**Reminder phone contact[1]**	**Home visit[2]**	**Visit 2**	**Visit 3**	**Visit 4 (Second adm, A2)[3]**	**Reminder phone contact[1]**	**Home visit[2]**	**Visit 5**	**Visit 6**	**Visit 7 (Third adm, A3)[3]**	**Reminder phone contact[1]**	**Home visit[2]**	**Visit 8**	**Visit 9**	**Visit 10 (Safety phone contact)**
Time points	**Day -28 to Day −1**	**Day 1**	**Day 2**	**Day 4**	**Day 2 to Day 7**	**Day 8**	**Day 29**	**Day 57**	**Day 60**	**Day 58 to Day 63**	**Day 64**	**Day 85**	**Day 169**	**Day 172**	**Day 170 to Day 175**	**Day 176**	**Day 197**	**Day 337**
Sampling time points		**Pre-A1**				**Post-A1**	**Post-A1**	**Pre-A2**			**Post-A2**	**Post-A2**	**Pre-A3**	**Post-A3**		**Post-A3**	**Post-A3**	**Post-A3**
Informed consent	●																	
Check inclusion/exclusion criteria	●	●						●					●					
Collect demographic data	●																	
Medical and vaccination history	●																	
Physical examination	●	●						●					●					
Symptom directed physical examination						○	○				○	○				○	○	
Vital sign assessment	●	●				●		●			●		●			●		
Body temperature* before study intervention administration		●						●					●					

Epoch	**Screening**	**First study intervention administration**						**Second study intervention administration**					**Third study intervention administration**					
Type of contact	**Screening Visit**	**Visit 1 (First adm, A1)**	**Sentinel Safety phone contact**	**Reminder phone contact[1]**	**Home visit[2]**	**Visit 2**	**Visit 3**	**Visit 4 (Second adm, A2)[3]**	**Reminder phone contact[1]**	**Home visit[2]**	**Visit 5**	**Visit 6**	**Visit 7 (Third adm, A3)[3]**	**Reminder phone contact[1]**	**Home visit[2]**	**Visit 8**	**Visit 9**	**Visit 10 (Safety phone contact)**
Time points	**Day -28 to Day −1**	**Day 1**	**Day 2**	**Day 4**	**Day 2 to Day 7**	**Day 8**	**Day 29**	**Day 57**	**Day 60**	**Day 58 to Day 63**	**Day 64**	**Day 85**	**Day 169**	**Day 172**	**Day 170 to Day 175**	**Day 176**	**Day 197**	**Day 337**
Sampling time points		**Pre-A1**				**Post-A1**	**Post-A1**	**Pre-A2**			**Post-A2**	**Post-A2**	**Pre-A3**	**Post-A3**		**Post-A3**	**Post-A3**	**Post-A3**
Height** and weight measurements	●	○				○	○	○			○	○	○			○	○	
Check contraindications and warnings, and precautions to study intervention administration	○	○						○					○					
Study group allocation		●																
Check criteria for temporary delay for enrollment and study intervention administration	○	○						○					○					
Urine pregnancy test	●	●						●					●					
Study intervention administration[$]		●						●					●					

Epoch	**Screening**	**First study intervention administration**						**Second study intervention administration**					**Third study intervention administration**					
Type of contact	**Screening Visit**	**Visit 1 (First adm, A1)**	**Sentinel Safety phone contact**	**Reminder phone contact[1]**	**Home visit[2]**	**Visit 2**	**Visit 3**	**Visit 4 (Second adm, A2)[3]**	**Reminder phone contact[1]**	**Home visit[2]**	**Visit 5**	**Visit 6**	**Visit 7 (Third adm, A3)[3]**	**Reminder phone contact[1]**	**Home visit[2]**	**Visit 8**	**Visit 9**	**Visit 10 (Safety phone contact)**
Time points	**Day -28 to Day −1**	**Day 1**	**Day 2**	**Day 4**	**Day 2 to Day 7**	**Day 8**	**Day 29**	**Day 57**	**Day 60**	**Day 58 to Day 63**	**Day 64**	**Day 85**	**Day 169**	**Day 172**	**Day 170 to Day 175**	**Day 176**	**Day 197**	**Day 337**
Sampling time points		**Pre-A1**				**Post-A1**	**Post-A1**	**Pre-A2**			**Post-A2**	**Post-A2**	**Pre-A3**	**Post-A3**		**Post-A3**	**Post-A3**	**Post-A3**
Recording of administered study intervention number		○						○					○					
Distribution of participant pDiary		○[4]						○[4]					○[4]					
Safety phone call/Home visit to sentinel participants in Steps 1 and 2 of Stage 1 and in Stage 2, one day post-study intervention administration to check for any holding rule events or SAEs			●		●[7]													
Phone contact/Home visit for pDiary card completion reminder				●	●				●	●				●	●			
Return of pDiaries						○[5]					○[5]					○[5]		

Epoch	**Screening**	**First study intervention administration**						**Second study intervention administration**					**Third study intervention administration**					
Type of contact	**Screening Visit**	**Visit 1 (First adm, A1)**	**Sentinel Safety phone contact**	**Reminder phone contact[1]**	**Home visit[2]**	**Visit 2**	**Visit 3**	**Visit 4 (Second adm, A2)[3]**	**Reminder phone contact[1]**	**Home visit[2]**	**Visit 5**	**Visit 6**	**Visit 7 (Third adm, A3)[3]**	**Reminder phone contact[1]**	**Home visit[2]**	**Visit 8**	**Visit 9**	**Visit 10 (Safety phone contact)**
Time points	**Day -28 to Day −1**	**Day 1**	**Day 2**	**Day 4**	**Day 2 to Day 7**	**Day 8**	**Day 29**	**Day 57**	**Day 60**	**Day 58 to Day 63**	**Day 64**	**Day 85**	**Day 169**	**Day 172**	**Day 170 to Day 175**	**Day 176**	**Day 197**	**Day 337**
Sampling time points		**Pre-A1**				**Post-A1**	**Post-A1**	**Pre-A2**			**Post-A2**	**Post-A2**	**Pre-A3**	**Post-A3**		**Post-A3**	**Post-A3**	**Post-A3**
pDiaries transcription by Investigator or delegate						●					●					●		
	Laboratory Assessments																	
Blood sampling for safety screening (hematology panel, biochemistry, viral serologic analyses and HLA-B27 testing***) (up to 15 mL)	●																	
Blood sampling for safety laboratory assays (hematology panel and biochemistry analyses) (up to 10 mL)		●				●	●	●			●	●	●			●	●	
Urinalysis	●																	
Blood sampling for antibody determination (approximately 10 mL)[#]		●					●	●				●	●				●	

Epoch	**Screening**	**First study intervention administration**						**Second study intervention administration**					**Third study intervention administration**					
Type of contact	**Screening Visit**	**Visit 1 (First adm, A1)**	**Sentinel Safety phone contact**	**Reminder phone contact[1]**	**Home visit[2]**	**Visit 2**	**Visit 3**	**Visit 4 (Second adm, A2)[3]**	**Reminder phone contact[1]**	**Home visit[2]**	**Visit 5**	**Visit 6**	**Visit 7 (Third adm, A3)[3]**	**Reminder phone contact[1]**	**Home visit[2]**	**Visit 8**	**Visit 9**	**Visit 10 (Safety phone contact)**
Time points	**Day -28 to Day −1**	**Day 1**	**Day 2**	**Day 4**	**Day 2 to Day 7**	**Day 8**	**Day 29**	**Day 57**	**Day 60**	**Day 58 to Day 63**	**Day 64**	**Day 85**	**Day 169**	**Day 172**	**Day 170 to Day 175**	**Day 176**	**Day 197**	**Day 337**
Sampling time points		**Pre-A1**				**Post-A1**	**Post-A1**	**Pre-A2**			**Post-A2**	**Post-A2**	**Pre-A3**	**Post-A3**		**Post-A3**	**Post-A3**	**Post-A3**
PBMC extraction for monoclonal antibodies generation for Stage 2 participants only (approximately 50 mL)																	●	
Malaria Rapid Diagnostic Test[6]	○	○																
	Safety assessments																	
Record any concomitant medications/vaccinations	●	●				●	●	●			●	●	●			●	●	
Record any intercurrent medical conditions		●				●	●	●			●	●	●			●	●	
Recording of solicited AEs in pDiary (Days 1 to 7 post-administration)		○[4]			○[4]			○[4]		○[4]			○[4]		○[4]			
Transcription of solicited AEs in the eCRF by the Investigator or delegate		●				●		●			●		●			●		

Epoch	**Screening**	**First study intervention administration**						**Second study intervention administration**					**Third study intervention administration**					
Type of contact	**Screening Visit**	**Visit 1 (First adm, A1)**	**Sentinel Safety phone contact**	**Reminder phone contact[1]**	**Home visit[2]**	**Visit 2**	**Visit 3**	**Visit 4 (Second adm, A2)[3]**	**Reminder phone contact[1]**	**Home visit[2]**	**Visit 5**	**Visit 6**	**Visit 7 (Third adm, A3)[3]**	**Reminder phone contact[1]**	**Home visit[2]**	**Visit 8**	**Visit 9**	**Visit 10 (Safety phone contact)**
Time points	**Day -28 to Day −1**	**Day 1**	**Day 2**	**Day 4**	**Day 2 to Day 7**	**Day 8**	**Day 29**	**Day 57**	**Day 60**	**Day 58 to Day 63**	**Day 64**	**Day 85**	**Day 169**	**Day 172**	**Day 170 to Day 175**	**Day 176**	**Day 197**	**Day 337**
Sampling time points		**Pre-A1**				**Post-A1**	**Post-A1**	**Pre-A2**			**Post-A2**	**Post-A2**	**Pre-A3**	**Post-A3**		**Post-A3**	**Post-A3**	**Post-A3**
Recording of unsolicited AEs (Days 1 to 28 post-administration)		○				○		○			○		○			○		
Transcription of unsolicited AEs in the eCRF by the Investigator or delegate		●				●	●	●			●	●	●			●	●	
Safety surveillance including vital sign and body temperature measurements (60 minutes post-administration)		●						●					●					
Recording of SAEs		●				●	●	●			●	●	●			●	●	●
Recording of pregnancies		●				●	●	●			●	●	●			●	●	
Recording of AEs leading to withdrawal		●				●	●	●			●	●	●			●	●	●

Epoch	**Screening**	**First study intervention administration**						**Second study intervention administration**					**Third study intervention administration**					
Type of contact	**Screening Visit**	**Visit 1 (First adm, A1)**	**Sentinel Safety phone contact**	**Reminder phone contact[1]**	**Home visit[2]**	**Visit 2**	**Visit 3**	**Visit 4 (Second adm, A2)[3]**	**Reminder phone contact[1]**	**Home visit[2]**	**Visit 5**	**Visit 6**	**Visit 7 (Third adm, A3)[3]**	**Reminder phone contact[1]**	**Home visit[2]**	**Visit 8**	**Visit 9**	**Visit 10 (Safety phone contact)**
Time points	**Day -28 to Day −1**	**Day 1**	**Day 2**	**Day 4**	**Day 2 to Day 7**	**Day 8**	**Day 29**	**Day 57**	**Day 60**	**Day 58 to Day 63**	**Day 64**	**Day 85**	**Day 169**	**Day 172**	**Day 170 to Day 175**	**Day 176**	**Day 197**	**Day 337**
Sampling time points		**Pre-A1**				**Post-A1**	**Post-A1**	**Pre-A2**			**Post-A2**	**Post-A2**	**Pre-A3**	**Post-A3**		**Post-A3**	**Post-A3**	**Post-A3**
Recording of SAEs related to study participation, or to a concurrent GSK medication/vaccine	●	●				●	●	●			●	●	●			●	●	●
Study Conclusion																		●

Abbreviations: adm = administration; AE = Adverse event; eCRF = electronic case report form; GSK = GlaxoSmithKline Biologicals SA; Pre-A1 = pre-first study intervention administration; Post-A1 = post-first study intervention administration; Pre-A2 = pre-second study intervention administration; Post-A2 = post-second study intervention administration; Pre-A3 = pre-third study intervention administration; Post-A3 = post-third study intervention administration; pDiary = paper diary; PBMC = peripheral blood mononuclear cells; RDT = rapid diagnostic test; SAE = Serious adverse event.

Note: The double-line border following Day 169 indicates the analyses which will be performed on all data obtained up to Day 169.

● A study procedure that requires documentation in the individual eCRF.

○ A study procedure that does not require documentation in the individual eCRF.

* The preferred location for measuring temperature will be the axilla. Fever is defined as body temperature ≥38.0°C/100.4°F.

** Height will be measured only at Screening.

*** HLA-B27 testing will be done in Stage 1 only.

[#] An additional 20 mL for assay development will be taken in Stage 1 on Day 85 from the participants who have given specific consent.

[$] Out-of-window vaccination is not allowed.

[1] For literate participants in Europe/Africa only

[2] For illiterate participants in Africa only

[3] The pre 2nd and 3rd vaccination screening in Malawi could take more than a day, necessitating additional site visits but not more than 72 hours prior to the actual receipt of the vaccination.

[4] For illiterate participants, pDiary cards will be completed by the site field worker.

[5] For illiterate participants, pDiary cards can be returned by the field worker at the end of the 7 days after administration.

[6] For Malawi (Stage 2) only, subjects who test positive for malaria at Screening will be temporarily excluded (even if asymptomatic) and enrollment/first vaccination delayed until a negative malaria highly sensitive RDT is available. Treatment will also be provided for such prospective participants at the Investigator's discretion according to local guideline. For subsequent vaccinations, malaria RDT testing will only be performed if participants have symptoms suggestive of malaria.

[7] Home visit for safety follow-up will take place only on Day 2.

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, eg, 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.

2.0 INTRODUCTION

2.1 Study Rationale

GlaxoSmithKline Biologicals SA (GSK) Vaccines Institute for Global Health (GVGH), with the support of Combating Antibiotic Resistant Bacteria-X (CARB-X), is developing a new candidate trivalent nontyphoidal Salmonella-generalized modules for membrane antigens (GMMA) vaccine (GVGH invasive nontyphoidal Salmonella-typhoid conjugate vaccine [iNTS-TCV]) against *Salmonella* Typhimurium (*S.* Typhimurium), *Salmonella* Enteritidis (*S.* Enteritidis), and *Salmonella* Typhi (*S.* Typhi). GVGH iNTS-TCV is based

on the previously developed GVGH monovalent TCV and bivalent *S*. Typhimurium and *S*. Enteritidis vaccine, using the GMMA-platform technology. The newly developed vaccine, GVGH iNTS-TCV vaccine, is new but its components are not new as iNTS vaccine is already in development by GVGH while TCV is registered in India and World Health Organization (WHO) prequalified.

This candidate vaccine targets diseases of major importance for African populations. The death toll from these diseases combined was 90 000 deaths in sub-Saharan Africa (sSA) in 2019 [IHME, 2021]. Until now, there is no vaccine for iNTS or TCV widely used in Africa. However, safety/effectiveness studies are ongoing in Africa to support TCV introduction, which is backed by the Global Alliance for Vaccines and Immunization.

The purpose of the current trial is to evaluate the safety and the immunogenicity of the primary response induced by this vaccine both in European and African adults. The current clinical trial will evaluate the GVGH iNTS-TCV candidate vaccine for the first time in humans in European adults (Stage 1). Following Stage 1, the same vaccine will be evaluated in African adults as part of Stage 2 of the trial. The details of the study objectives and endpoints are mentioned in Table 3.

2.2 Background

Invasive nontyphoidal Salmonella disease is an important neglected and poverty-related disease [Balasubramanian, 2019; Feasey, 2012], primarily in resource-poor settings of sSA. In sSA, iNTS is one of the most common causes of bacteremia and reflects a major public health and socioeconomic burden. Infection with iNTS has been reported in sSA since the 1980s as a cause of child febrile illness and bacteremia, but often misdiagnosed as malaria [Feasey, 2012]. An estimated 59 100 iNTS deaths with more than half of them in children <5 years of age and a 14.5% case fatality rate have been reported in 2017 [Collaborators GBDN-TSID, 2019]. The iNTS disease causative agents are associated with increasing antimicrobial resistance (AMR) and are classified by the WHO as high priority pathogens for developing new antibiotics. The most common African *S*. Enterica serovars associated with iNTS disease are *S*. Enteritidis and *S*. Typhimurium, accounting for >90% of iNTS cases in sSA [Reddy, 2010].

Infants and young children aged 9 to 24 months and human immunodeficiency virus infected individuals of all ages are most affected [Balasubramanian, 2019]. The number of cases per year were estimated around 535 000 in 2017, of which >400 000 were in sSA [Collaborators GBDN-TSID, 2019]. The iNTS cases have been reported across Africa, demonstrating that disease and mortality is a widespread threat throughout the continent [Uche, 2017]. The population-based surveillance study Typhoid Surveillance in Africa Program revealed among all bacteremia an overall iNTS prevalence of 17% in 10 sSA countries and 13 different sentinel sites [Marks, 2017].

Fluoroquinolone-resistant Salmonella species are included in the WHO antibiotic-resistant high priority pathogens for Research and Development of new antibiotics. Specifically, African iNTS causative isolates show a concerning increase and high level of AMR with a high percentage of strains associated with multidrug resistance [Aldrich, 2019; Feasey, 2015; Kariuki, 2019; Puyvelde, 2019]. The only current intervention for iNTS disease is treatment by antibiotics. Resistance against the first-line antimicrobials ampicillin, chloramphenicol, and trimethoprim/sulfamethoxazole and multidrug resistance to all three agents among iNTS isolates is common in sSA. Furthermore, the emergence of iNTS strains resistant to fluoroquinolones, azithromycin, and third generation cephalosporins is posing a further challenge to clinical management of the disease in resource-limited settings where the few remaining effective antimicrobials are too expensive or unavailable.

There is no licensed human vaccine against iNTS and currently no preventive intervention.

GSK is developing a 2-component (ie, STmGMMA and SEnGMMA) GMMA-based candidate vaccine, invasive nontyphoidal Salmonella-generalized modules for membrane antigens (iNTS-GMMA), for the prevention of iNTS disease caused by *S*. Typhimurium and *S*. Enteritidis in infants from 6 weeks of age.

The GMMA-technology is a novel vaccine platform based on bacterial outer membranes used to deliver the O antigen (Ag) portion of lipopolysaccharide (LPS) of *S*. Typhimurium and *S*. Enteritidis as active moieties [Lanzilao, 2015].

The GMMA are outer membrane particles (also known as blebs or exosomes), which are spontaneously released from Gram-negative bacteria. The bacteria are genetically manipulated to increase blebbing and reduce endotoxicity mainly associated with lipid A portion of LPS molecules. GMMA consist of LPS, outer membrane proteins, outer membrane lipids (eg, phospholipids), and enclosed periplasmic proteins [Benedetto, 2017; Maggiore, 2016].

S. Enteritidis O Ag and *S*. Typhimurium O Ag are structurally similar, sharing the same trisaccharide repeating unit of the O Ag backbone (mannose – rhamnose – galactose), with the mannose bearing abequose in *S*. Typhimurium and tyvelose in *S*. Enteritidis. The GSK 2-component vaccine is composed of STmGMMA and SEnGMMA derived respectively from genetically modified *S*. Typhimurium and *S*. Enteritidis bacteria that each produce high-yield of outer membrane exosomes with a detoxified LPS.

The GMMA-production strains have been named NVGH2157 (*S*. Enteritidis) and NVGH2363 (*S*. Typhimurium). The GMMA (Drug Substances) produced from these strains are called SEnGMMA (also referred to as 2157-GMMA) and STmGMMA (also referred to as 2363-GMMA), respectively. CCI [redacted]

CCI [redacted]

The development of an iNTS vaccine combined with TCV is a straightforward approach to sustainability of a much-needed neglected iNTS vaccine. The iNTS-TCV would potentially prevent approximately 70 000 deaths per year in sSA and help limit the spread of AMR bacteria.

2.3 Benefit/Risk Assessment

2.3.1 Risk Assessment

During the current trial, there may be risks related to the blood sampling (eg, bruising and pain at the blood draw site).

The iNTS-TCV candidate vaccine is yet to be tested in humans.

Of the 3 iNTS-TCV vaccine components, the BioE-TCV has been licensed in India since January 2020 and WHO Prequalified in December 2020. It was well tolerated during clinical trials in 6-month-old to 64-year-old participants and has a safety profile similar to other injectable vaccines.

The GSK GMMA-technology has been applied to a candidate vaccine against Shigella Sonnei. The *S.* Sonnei candidate vaccine 1790GAHB has been tested in two Phase 1, an extension study, Phase 2a and Phase 2b clinical studies and was shown to be immunogenic and well tolerated in healthy European, African, and US adults [Launay, 2017; Launay, 2019; Obiero, 2017; Robert, 2021; Frenck, 2021].

The human data on BioE-TCV and iNTS-GMMA (trials with BioE-TCV and iNTS-GMMA are being conducted in parallel with the current trial), will de-risk the development of the iNTS-TCV candidate vaccine.

CCI [redacted]

Based on GSK's preclinical data produced with other antigens, co-formulation of GMMA and TCV is unlikely to adversely impact on the antibody response induced by each component.

As for any vaccine administered intramuscularly, local reactions such as injection site pain, injection site redness, and injection site swelling may occur within days after administration. Injection of saline does not usually cause side effects other than the ones known for any injection (eg, local pain, injection site reactions, muscle pain).

More detailed information about the known and expected benefits and risks and reasonably expected AEs related to iNTS-TCV may be found in the current Investigator's Brochure (IB).

Detailed information about the known and expected benefits and risks and expected AEs of Menveo, Boostrix, and Typhoid Vi polysaccharide vaccine (Typhim Vi) can be found in their respective Prescribing Information/Package Insert/ Summary of Product Characteristics (SmPC).

Coronavirus Disease 2019

During special circumstances (eg, coronavirus disease 2019 [COVID-19] pandemic), the specific guidance from local public health and other competent authorities regarding the protection of individuals' welfare must be applied.

2.3.2 Risk Mitigation Strategies

For the safety of the participants, the protocol has incorporated various risk mitigation measures, including sentinel approach (refer to Section 4.1), staggered administration of study intervention (refer to Section 4.1), study holding criteria (refer to Section 4.5), appropriate inclusion and exclusion criteria (refer to Section 5.1 and Section 5.2), checking contraindications to study intervention (refer to Section 7.2), and close monitoring of participants after administration of study intervention.

All study activities at the study center will be performed by trained clinical staff authorized by the study Investigator.

After the administration of study intervention, all participants will be observed for a minimum of 60 minutes, with medical attention available in case of anaphylaxis.

The blinded monitoring of study data will be performed by the Sponsor's designee/Contract Research Organization (IQVIA).

Additional safety monitoring will be performed by an internal GSK Safety Review Team (SRT) and an internal Safety Review Committee (iSRC).

The Sponsor will immediately notify the Principal Investigator if any additional safety or toxicology information becomes available during the study.

This study will be performed in compliance with the protocol, International Council for Harmonisation (ICH) Good Clinical Practice (GCP) and applicable regulatory requirements. Aspects of the study concerned with the investigational medicinal product(s) will meet the requirements of European Union – Good Manufacturing Practice.

2.3.3 Benefit Assessment

By receiving iNTS-TCV, the participants may be protected against iNTS and typhoid fever.

By receiving the comparator vaccines, the participants are expected to be protected against meningococcal disease (Menveo), tetanus, diphtheria, and pertussis (Boostrix), and typhoid (Typhim Vi).

All participants will undergo a physical medical examination at the first study visit; these evaluations, made by skilled and trained clinical staff, may potentially provide valuable knowledge about the participant's health. In case the study staff discovers any medical condition, the participant may be referred to the local healthcare system, in case any abnormalities/diseases are observed.

The participants will contribute to the process of developing therapies in an area of unmet need. They may also help provide valuable data, about the tolerability and immunogenicity of the investigational vaccine and about its potential ability to provide clinical protection against iNTS and typhoid fever.

2.3.4 Overall Benefit/Risk Conclusion

Considering the measures taken to minimize possible risks to the participants in this study, the potential risks associated with the study interventions and study assessments are balanced by the potential benefits that may be provided to the participants.

3.0 OBJECTIVES AND ENDPOINTS

Table 3 Study Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the safety and reactogenicity profile of GSK Vaccines Institute for Global Health (GVGH) invasive nontyphoidal Salmonella-typhoid conjugate vaccine (iNTS-TCV) vaccine in healthy European/African adults	• Number of participants in Europe/Stage 1 with solicited administration site and systemic events during 7 days after each study intervention administration (ie, on the day of study intervention administration and the 6 subsequent days) occurring at Day 1, Day 57, and Day 169, by study intervention group • Number of participants in Europe/Stage 1 with unsolicited adverse events (AEs) during 28 days after each study intervention administration (ie, on the day of study intervention administration and the 27 subsequent days) occurring at Day 1, Day 57, and Day 169, by study intervention group • Number of participants in Europe/Stage 1 with serious adverse events (SAEs) from first study intervention administration (Day 1) to 28 days after third study intervention administration (Day 197), by study intervention group • Number of participants in Europe/Stage 1 with AEs/SAEs leading to withdrawal from the study and/or withholding doses of study intervention, from first study intervention administration up to 28 days after third study intervention administration (Day 1 to Day 197), by study intervention group • Number of participants in Europe/Stage 1 with deviations from normal or baseline values for hematological, renal, and hepatic panels test results at 7 days after each study intervention administration (Day 8, Day 64, and Day 176) and at 28 days after each study intervention administration (Day 29, Day 85, and Day 197), by study intervention group • Number of participants in Africa/Stage 2 with solicited administration site and systemic events during 7 days after each study intervention administration (ie, on the day of study intervention administration and the 6 subsequent days) occurring at Day 1, Day 57, and Day 169, by study intervention group • Number of participants in Africa/Stage 2 with unsolicited AEs during 28 days after each study intervention administration (ie, on the day of study intervention administration and the 27 subsequent days) occurring at Day 1, Day 57, and Day 169, by study intervention group • Number of participants in Africa/Stage 2 with SAEs from first study intervention administration (Day 1) to 28 days after third study intervention administration (Day 197), by study intervention group • Number of participants in Africa/Stage 2 with AEs/SAEs leading to withdrawal from the study and/or withholding doses of study intervention, from first study intervention administration up to 28 days after third study intervention administration (Day 1 to Day 197), by study intervention group

Objectives	Endpoints
	• Number of participants in Africa/Stage 2 with deviations from normal or baseline values for hematological, renal, and hepatic panel test results at 7 days after each study intervention administration (Day 8, Day 64, and Day 176) and at 28 days after each study intervention administration (Day 29, Day 85, and Day 197), by study intervention group
Secondary	
• To evaluate the long-term safety profile of GVGH iNTS-TCV vaccine in healthy European/African adults	• Number of participants with any SAE from 28 days after third study intervention administration (Day 197) up to Day 337, per study intervention group in Stage 1/Stage 2. • Number of participants with AEs/SAEs leading to withdrawal from the study, from 28 days after third study intervention administration (Day 197) up to Day 337, by study intervention group in Stage 1/Stage 2.
• To evaluate the immunogenicity profile of GVGH iNTS-TCV vaccine in healthy European adults	• Anti-serotype specific immunoglobulin (Ig) G* geometric mean concentrations (GMCs), in participants in Europe/Stage 1, as determined by enzyme-linked immunosorbent assay (ELISA), before each study intervention administration (Day 1, Day 57, and Day 169) and 28 days after each study intervention administration (Day 29, Day 85 and Day 197), for each study intervention group and between groups ratios • Anti-serotype specific IgG* within-participant geometric mean ratios (GMRs), in participants in Europe/Stage 1, as determined by ELISA at 28 days after each study intervention administration compared to each study intervention administration baseline (Day 29 versus Day 1, Day 85 versus Day 57 and Day 197 versus Day 169) * 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.
• To evaluate seroresponse with the GVGH iNTS-TCV vaccine after each study intervention administration in healthy European adults	• Number of participants in Europe/Stage 1 achieving, for each Ag, at least a 4-fold** rise in Anti-serotype specific IgG* antibody concentration 28 days after each study intervention administration (Day 29, Day 85, and Day 197) compared to first study intervention administration baseline (Day 1), as measured by ELISA, by study intervention group • Number of participants in Europe/Stage 1 with Anti-*S.* Typhi Vi Ag IgG antibody concentrations equivalent to ≥4.3 µg/mL***, before each study intervention administration (Day 1, Day 57, and Day 169) and 28 days after each study intervention administration (Day 29, Day 85, and Day 197), as measured by ELISA, by study intervention group * Anti-*S.* Typhi Vi Ag total IgG, Anti-*S.* Typhimurium O Ag total IgG, Anti-*S.* Enteritidis O Ag total IgG will be tested ** 4-fold is considered clinically meaningful measure of seroconversion in the absence of an established correlate of protection. *** 4.3 µg/mL threshold is clinically meaningful as accepted by World Health Organization (WHO) as immunological protection threshold for

Objectives	Endpoints
	Vi containing typhoid vaccines and has been used in previous studies for registration of these vaccines
• To evaluate the immunogenicity profile of GVGH iNTS-TCV vaccine in healthy African adults	• Anti-serotype specific IgG* GMC, in participants in Africa/Stage 2, as determined by ELISA, before each study intervention administration (Day 1, Day 57, and Day 169) and 28 days after each study intervention administration (Day 29, Day 85, and Day 197), for each study intervention group and between-groups ratios • Anti-serotype specific IgG* within-participant GMRs, in participants in Africa/Stage 2, as determined by ELISA at 28 days after each study intervention administration compared to each study intervention administration baseline (Day 29 versus Day 1, Day 85 versus Day 57, and Day 197 versus Day 169) * Anti-*S.* Typhi Vi Ag total IgG, Anti-*S.* Typhimurium O Ag total IgG, Anti-*S.* Enteritidis O Ag total IgG will be tested.
• To evaluate seroresponse with the GVGH iNTS-TCV vaccine after each study intervention administration in healthy African adults	• Number of participants in Africa/Stage 2 achieving, for each Ag, at least a 4-fold** rise in Anti-serotype specific IgG* antibody concentration 28 days after each study intervention administration (Day 29, Day 85, and Day 197) compared to first study intervention administration baseline (Day 1), as measured by ELISA, by study intervention group • Number of participants in Africa/Stage 2 with Anti-*S.* Typhi Vi Ag IgG* antibody concentrations equivalent to ≥4.3 µg/mL***, before each study intervention administration (Day 1, Day 57, and Day 169) and 28 days after each study intervention administration (Day 29, Day 85, and Day 197), as measured by ELISA, by study intervention group * Anti-*S.* Typhi Vi Ag total IgG, Anti-*S.* Typhimurium O Ag total IgG, Anti-*S.* Enteritidis O Ag total IgG will be tested ** 4-fold is considered clinically meaningful measure of seroconversion in the absence of an established correlate of protection. *** 4.3 µg/mL threshold is clinically meaningful as accepted by WHO as immunological protection threshold for Vi containing typhoid vaccines and has been used in previous studies for registration of these vaccines
Tertiary	
CCI [redacted]	

Objectives	Endpoints
CCI	[redacted]

4.0 STUDY DESIGN

4.1 Overall Design

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

The full dose of the TCV component is the licensed dose of the TCV vaccine, while the full dose of both iNTS components have been tested in repeat-dose toxicology studies in rabbits and were well tolerated. The details of the selected doses are provided in Section 4.3.

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 (refer to Section 4.1.1). The healthy African adults will be randomly assigned to 1 of the groups indicated for Stage 2 (refer to Section 4.1.2).

Each group will receive 2 of the 11 study interventions at each administration, except for the Control_Stage 2 group which will receive 4 study interventions (a different active comparator at each administration time point together with saline) (Table 4).

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

The primary completion date of the study will be at Visit 9 (Day 197), 28 days after the third study intervention. An extended safety follow-up will be performed until 6 months after the third study intervention administration (Day 337) for collection of SAEs.

Table 1 shows the full schedule of activities (SoA) for Stages 1 and 2 and the details of the intervals between study visits are as shown in Table 2.

4.1.1 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 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, or
- Separate administration of low doses of iNTS-GMMA and TCV vaccines in different arms, or
- Placebo and saline in different arms.

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 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 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, or
- Separate administration of full doses of iNTS-GMMA and TCV vaccines in different arms, or
- Placebo and saline in different arms.

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.

4.1.2 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, or
- Separate administration of full doses of iNTS-GMMA and TCV vaccines in different arms, or
- MenACWY (Menveo) and saline for the first administration, TdaP (Boostrix) and saline for the second administration and Typhim Vi and saline for the third administration in different arms. 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. 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 possible 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. 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.

Table 4 Study Groups, Intervention, and Blinding

Study groups				Number of participants	Age (Min-Max)	Study interventions first administration	Study interventions second administration	Study interventions third administration	Blinding Visit 1→Visit 10 (Observer-blind)*
Stage 1 (50 participants)	Step 1 (10 participants)	1	Invasive nontyphoidal Salmonella-typhoid conjugate vaccine (iNTS-TCV) low dose	4	18 – 50 years	iNTS-TCV low dose	iNTS-TCV low dose	iNTS-TCV low dose	X
						Saline	Saline	Saline	
		2	Invasive nontyphoidal Salmonella-generalized modules for membrane antigens vaccine (iNTS-GMMA) and Typhoid conjugate vaccine (TCV) low doses	4	18 - 50 years	iNTS-GMMA low dose	iNTS-GMMA low dose	iNTS-GMMA low dose	X
						TCV low dose	TCV low dose	TCV low dose	
		3	Placebo_Step 1	2	18 – 50 years	Placebo	Placebo	Placebo	X
						Saline	Saline	Saline	
	Step 2 (40 participants)	4	iNTS-TCV full dose_1	16	18 – 50 years	iNTS-TCV full dose	iNTS-TCV full dose	iNTS-TCV full dose	X
						Saline	Saline	Saline	
		5	iNTS-GMMA and TCV full doses_1	16	18 - 50 years	iNTS-GMMA full dose	iNTS-GMMA full dose	iNTS-GMMA full dose	X
						TCV full dose	TCV full dose	TCV full dose	
		6	Placebo_Step 2	8	18 – 50 years	Placebo	Placebo	Placebo	X
						Saline	Saline	Saline	

Study groups			Number of participants	Age (Min-Max)	Study interventions first administration	Study interventions second administration	Study interventions third administration	Blinding Visit 1→Visit 10 (Observer-blind)*
Stage 2 (105 participants)	7	iNTS-TCV full dose_2	45	18 – 50 years	iNTS-TCV full dose	iNTS-TCV full dose	iNTS-TCV full dose	X
					Saline	Saline	Saline	
	8	iNTS-GMMA and TCV full doses_2	45	18 - 50 years	iNTS-GMMA full dose	iNTS-GMMA full dose	iNTS-GMMA full dose	X
					TCV full dose	TCV full dose	TCV full dose	
	9	Control_Stage 2	15	18 – 50 years	Menveo	Boostrix	Typhim Vi	X
					Saline	Saline	Saline	

* The Sponsor representatives are unblinded after Visit 9 is completed for all subjects.

Blood samples will be collected:

- For selected hematology, biochemistry, viral serologic analyses, and human leukocyte antigen B27 (HLA-B27) testing, as part of the Screening. HLA-B27 testing will be done in Stage 1 only.
- For selected hematology and biochemistry analyses, before each study intervention administration and at 7 and 28 days after each study intervention administration, from all participants.
- For immunological assays, before and 28 days after each study intervention administration, from each randomized participant.
- An additional 20 mL for assay development will be taken in Stage 1 on Day 85 from the participants who have given specific consent.
- For peripheral blood mononuclear cells extraction for monoclonal antibodies generation at Visit 9 (for Stage 2 only)

Data will be collected through standardized electronic Case Report Forms (eCRFs). The collection of solicited administration site and systemic events will be done through a participant paper diary (pDiary).

An internal GSK SRT and iSRC will be involved in the safety oversight for this study. Safety precautions such as study design with staggered enrollment, stepwise dose-escalation (Figure 1), limited dosing, and study holding rules have been predefined to ensure maximum safety of the participants. Refer to Section 9.7 for detailed description of safety monitoring.

Details of the formulations of investigational and active comparator vaccines are indicated in Table 6 and Table 7, respectively.

4.2 Scientific Rationale for Study Design

The European Medicine Agency's "Guideline on strategies to identify and mitigate risks for first-in-human (FIH) clinical trials with investigational medicinal products; (EMEA/CHMP/SWP/28367/07 Rev 1)", is intended to assist Sponsors in the transition from nonclinical to early clinical development. It outlines factors influencing risk to be considered in the nonclinical testing strategy and designs of FIH clinical studies or investigational medicinal products. This guideline applies to all new chemical and biological investigational medicinal products except gene and cell therapy products. This guideline also applies to relevant Clinical Trial Authorization applications submitted in accordance with Directive 2001/20/EC (EU No 536/2014).

The study is designed in 2 stages to allow for the evaluation of the vaccine safety and immunogenicity across 2 geographic locations. This allows an assessment of the vaccine in both low and high endemicity settings and evaluate the potential impact of environmental exposure on the vaccine immune response. The first stage of the trial

which is the First Time in Human part of the trial is designed with the required safety measures to serve as risk mitigation (refer to Section 2.3.2). The vaccination schedule is selected based on the number of doses expected to be immunogenic in the target population for primary immunization with the vaccine if eventually licensed (ie, young infants from 6 weeks of age). The specific time points are selected to allow integration with existing Expanded Programme on Immunization schedules in the target regions for the vaccine (ie, 6 weeks, 14 weeks, and 9 months of age). Evaluating the safety of three doses in adults will allow the eventual testing of the same number of doses in the target population.

4.2.1 Choice of Comparator Vaccines

For the adults in Europe, a placebo will be used. The placebo will be the diluent for the study intervention (iNTS-TCV and iNTS-GMMA) to obtain the low dose. It has been used in past GVGH-managed trials and in many licensed vaccines without any safety concerns. For the population in Europe, it is important to compare the reactogenicity of the candidate vaccine against a placebo to objectively assess its safety profile.

A saline solution is used in this study to ensure adequate blinding and to also ensure an appropriate comparison of the study arms based on the effects of the vaccine components (all participants to receive an equal amount of alum).

For the adults in Stage 2 in Africa, Menveo and Boostrix have been used as comparators in a previous study conducted in Kenya during the development of the *S. Sonnei* 1790GAHB vaccine [Obiero, 2017]. Menveo is indicated for active immunization to prevent invasive meningococcal disease caused by Neisseria meningitidis serogroups A, C, Y and W-135. The vaccine contains no preservative or adjuvant. Meningitis being prevalent in Malawi, administering a dose of Menveo will provide some benefits to the participants. Boostrix provides protection against tetanus, diphtheria, and pertussis. It can be administered as a booster in this age population. Typhim Vi is licensed for the prevention of typhoid fever in individuals from 2 years of age, however it is also not routinely administered to adults in Malawi. In the typhoid-endemic region of Malawi, providing a dose of Typhim Vi will provide some benefits to the participants.

The separate administration of the iNTS-GMMA and TCV vaccines as comparators is to allow for the evaluation of the vaccines' immunogenicity as a combination (trivalent) vaccine and as separate vaccines, evaluate the likelihood of interference of iNTS-GMMA with the immunogenicity of TCV vaccines, and vice versa, and aid the planning of future development of either a combination trivalent vaccine or a bivalent iNTS-GMMA vaccine.

4.2.2 Rationale for Blinding

Because of the difference in the presentation of the investigational vaccine and the comparator vaccines, ie, the difference in the labeling of the vaccine vials and the difference in the appearance of the diluent presentation, double blinding is not possible. The study will be conducted in an observer-blind manner. Refer to the definitions of double blinding and observer-blind in Appendix 1 and refer to Section 6.3.3 for details.

When all data up to Day 85 in Stage 2 are available, a group-unblinded interim statistical analysis for immunogenicity will be performed. This analysis may lead to the unblinding of the study team with respect to some participants. A statistician will be unblinded for the analysis.

The remaining study personnel will stay blinded until study end (Day 337 in Stage 2). The Investigator and the participants will not have access to the treatment allocation up to study end (Day 337 in Stage 2).

4.3 Justification for Dose

- In preclinical studies, CCI [redacted] The TCV component of the vaccine is already licensed by Biological E with good immunogenicity demonstrated in populations aged 6 months to 64 years. CCI [redacted] There was also no signal of interference between the different components of the vaccine in the animal experiments.
- The highest dose of the iNTS-TCV vaccine to be used in this trial was tested in a repeated-dose toxicology study in rabbits and it concluded that based on the findings from the study, 4 IM administrations of the vaccine at 2-week intervals to New Zealand White rabbits were well tolerated with no evidence of systemic toxicity. Additionally, the vaccine-related changes were mild in severity and likely represented a physiological reaction following the immune stimulation in response to the vaccine candidate.

Lower starting doses will be used for the first stage of the trial before escalating to the full dose to mitigate any potential risks related to dose increases.

The selected full dose of the TCV component is the dose of the licensed TCV vaccine, while the full dose of both iNTS components have been tested in repeat-dose toxicology studies in rabbits and were well tolerated. Two doses will be tested, CCI [redacted] dilutions of the full doses (low dose) of all study interventions and the full doses of all the study interventions. The licensed TCV is 25 µg in 0.5 mL dose and in the absence of a commercial diluent, it is most feasible to achieve the fractional low dose of CCI [redacted] mL, CCI [redacted]

CCI [redacted]. The selected low dose will be used as a safety lead-in before testing the full dose in the FIH stage of this trial and will allow an initial assessment of the vaccine immunogenicity using a lower antigen content. The alum component is the same as has been tested in previous trials with GMMA vaccines and will be the same irrespective of the dose-level.

4.4 End of Study Definition

A participant is considered to have completed the study if he/she returns for the last visit/contact or is available for the last scheduled procedure/contact as described in the protocol.

The end of study (EoS) is defined as the date of the Last Subject Last Visit (LSLV) or date of last testing results released, whichever comes last. In the latter, EoS must be achieved no later than 8 months after LSLV.

4.5 Study Holding Criteria

4.5.1 Study Holding Rules

Holding rules will be introduced to ensure a well-controlled exposure to the investigational candidate vaccine and to prevent participants from being exposed to any unnecessary safety risks in this FIH study. The holding rules will point attention to safety signals and indicate requirements for formal committee reviews that will decide whether additional participants can be exposed to the study intervention if particular criteria are met. Study holding rules are defined in Table 5.

Holding rule 1 and 2c (threshold ≥1) will be assessed by the Investigator on a continuous basis irrespective of the number of enrolled participants and meeting any of these holding rules will trigger a hold of study intervention administration irrespective of number of enrolled participants and/or timing of the event relative to study intervention administration. Holding rule 2 (2a-b) and 1d.2 in Stage 2 (threshold ≥2) will be assessed during the safety evaluations on blinded or unblinded data.

These holding rules have been written under the assumption that the safety data from all participants will be available. If the data from some participants are not available (eg, in case a participant is lost to follow-up), then the holding rules will be assessed on a pro-rata basis.

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 (holding rules 1a-d and 2c).

However, for the other holding rules (1d.2 in Stage 2, 2a and 2b) which have a threshold ≥2, the Investigator will inform the Sponsor's delegate immediately, without suspending the administration of the study intervention.

The Sponsor's delegate will inform the Investigator if holding rules 1d.2 in Stage 2 and 2a-b are met.

The following communication sequence must be followed:

- The concerned site staff has to put study intervention administration on hold.
- The concerned site staff must immediately inform IQVIA CRA and Medical Monitor (contact details will be provided in a separate document) via email and phone communication who will in-turn inform the GVGH Study Responsible Project Physician.
- All informed site staff will confirm to their local contact that action has been taken providing appropriate documentation to GVGH through the IQVIA CRA and Medical Monitor.
- GSK will further evaluate the case with the iSRC and GSK Global Safety Board and will take the decision to stop or to restart the study intervention administration. GVGH project physician will inform the IQVIA project lead of the decision and the rationale for the decision and all site staff will be informed about that final decision by IQVIA project lead.

Table 5 Study Holding Rules

	Events	Number or % of participants needed to pause administration of study intervention	
		Stage 1 Step 1 and Step 2	Stage 2
1a	Death or any life-threatening SAE regardless of causality	≥1	≥1
1b	Any non-life-threatening SAE that cannot be reasonably attributed to another cause other than study intervention administration	≥1	≥1
1c	Any withdrawal from the study (by Investigator or participant request) following a Grade 3 AE that cannot be reasonably attributed to another cause other than study intervention administration	≥1	≥1
1d.1	Any administration site or general solicited event leading to hospitalization, OR Necrosis at the injection site, each within the 7-day (Days 1 to 7) post-administration period	≥1	≥1
1d.2	Fever >40°C (104°F) within the 7-day (Days 1 to 7) post-administration period	≥1	≥2
2a	Any Grade 3 solicited administration site event (lasting 48 h or more) in an investigational group, within the 7-day (Days 1 to 7) post-administration period	≥2	NA
2b	Any Grade 3 solicited general AE (lasting 48 h or more) in an investigational group, within the 7-day (Days 1 to 7) post-administration period	≥2	NA
2c	Any Grade 3 unsolicited AE in an investigational group, that can be reasonably attributed to the study intervention administration, within the 7-day (Days 1 to 7) post-administration period or Any Grade 3 abnormality in prespecified hematological or biochemical laboratory parameters in an investigational group within the 7-day (Days 1 to 7) post-administration period	≥1	NA

Abbreviations: AE = adverse event; h = hours; SAE = serious adverse event; NA = not applicable

4.5.1.1 Risk Assessment Curves for Holding Rules Cutoff Definition

Figure 2 Blinded Review: Safety Holding Rules 1a, 1b, 1c, 1d.1 and 2c After 10, 21, 40 and 105 Participants

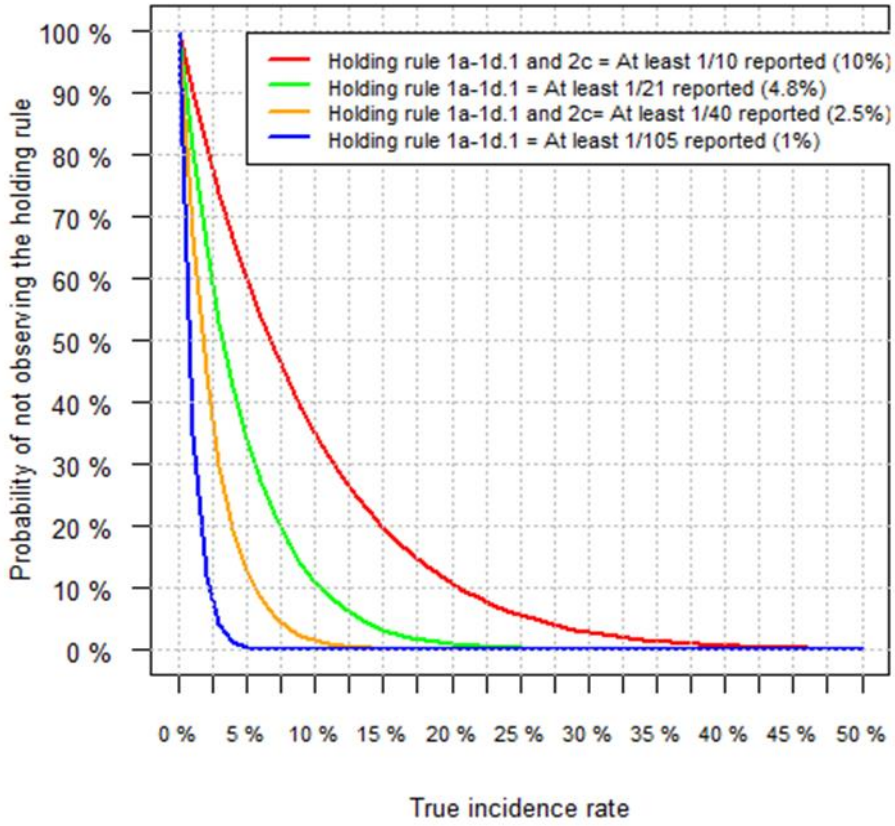


Figure 2 illustrates the following:

- With 10 participants, each holding rule 1a-d.1, and 2c has more than 90% chance of not being met for study intervention administration with a true incidence rate below 1% and has more than 65% chance of being met for study intervention administration with a true incidence rate above 10%.
- With 21 participants, each holding rule 1a-d.1 has more than 80% chance of not being met for study intervention administration with a true incidence rate below 1% and has more than 65% chance of being met for study intervention administration with a true incidence rate above 4.8%.
- With 40 participants, each holding rule 1a-d.1, and 2c has more than 70% chance of not being met for study intervention administration with a true incidence rate below 1% and has more than 65% chance of being met for study intervention administration with a true incidence rate above 2.5%.
- With 105 participants, each holding rule 1a-d.1 has more than 90% chance of not being met for study intervention administration with a true incidence rate below 1% and has more than 88% chance of being met for study intervention administration with a true incidence rate above 2.0%.

Figure 3 Unblinded Review: Safety Holding Rules 1d.2 After 4, 9, 16 and 45 Participants

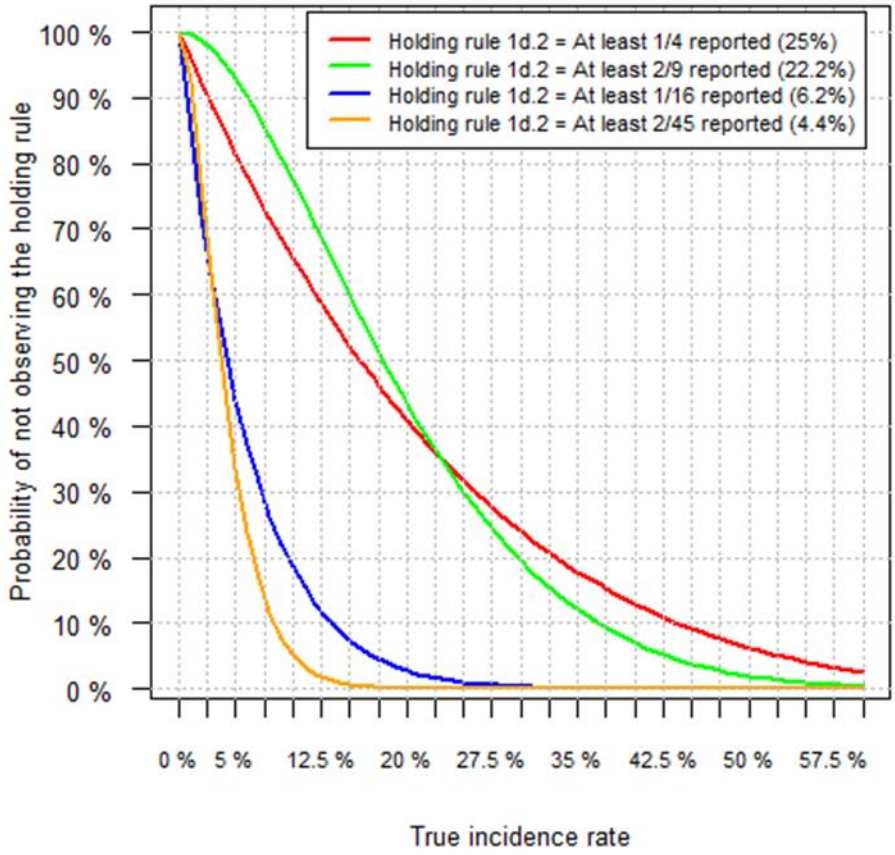


Figure 3 illustrates the following:

- With 4 participants in administration cohort, holding rule 1d.2 has more than 90% chance of not being met for study intervention administration with a true incidence rate below 2.5% and has more than 68% chance of being met with a true incidence rate above 25%.
- With 9 participants in administration cohort, holding rule 1d.2 has more than 90% chance of not being met for study intervention administration with a true incidence rate below 6% and has more than 63% chance of being met for study intervention administration with a true incidence rate above 22.2%.
- With 16 participants in administration cohort, holding rule 1d.2 has more than 85% chance of not being met for study intervention administration with a true incidence rate below 1% and has more than 65% chance of being met with a true incidence rate above 6.2%.
- With 45 participants in administration cohort, holding rule 1d.2 has more than 80% chance of not being met for study intervention administration with a true incidence rate below 2% and has more than 60% chance of being met with a true incidence rate above 4.4%.

Figure 4 Unblinded Review: Safety Holding Rules 2a and 2b After 4 and 16 Participants

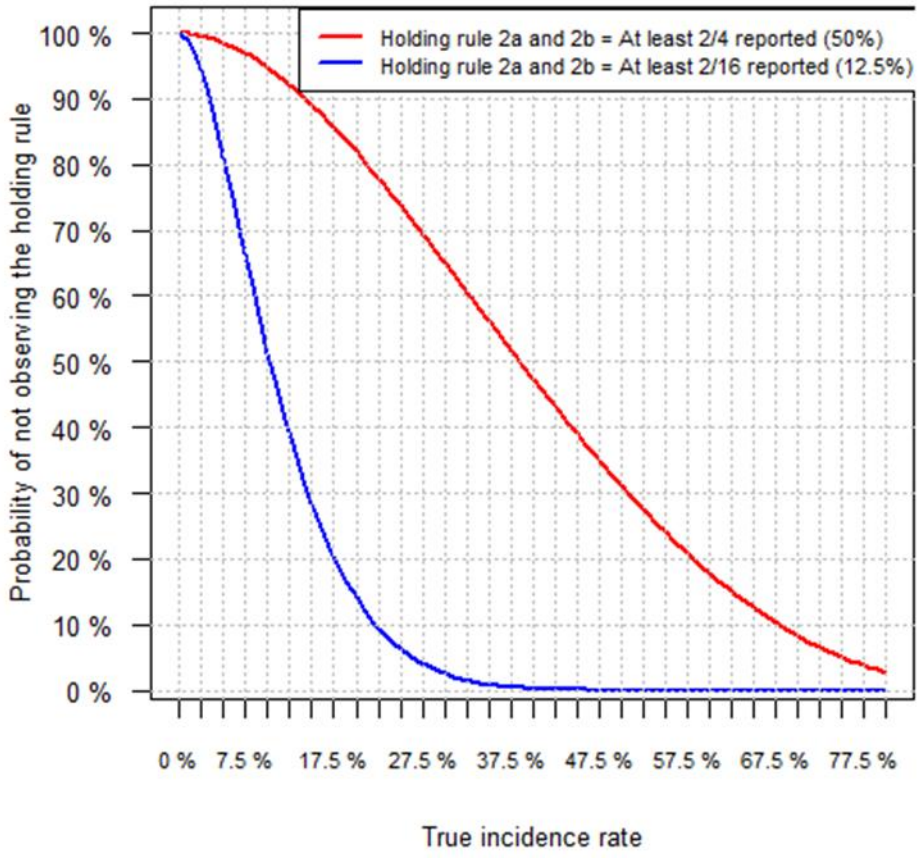


Figure 4 illustrates the following:

- With 4 participants in administration cohort, each holding rule 2a and 2b has more than 90% chance of not being met for study intervention administration with a true incidence rate below 14% and has more than 69% chance of being met for study intervention administration with a true incidence rate above 50%.
- With 16 participants in administration cohort, each holding rule 2a and 2b has more than 90% chance of not being met for study intervention administration with a true incidence rate below 3% and has more than 61% chance of being met for study intervention administration with a true incidence rate above 12.5%.

5.0 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

All participants must satisfy ALL the following criteria at the entry of the trial:

- Participants, who, in the opinion of the Investigator, can and will comply with the requirements of the protocol (eg, completion of the pDiary cards, return for follow-up visits).
- Written or witnessed/thumb printed informed consent obtained from the participant prior to performance of any study-specific procedure.
- Healthy participants as established by medical history, clinical examination, and laboratory assessment.
- Participant satisfying screening requirements.
- A male or female between and including 18 and 50 years of age at the time of the first study intervention administration.
- Female participants of nonchildbearing potential may be enrolled in the study. Nonchildbearing potential is defined as pre-menarche, current bilateral tubal ligation or occlusion, hysterectomy, bilateral ovariectomy, or post-menopause.
- Female participants of childbearing potential may be enrolled in the trial if the participant:
  - Has practiced adequate contraception (as indicated in Appendix 4) for 1 month prior to study intervention administration, and
  - Has a negative pregnancy test on the day of study intervention administration, and
  - Has agreed to continue adequate contraception during the entire treatment period and for 1 month after completion of the study intervention administration series.
- Blood sample for simultaneous follicle-stimulating hormone (FSH) and estradiol levels may be collected at the discretion of the Investigator to confirm non-reproductive potential according to local laboratory reference range.
- Genetic testing for HLA-B27 will be performed at Screening and only participants with a negative result will be allowed to participate in the study*.
  *Only for Stage 1
- For Malawi (Stage 2), the participant lives in Blantyre and has agreed to remain in Blantyre for the study duration.

5.2 Exclusion Criteria

Participants will be excluded from the trial if any of the following criteria apply:

5.2.1 Medical Conditions

- Known exposure to *S.* Typhi and nontyphoidal Salmonella confirmed by blood culture during the period starting 3 years prior to first study intervention administration confirmed using past medical history.
- History of any reaction or hypersensitivity associated with any component of the study interventions.
- Any confirmed or suspected immunosuppressive or immunodeficient condition, based on medical history and physical examination (no laboratory testing required).
- Acute or chronic, clinically significant pulmonary, cardiovascular, hepatic, or renal functional abnormality, as determined by physical examination or laboratory screening tests (Appendix 7).
- Recurrent history or uncontrolled neurological disorders or seizures.
- Any clinically significant* hematological and/or biochemical laboratory abnormality.

* The Investigator should use his/her clinical judgment to decide which abnormalities are clinically significant from the panel of tests in the list of safety assays (Table 9).

- Clinical conditions representing a contraindication to IM injections and/or blood draws.
- Any behavioral or cognitive impairment or psychiatric disease that in the opinion of the Investigator, may interfere with the participant's ability to participate in the study.
- Confirmed positive COVID-19 polymerase chain reaction or lateral flow test during the period starting 28 days before the first administration of study vaccines (Day −28 to Day 1).
- Acute or chronic illness which may be severe enough to preclude participation.
- Any other clinical condition that, in the opinion of the Investigator, might pose additional risk to the participant due to participation in the study.
- All medical conditions will be assessed by the Investigator who may use his/her discretion to decide if the participant meets the exclusion criteria.

5.2.2 Prior/Concomitant Therapy

- History of receiving any typhoid vaccine (Ty21a, Vi capsular polysaccharide, or TCV) in the participant's life.
- History of receiving any investigational iNTS or GMMA vaccines in the participant's life.

- Use of any investigational or non-registered product (drug, vaccine, or medical device) other than the study interventions during the period beginning 30 days (Days −30 to 1) before the first dose of study interventions, or their planned use during the study period.
- A vaccine not foreseen by the study protocol administered during the period starting at 14 days before the first dose and ending 28 days after the last dose of study interventions administration*, with the exception of flu vaccines or COVID-19 vaccine.

*In case emergency mass vaccination for an unforeseen public health threat (eg, a pandemic) is recommended and/or organized by public health authorities outside the routine immunization program, the time period described above can be reduced if, necessary for that vaccine, provided it is used according to the local governmental recommendations and that the Sponsor is notified accordingly.

When regulations allow, 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.

- Administration of long-acting immune-modifying drugs at any time during the study period (eg, infliximab).
- Administration of immunoglobulins and/or any blood products or plasma derivatives during the period starting 3 months before the administration of the first dose of study interventions or planned administration during the study period.
- Chronic administration (defined as more than 14 days in total) of immunosuppressants or other immune-modifying drugs during the period starting 3 months prior to the first study intervention dose(s). For corticosteroids, this will mean prednisone equivalent ≥20 mg/day for adult participants. Inhaled and topical steroids are allowed.

5.2.3 Prior/Concurrent Clinical Study Experience

- Concurrently participating in another clinical trial, at any time during the study period, in which the participant has been or will be exposed to an investigational or a non-investigational intervention (vaccine and drug).

5.2.4 Other Exclusions

- Pregnant or lactating female
- Female planning to become pregnant or planning to discontinue contraceptive precautions

- History of/current chronic alcohol consumption and/or drug abuse. This will be decided at the discretion of the Investigator. Chronic alcohol consumption is defined as one or more of the following:
  - A prolonged period of frequent and heavy alcohol use
  - The inability to control drinking once it has begun
  - Physical dependence manifested by withdrawal symptoms when the individual stops using alcohol
  - Tolerance or the need to use increasing amounts of alcohol to achieve the same effects
  - A variety of social and/or legal problems arising from alcohol use.
- Any study personnel or their immediate dependents, family, or household members.

5.3 Lifestyle Considerations

There are no lifestyle restrictions in this trial.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study due to hematological/biochemical values out of normal range which are expected to be temporary (screen failure) may be rescreened at a later date. Rescreened participants should not be assigned the same participant number as for the initial screening. Rescreening will follow the same process as the initial screening.

5.5 Criteria for Temporarily Delaying Enrollment/Study Intervention Administration

Enrollment/study intervention administration may be postponed within the permitted time interval until transient conditions cited below are resolved:

- Participants with hematological/biochemical values out of normal range (and deemed clinically significant by the Investigator) as per the latest available test result, which are expected to be temporary may be rescreened/re-dosed at a later date within the allowed time interval (The latest laboratory results will be used to assess eligibility for second and third study intervention administration).
- Acute disease or fever at the time of enrollment and/or study intervention administration.
- Refer to the SoA (Table 1) for definition of fever and preferred location for measuring temperature in this study.
- Participants with a minor illness (such as mild diarrhea, mild upper respiratory infection) without fever may be enrolled and/or dosed at the discretion of the Investigator.
- Use of antipyretics and/or analgesics and/or antibiotics within 3 days prior to study intervention administration.
- Participants with a positive COVID-19 test in the 14 days before a planned study intervention administration will be allowed to receive the study intervention at least 14 days after the date of their first positive COVID-19 test.

6.0 STUDY INTERVENTION AND CONCOMITANT THERAPY

Study intervention is defined as any investigational treatment(s), marketed product(s), placebo, or medical device(s) intended to be administered to a participant according to the study protocol.

6.1 Study Intervention(s) Administered

Please refer to Table 6 and Table 7.

Table 6 Study Interventions Administered (Investigational Vaccines)

Study intervention name:	**iNTS-TCV low dose**		**iNTS-GMMA low dose**			**TCV low dose**	**iNTS-TCV full dose**	**iNTS-GMMA full dose**		**TCV full dose**
Study intervention formulation:	CCI [redacted]									
Presentation:	Suspension for injection (vial)	Suspension for injection (vial)	Suspension for injection (vial)	Suspension for injection (vial)	Suspension for injection (vial)	Solution for injection (vial)	Suspension for injection (vial)	Suspension for injection (vial)	Suspension for injection (vial)	Solution for injection (vial)
Type:	Study		Study			Study	Study	Study		Study
Product category:	Biologic product		Biologic product			Biologic product	Biologic product	Biologic product		Biologic product
Route of administration:	Intramuscular use		Intramuscular use			Intramuscular use	Intramuscular use	Intramuscular use		Intramuscular use

Study intervention name:	iNTS-TCV low dose	iNTS-GMMA low dose	TCV low dose	iNTS-TCV full dose	iNTS-GMMA full dose	TCV full dose
Administration site:						
Location:	Deltoid	Deltoid	Deltoid	Deltoid	Deltoid	Deltoid
Directionality:	Upper	Upper	Upper	Upper	Upper	Upper
Laterality:	Random	Random	Random	Random	Random	Random
Number of doses to be administered:	3	3	3	3	3	3
Volume to be administered:	CCI [redacted]					
Packaging and labeling:	SPM					
Manufacturer:	GSK	GSK	Biological E	GSK	GSK	Biological E

Abbreviations: CCI [redacted]; GMMA = generalized modules for membrane antigens; GSK = GlaxoSmithKline Biologicals SA ; iNTS-GMMA = invasive nontyphoidal Salmonella-generalized modules for membrane antigens; iNTS-TCV = invasive nontyphoidal Salmonella-typhoid conjugate vaccine; CCI [redacted]; TCV = typhoid conjugate vaccine

Table 7 Study Interventions Administered (Comparator and Control Vaccines)

Study intervention name:	**Menveo**		**Boostrix**	**Typhim Vi**	**Placebo**	**Saline**
Study intervention formulation:	[redacted]					
Presentation:	Powder for solution for injection (vial)	Solution for solution for injection (vial)	Suspension for injection (syringe)	Solution for injection (syringe)	Suspension for injection (vial)	Solution for injection (ampoule)
Type:	Control		Control	Control	Control	Control
Product category:	Biologic product		Combination product	Combination product	Drug	Drug
Route of administration:	Intramuscular use		Intramuscular use	Intramuscular use	Intramuscular use	Intramuscular use
Administration site:						
Location:	Deltoid		Deltoid	Deltoid	Deltoid	Deltoid
Directionality:	Upper		Upper	Upper	Upper	Upper

Study intervention name:	**Menveo**	**Boostrix**	**Typhim Vi**	**Placebo**	**Saline**
Laterality:	Random	Random	Random	Random	Random
Number of doses to be administered:	1	1	1	3	3
Volume to be administered:	CCI [redacted]				
Packaging, labeling and TM:	SPM				
Manufacturer:	GSK	GSK	Sanofi Pasteur	GSK	Hameln Pharma

Abbreviations : CCI [redacted]
GSK = GlaxoSmithKline Biologicals SA ; CCI [redacted]

6.2 Preparation, Handling, Storage, and Accountability

The study interventions must be stored in a secured place within the temperature range specified on the study intervention's label. The storage temperature should be continuously monitored and recorded with a calibrated (if not validated) temperature monitoring device(s).

Only authorized study personnel should be allowed access to the study interventions. Storage conditions will be assessed by a Sponsor's delegate study contact during prestudy activities. Refer to the Study Reference Manual for more details on storage and handling of the study interventions.

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Participant Identification

Participant identification numbers will be assigned by the study center sequentially to the participants who have consented to participate in the trial, according to the range of participant identification numbers allocated to the study center.

6.3.2 Intervention Allocation to the Participant

Allocation of the participant to a study group at the study center will be performed using envelopes prior to first study intervention administration, according to a randomization schedule generated prior to the study by an independent statistician.

In Stage 1 (Europe), 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, or
- Separate administration of low doses of iNTS-GMMA and TCV vaccines in different arms, or
- Placebo and saline in different arms.

In Stage 1 (Europe), Step 2, 40 healthy European adults, randomized in a 2:2:1 ratio, will receive:

- The full dose of the candidate iNTS-TCV vaccine and concomitant saline to be administered in different arms, or
- Separate administration of full doses of iNTS-GMMA and TCV vaccines in different arms, or
- Placebo and saline in different arms.

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, or
- Separate administration of full doses of iNTS-GMMA and TCV vaccines in different arms, or
- MenACWY (Menveo) and saline for the first administration, TdaP (Boostrix) and saline for the second administration and Typhim Vi and saline for the third administration in different arms.

6.3.3 Blinding and Unblinding

Data will be collected in an observer-blind manner. By observer-blind, it is meant that during the course of the study, the vaccine recipient and those responsible for the evaluation of any study endpoint (eg, safety and reactogenicity) will all be unaware of which study intervention was administered.

To do so, vaccine preparation and administration will be done by authorized medical personnel who will not participate in any of the study clinical evaluations.

The laboratory in charge of the laboratory testing will be blinded to the treatment, and codes will be used to link the participant and study (without any link to the treatment attributed to the participant) to each sample.

6.3.3.1 Emergency Unblinding

Unblinding a participant's individual study intervention number should occur ONLY in case of a medical emergency when this information is essential for the clinical management or welfare of the participant.

In case of emergency, the Investigator can have unrestricted, immediate, and direct access to the participant's study intervention information via emergency envelopes.

A physician other than the Investigator (eg, an emergency room physician) or participant/participant's care giver or family member may also request emergency access to the participant's study intervention information either via the Investigator or Investigator's back up (preferred option).

6.3.3.2 Unblinding Prior to Regulatory Reporting of SAEs

GSK policy requires unblinding of any unexpected SAE which is attributable/suspected to be attributable to the study intervention(s), prior to regulatory reporting. GSK Global Safety is responsible for unblinding the study intervention assignment within the timeframes defined for expedited reporting of SAEs.

In addition, GSK Global Safety staff may unblind the intervention assignment for any participant with a Suspected Unexpected Serious Adverse Reaction (SUSAR) or a SAE that is fatal or life-threatening. For SAEs requiring expedited reporting to 1 or more regulatory agencies, a copy of the report containing participant's intervention assignment may be sent to investigators in accordance with local regulations and/or GSK policy.

6.4 Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the Investigator or designee, under medical supervision. The date and time when each dose is administered in the clinic will be recorded in the source documents.

6.4.1 Treatment Strategy

The clinical staff is responsible for the ongoing safety and wellbeing of the participants while they are in the study center. There is a warning system to alert the clinical staff to any area in the center where a participant may need medical attention. In the case of an emergency, epinephrine, ventilation balloon, and defibrillation material are available on site and the site staff is trained on a regular basis in cardiopulmonary resuscitation. There is a physician on site during the working hours of the center. Outside working hours, a site physician can be reached by phone for medical questions related to the study. In addition, if necessary, the clinical staff can contact further on-call physicians or public emergencies services in the event of a serious medical event. Equipment and emergency drugs are available to treat common medical emergencies that might occur in the Phase 1/2a vaccine study.

Participants will be observed by trained research staff in the research clinic rooms after vaccination for at least 60 minutes. This procedure is to mitigate the very low risk of any immediate reaction to study intervention administration. In Stage 2 in Malawi, the 3A research clinic rooms are situated directly opposite to a respiratory high dependency unit at Queen Elizabeth Central Hospital. In the unlikely event that a participant became unwell after vaccination, they would be transported to this ward, for treatment and close monitoring. The study will also have an emergency/anaphylaxis kit available at the study visit clinic room itself, in order to be able to react immediately. A safety information leaflet will be provided.

6.4.2 Warnings and Precautions

As this is the first administration of the study intervention to man, all effects cannot be reliably predicted. The preclinical data suggest an acceptable safety profile.

Warnings and precautions to administration of study interventions must be checked at each visit with planned administration of study intervention.

Refer to the approved product label/package insert for marketed products.

6.5 Dose Modification

Not applicable.

6.6 Continuing Access to Study Intervention After the End of the Study

During the study conclusion visit, the Investigator will ask each participant if they are interested in participating in a long-term study. If a participant is not interested in joining the long-term study, the reason for refusal will be documented, when available, in the participant's eCRF.

The Investigator is encouraged to share the immunological assay results of non-responders with the study participants.

6.7 Treatment of Overdose

Not applicable.

6.8 Concomitant Therapy

At each study visit/contact, the Investigator or his/her delegate should question the participant about all medications/products taken, and vaccinations received by the participant.

The following concomitant medication(s)/product(s)/vaccine(s) must be recorded in the eCRF:

- All concomitant medication associated with an AE, including vaccines/products, except vitamins and dietary supplements, administered after the first dose of study intervention (Day 1 to Day 197).
- All concomitant medication leading to discontinuation of the study intervention or elimination from the analysis, including products/vaccines.
- All concomitant medication which may explain/cause/be used to treat an SAE including vaccines/products (refer to Section 8.3.4). These must also be recorded in the Expedited AEs report. For further details related to AEs, please refer to Section 8.3 and Appendix 3.
- Prophylactic medication (ie, medication administered in the absence of any symptom and in anticipation of a reaction to the vaccination).
- The IQVIA Clinical Research Associate should be contacted if there are any questions regarding concomitant or prior therapy.

7.0 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Intervention

If a participant who does not meet enrollment criteria is inadvertently enrolled, that participant must be discontinued from study treatment and the Sponsor or Sponsor designee must be contacted. An exception may be granted in rare circumstances for which there is a compelling safety reason to allow the participant to continue. In these rare cases, the Investigator must obtain documented approval from the Sponsor or Sponsor designee to allow the participant to continue in the study.

In case of premature discontinuation of the study intervention, the primary reason for premature discontinuation of the study intervention will be documented on the eCRF as follows:

- Adverse event requiring expedited reporting to Sponsor
- Unsolicited non-serious adverse event
- Solicited adverse event
- Not willing to be vaccinated
- Other (specify)

Participants who discontinue study treatment will not be replaced.

7.2 Contraindications to Subsequent Study Intervention(s) Administration

The eligibility for subsequent study intervention administration must be confirmed before administering any additional dose.

Participants who meet any of the criteria listed below or criteria listed in Sections 5.2.1 and 5.2.2 should not receive additional doses of any study intervention. Such participants should be encouraged to continue other study procedures, at the Investigator's discretion. All relevant criteria for discontinuation of study intervention administration must be recorded in the eCRF.

- Participants who experience any SAE judged to be possibly or probably related to study intervention or non-study concomitant vaccine/product, including hypersensitivity reactions.
- Participants who develop any new condition which, in the opinion of the Investigator, may pose additional risk to the participant if he/she continues to participate in the study.
- Suspected or confirmed anaphylaxis following the administration of study intervention(s).

- Any condition that in the judgment of the Investigator would make intramuscular injection unsafe.

For contraindications to administered marketed study vaccines, refer to their approved product label/package insert.

Please also refer to Appendix 3 for further details about discontinuations due to AEs.

7.3 Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons.
- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the study center study records.
- All data and samples collected up to and including the date of withdrawal of/last contact with the participant will be included in the study analyses.
- Participants who are withdrawn from the study because of AEs/SAEs must be clearly distinguished from participants who are withdrawn for other reasons. Investigator will follow participants who are withdrawn from the study due to an AE/SAE until the event is resolved.
- Should a participant request or decide to withdraw from the study, all efforts must be made to complete and report the observations as thoroughly as possible up to the date of withdrawal. Participants withdrawing due to an AE should be followed up according to the follow-up visit.
- Immunogenicity samples should not be taken from participants that are discontinued from the study due to AEs or other reason. Safety follow-up should be continued for the participants discontinued due to AE.
- Participants who voluntarily withdraw are termed dropouts. Dropouts and participants withdrawn due to protocol violations will not be replaced.

The primary reason for study withdrawal will be documented in the eCRF.

Adverse events requiring expedited reporting to GSK (refer to the Appendix 3)

- Unsolicited non-serious adverse events
- Solicited adverse event
- Withdrawal by participant, not due to an adverse event*
- Migrated/Moved from the study area
- Lost to follow-up
- Sponsor study termination

- Other (specify)

Participants withdrawn due to an AE will not be replaced.

*If a participant is withdrawn from the study because the participant has withdrawn consent and the reason for withdrawal was provided, the Investigator must document this reason in the eCRF.

Participants who are withdrawn from the study because of AEs/SAEs, must be clearly distinguished from participants who are withdrawn for other reasons. Investigator will follow participants who are withdrawn from the study due to an AE/SAE until the event is resolved.

7.4 Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study center.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The study center must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

8.0 STUDY ASSESSMENTS AND PROCEDURES

Protocol waivers or exemptions are only permitted when necessary for the management of immediate safety concerns for the participant.

Immediate safety concerns should be discussed with the Sponsor as soon as they occur or when the study team becomes aware of them. The purpose of this communication is to determine if the participant(s) should discontinue the study intervention.

Study procedures and their timing are summarized in the SoA (refer to Section 1.3).

All screening evaluations must be completed, and the results reviewed before confirming that potential participants meet all eligibility criteria.

The Investigator will maintain a log of all participants screened. All relevant information, such as confirmation of eligibility and reasons for screening failure will be mentioned in this screening log.

The Study Reference Manual provides the Investigator and study center personnel with detailed administrative and technical information that does not impact the participant safety.

8.1 Immunogenicity Assessments

8.1.1 Biological Samples

Biological samples will be used for research planned in the protocol and for purposes related to the improvement, development and quality assurance of the laboratory tests described in this protocol or in future protocols part of the same development plan. The details of samples for immunogenicity assessments are shown in Table 8.

Findings in this or future studies may make it desirable to use samples acquired in this study for research not planned in this protocol. In this case, all participants in countries where this is allowed will be asked to give consent to allow GSK or a contracted partner, to use the samples for further research. The further research will be subjected to prior Institutional Review Boards (IRB)/Independent Ethics Committees (IEC) approval, if required by local legislation.

Information on further research and its rationale can be obtained from GSK.

Sample testing will be done in accordance with the recorded consent of the individual participant. No immunogenicity sample should be taken from participants that are discontinued or withdrawn from the study due to AEs or other reason.

By default, collected samples will be stored for a maximum of 20 years. This storage period begins when the last participant performs the last study visit. This timeline can be adapted based on local laws, regulations or guidelines requiring different timeframes or procedures. In all cases, the storage period should be aligned with participant's consent. These additional requirements must be formally communicated to, discussed, and agreed with GSK.

Table 8 Biological Sample

Sample type	Quantity	Unit	Time point	Participants sampled
Blood for serum preparation	Approximately 10 mL/Visit for antibody determination; approximately 15 mL/Visit for safety screening; up to 10 mL/Visit for pre/post-vaccination safety assays	mL	As scheduled (refer to Figure 1 and Table 1)	All participants in Stage 1 and Stage 2
	Approximately 20 mL/Visit for assay development			Only participants in Stage 1 who have given specific consent for this collection
Blood for PBMC preparation	Approximately 50 mL/Visit for PBMC extraction for monoclonal antibodies generation			All participants in Stage 2

Abbreviation: PBMC = peripheral blood mononuclear cells

8.1.2 Laboratory Assays

All laboratory testing will be performed using characterized and fit-for-purpose qualified assays as indicated in Table 9 at GVGH laboratory or in a laboratory designated by GVGH.

Table 9 Laboratory Assays

Assay type	System	Sampling time points	Component	Method	Unit of measure	Number of participants
Humoral Immunity (Antibody determination)	Serum	Stage 1 Days 1, 29, 57, 85, 169 and 197 Stage 2 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	
			Anti-*S.* Enteritidis O Ag total IgG		EU/mL	
	CCI [redacted]					
Clinical Safety	Whole blood	Screening: Day -28 to Day -1 Stage 1 Days 1, 8, 29, 57, 64, 85, 169, 176 and 197 Stage 2 Days 1, 8, 29, 57, 64, 85, 169, 176 and 197	Leukocytes (white blood cells) Eosinophils Basophils Neutrophils Monocytes Lymphocytes Erythrocytes (red blood cells)[s] Hemoglobin Hematocrit[s] Platelets Prothrombin time[s, **]	Hematology panel		155 (Screening) 50 (Stage 1) 105 (Stage 2)
	Serum/ whole blood	Screening: Day -28 to Day -1 Stage 1	Total bilirubin[s] Aspartic Aminotransferase Alanine Aminotransferase γ-Glutamyl Transferase[s]	Biochemistry		155 (Screening) 50 (Stage 1) 105 (Stage 2)

Assay type	System	Sampling time points	Component	Method	Unit of measure	Number of participants
		Days 1, 8, 29, 57, 64, 85, 169, 176 and 197 Stage 2 Days 1, 8, 29, 57, 64, 85, 169, 176 and 197	Lactic Dehydrogenase[s] Alkaline Phosphatase[s] Total Proteins[s] Glycosylated hemoglobin (HbA1c)[s] Urea/Blood Urea Nitrogen Creatinine Sodium[s] Potassium[s]			
	Serum	Screening: Day -28 to Day -1	HBsAg HCV antibodies HIV antibodies	Serology for virology		155 (Screening)
	Urine	Screening: Day -28 to Day -1 Stage 1: Days 1, 57 and 169 Stage 2: Days 1, 57 and 169	Human chorionic gonadotropin	Pregnancy test		NK (Stage 1) NK (Stage 2)
	Urine	Screening	Urinalysis	Dipstick		155 (Screening)
	Serum	Screening	Human leukocyte antigen B27*	PCR		50 (Stage 1, Screening)

Abbreviations: Ab = Antibody; CCI ; IgG = Immunoglobulin G; EU = ELISA Units; ELISA = enzyme-linked immunosorbent assay; GVGH = GlaxoSmithKline Biological SA Vaccines Institute for Global Health; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus; NK = Not Known; PCR = polymerase chain reaction; [S] = test performed only during Screening period; CCI ;
CCI

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.

* The assay will be performed by the site laboratory, or a laboratory designated by the site. In case of participant rescreening, this test should not be repeated since the result is not expected to change in the participant lifetime.

**Prothrombin time will only be applicable for Stage 1 participants.

8.2 Safety Assessments

The primary safety endpoints will assess the occurrence of laboratory abnormal values, solicited administration site and systemic events 7 days following each study intervention administration, unsolicited AEs which occur within 28 days after each study intervention administration and SAEs throughout the study duration. The occurrence of withdrawals due to AEs will also be assessed throughout the study duration. Currently, there are no AEs of special interest foreseen in this study.

Grading of laboratory values will be based on the US Food & Drug Administration Guidance for Industry "Toxicity Grading Scale for Healthy Adults and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials" [US Department of Health and Human Services, 2007] and Division of AIDS Table for Grading the Severity of Adult AEs [US Department of Health and Human Services, 2017]. Refer to Appendix 7.

Planned time points for all safety assessments are provided in the SoA (Table 1).

8.2.1 Pre-intervention Administration Procedures

8.2.1.1 Collection of Demographic Data, Medical/Vaccination History, and Physical Examination

Demographic data such as age in years, sex, and race (ethnic background) will be collected from each participant. Collection of sex and race (ethnic background) data is necessary to assess and monitor the diversity of the trial participants, and to determine if the trial participants are truly representative of the impacted population and the impact of race (ethnic background) on the trial endpoints. Medical history should be collected, and it should be verified that none of exclusion criteria related to medical and vaccination history (refer to Section 5.2) are met. Vaccine history will be recorded for each participant. Physical examination will be performed for each participant. Physical examination includes assessment of body temperature (axillary) and resting vital signs (systolic/diastolic blood pressure, heart rate, and respiratory rate). On days of vaccination, body temperature and vital signs will be measured before and 60 minutes after vaccination. If the Investigator determines that the participant's health on the day of the study intervention administration temporarily precludes dosing, the visit will be rescheduled.

8.2.1.2 Pregnancy

- Details of all pregnancies in female participants will be collected after the start of study treatment and 1 month after completion of the last study intervention administration.

- If a pregnancy is reported, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

Generally, follow-up will be no longer than 6 to 8 weeks after the estimated delivery date. Pregnancy termination will be reported regardless of fetal status (presence or absence of anomalies) or indication for procedure.

8.2.2 Clinical Safety Laboratory Assessments

All laboratory testing will be performed at GVGH laboratory or in a laboratory designated by GVGH. Please refer to Table 9 for the list of clinical laboratory safety assessments required by the protocol.

The Investigator may perform additional tests, if considered essential for the participant's safety.

8.3 Adverse Events

The definitions of an AE or SAE can be found in Appendix 3.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The Investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or study procedures, or that caused the participant to discontinue the study intervention (refer to Section 7.0). For further details, please refer to Appendix 3.

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

The definition of an AE or SAE are provided in Appendix 3. All initial SAEs will be recorded and reported to the Sponsor or designee immediately, without undue delay but not later than within 24 hours of obtaining knowledge, as indicated in Appendix 3. The SAEs will be reported for every participant throughout the study until study end (Day −28 to Day 337).

The Investigator or designee will record and immediately report all SAEs in screened and enrolled participants to the Sponsor or designee via the Expedited AE Reporting Form. Reporting should, under no circumstances, occur later than 24 hours after the Investigator becomes aware of an SAE. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the Investigator must promptly notify Sponsor or Sponsor's delegate.

8.3.2 Method of Detecting AEs and SAEs

The methods for detecting and recording AEs and SAEs, and the assessment of AE/SAE intensity, causality, and outcome are provided in Appendix 3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up. Further information on follow-up procedures is given in Appendix 3.

8.3.2.1 Clinically Significant Abnormal Laboratory Findings

The Investigator must review the laboratory report, document that he/she did so, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. Clinically significant abnormal laboratory findings are those which are not associated with an underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.

All clinically significant abnormal laboratory test values reported during the study will be repeated until the values return to normal/baseline, or until they are no longer considered significantly abnormal by the Investigator.

If such values do not return to normal/baseline after an interval judged reasonable by the Investigator, the etiology of the abnormal value should be identified, and the Sponsor notified.

8.3.3 Regulatory Reporting Requirements for SAEs

Once the Investigator or designee becomes aware that a study participant has experienced an SAE, they or designated study staff must report it to Sponsor's delegate immediately, no later than 24 hours of obtaining knowledge, using an electronic Expedited AE Report in the eCRF. The Investigator will provide an assessment of causality at the time of the initial report, as defined in the Appendix 3. New or updated information will be recorded on the originally completed form with all changes signed and dated by the Investigator and reported to IQVIA within 24 hours. This is essential for meeting GSK legal

obligations and ethical responsibilities for the participant's safety and the safety of a study intervention under clinical investigation.

For COVID-19-related SAEs, reports should be submitted following routine procedures for SAEs. Local regulatory requirements and GSK's policy for the preparation of an Investigator safety report for SUSARs must be followed. These reports will be forwarded to investigators as necessary.

GSK has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. GSK and IQVIA will comply with country-specific requirements related to safety reporting to the regulatory authority, IRB, and investigators.

8.3.4 Treatment of Adverse Events

Any medication administered for the treatment of an SAE should be recorded in the Expedited AE Report.

8.3.5 Solicited Adverse Events

The solicited administration site and systemic events that will be collected during the 7-day follow-up period after each administration (ie, from Day 1 to Day 7, from Day 57 to Day 63, and from Day 169 to Day 175) are presented in Table 17.

The intensity of the solicited AEs will be assessed as described in Table 18.

8.3.6 Participant Card

The Investigator or Investigator's designee must provide the participants with a "participant card" containing information about the clinical study. The participants will be instructed to keep the participant card in their possession at all times throughout the study. In an emergency, this card serves to inform the responsible attending physician/family member that the participant is in a clinical study and that relevant information may be obtained by contacting the Investigator or his/her backup.

8.3.7 Medical Device Deficiencies

Some of the comparator control vaccines used in this study are combination products constituted of a biologic product in a medical device (pre-filled syringes). Refer to Appendix 1 for the definition of combination product and medical device deficiency and Appendix 6 for further details.

8.3.7.1 Detection, Follow-up, and Prompt Reporting of Medical Device Deficiency

The Investigator is responsible for the detection, documentation, and prompt reporting of any medical device deficiency occurring during the study to Sponsor or Sponsor's delegate. This applies to any medical device provided for the conduct of the study.

Device deficiencies will be reported to Sponsor or Sponsor's delegate within 24 hours after the Investigator determines that the event meets the protocol definition of a device deficiency.

The Investigator will ensure that follow-up includes any additional investigations to elucidate the nature and/or related of the device deficiency to the incident. Follow-up applies to all participants, including those who discontinue study intervention or the study.

New or updated information will be recorded on the originally completed form with all changes signed and dated by the Investigator and reported to Sponsor or Sponsor's delegate within 24 hours.

Medical device deficiencies and any associated AE/SAEs for associated person (ie, spouse, caregiver, site staff) will also be collected. The associated person will be provided with a safety reporting information and authorization letter.

Follow-up applies to all participants, including those who discontinue study intervention or the study, and associated persons.

8.3.7.2 Regulatory Reporting of Medical Device Deficiency When Used as Combination Product

The Investigator will promptly report all device deficiencies occurring with any medical device provided for use in the study to Sponsor or Sponsor's delegate. Sponsor or Sponsor's delegate has a legal responsibility to notify appropriate regulatory authorities and other entities about safety information linked to medical devices being used in clinical studies.

The Investigator, or responsible person according to local requirements (eg, the head of the medical institution), will comply with the applicable local regulatory requirements relating to the reporting of device deficiencies to the IRB/IEC.

8.4 Pharmacokinetics and Pharmacodynamics

Pharmacokinetics and pharmacodynamic parameters are not evaluated in this study.

8.5 Study Procedures During Special Circumstances

During special circumstances (eg, COVID-19 pandemic), the specific guidance from local public health and other competent authorities regarding the protection of individuals' welfare must be followed. For the duration of such special circumstances, the following measures may be implemented for enrolled participants:

- Safety follow-up may be made by a phone call, other means of virtual contact, or home visit, if appropriate.
- Visits for suspected AEs may take place in a different location* other than the study center or at participant's home. If this is not feasible, then the medical evaluation of AEs may take place through remote visit with documentation of symptoms by other means of communication (eg, phone call or videoconference), if possible. Refer to Appendix 1 for the definition of remote visit.
- Biological samples may be collected at a different location* other than the study center or at participant's home. Biological samples should not be collected if they cannot be processed in a timely manner or appropriately stored until the intended use.
- COVID-19 test will be performed pre and post-study intervention administration on participants with symptoms or clinical suspicion of COVID-19, as per the Investigator's discretion.

*Note: It is the Investigator's responsibility to identify an alternate location. The Investigator should ensure that this alternate location meets ICH GCP requirements, such as adequate facilities to perform study procedures, appropriate training of the staff, and documented delegation of responsibilities in this location. This alternate location may need to be covered by proper insurance for the conduct of study on participants by Investigator and study center staff other than the designated study center.

8.6 Genetic Testing

Based on advice from Belgian CA (FAHMP), to minimize any risk of autoimmune reactions, and spondyloses specifically, blood samples collected for safety during Screening in stage 1 will undergo sampling for HLA-B27 genetic marker and only prospective participants who are found to be negative for HLA-B27 will be included in the study [McColl, 2000; Ekman, 2000; Zeidler, 2021]. Refer to Appendix 5 for details.

9.0 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

No formal statistical hypotheses are to be tested.

9.2 Sample Size Determination

A total of 155 participants are planned to be randomized to achieve at least 133 evaluable participants in the Per Protocol analysis set for immunogenicity, assuming a 12% dropout rate for each group. Participants who withdraw from the study will not be replaced.

No confirmatory objectives are planned in this trial; however, the sample size was chosen to allow an exploratory comparison of immunogenicity 28 days after the third administration in Stage 2 (Day 197), between participants receiving full dose of candidate iNTS-TCV vaccine and separate full doses of iNTS-GMMA and TCV vaccines, with respect to Anti-*S.* Typhi Vi Ag total IgG, Anti-*S.* Typhimurium O Ag total IgG, Anti-*S.* Enteritidis O Ag total IgG.

9.3 Populations for Analyses

For purposes of analysis, the analysis sets in Table 10 are defined.

Table 10 Analysis Sets

Analysis Set	Description
Enrolled Set	Participants who were randomized or received study intervention or underwent a post-screening procedure. Note that as per Good Clinical Practice, an enrolled participant should have completed the informed consent process and participants should be eligible before initiating any study procedure. The allocation in a group is based on the administered intervention.
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.
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.
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 and without prohibited concomitant medication/vaccination. The PPS for immunogenicity will be defined by time point.
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.
Solicited Safety Set	All participants who received at least 1 dose of the study intervention (ES) who have solicited safety data. The allocation in a group is based on the administered intervention.

If the participant meets one of the criteria mentioned below or ones listed in the Section 7.2, he/she may be eliminated from per protocol analysis.

- Use of any investigational or non-registered product (drug or vaccine) other than the study vaccine(s) used during the study period.
- Use of immunosuppressants or other immune-modifying drugs administered chronically (ie, more than 14 days in total) during the study period. For corticosteroids, this will mean prednisone 20 mg/day (for adult participants), or equivalent. Inhaled and topical steroids are allowed.
- Use of any long-acting immune-modifying drugs administered at any time during the study period (eg, infliximab).
- Use of any vaccine not foreseen by the study protocol administered during the entire period of participant's study participation, with the exception of flu vaccines, COVID-19 vaccines, and vaccines administered routinely according to the national immunization program.
- Use of any Immunoglobulins and/or any blood products administered during the study period.
- Any drug and/or alcohol abuse.
- Occurrence of a condition that has the capability of altering their immune response (ie, varicella) or are confirmed to have an alteration of their initial immune status.
- Occurrence of a serious chronic or progressive disease according to judgment of the Investigator (eg, neoplasm, insulin dependent diabetes, cardiac, renal, or hepatic disease).
- Occurrence of any malignancy or lymphoproliferative disorder.
- Occurrence of any confirmed or suspected immunosuppressive or immunodeficient condition, based on physical examination.
- Unblinding after any study intervention has been performed.
- Other details to be included in the Statistical Analysis Plan.

9.4 Statistical Analyses

The Statistical Analysis Plan will be developed and finalized before database lock and will describe the participant analysis sets to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

9.4.1 Primary Endpoints

The analysis on primary objective will be based on the Solicited, Unsolicited, and Exposed Sets, as indicated in Table 11.

Table 11 Primary Endpoints-Statistical Analyses

Endpoint	Statistical Analysis Methods
Primary safety	• The number and percentage of participants with at least 1 solicited administration site and systemic event during the 7-day follow-up period will be tabulated by group after each study intervention administration and overall. The same calculations will be performed for symptoms rated as Grade 3. • The number and percentage of participants with at least 1 unsolicited adverse event (AE) during the 28-day follow-up period will be tabulated by group after each study intervention administration and overall. The same calculations will be performed for symptoms rated as Grade 3. • The percentage of doses associated with at least 1 solicited administration site and systemic event during the 7-day follow-up period will be tabulated for the overall administration course. The same calculations will be performed for symptoms rated as Grade 3. • The percentage of doses associated with at least 1 unsolicited AE during the 28-day follow-up period will be tabulated for the overall administration course. The same calculations will be performed for symptoms rated as Grade 3. • The number and percentage of participants reporting each individual solicited administration site (ie, injection site pain, erythema [redness], swelling) and systemic event (ie, fever [temperature ≥38.0°C], headache, myalgia, arthralgia, fatigue; any Grade and Grade 3) during the 7-day solicited follow-up period after each study intervention administration and by group will be tabulated. The percentage of doses associated with each individual solicited administration site and systemic event will be tabulated for the overall administration course. • 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 follow-up period. This will be tabulated for each group after each dose. • The number and percentage of participants with at least 1 reported unsolicited AE during the 28-day follow-up period after each study intervention administration and by group, as classified by the Medical Dictionary for Regulatory Activities (MedDRA) preferred term, by system organ class and by group will be tabulated. The same tabulation will be performed for Grade 3 unsolicited AEs and for unsolicited AEs according to relationship to study intervention administration. • The number and percentage of participants reporting serious AEs (SAEs) and AEs/SAEs leading to withdrawal from the study and/or withholding doses of study intervention, collected from first study intervention administration up to 28 days after third study intervention administration (Day 1 to Day 197) will be tabulated. The detailed listings will also be produced. • For each group, for hematological, renal, and hepatic panel test results at 7 days after each study intervention administration (Day 8, Day 64, and Day 176) and at 28 days after each study intervention administration (Day 29, Day 85, and Day 197), and for other tests at baseline: - The percentage of participants having hematological, renal, and hepatic results below or above the laboratory normal ranges will be tabulated by time point.

Endpoint	Statistical Analysis Methods
	- The maximum Grade from Day 1 until the end of the participant's participation 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.

9.4.2 Secondary Endpoints

The analysis on secondary objectives will be based on the Per Protocol Set (PPS) for immunogenicity, as shown in Table 12. If, in any study group and at any time point, the percentage of vaccinated participants with serological results excluded from the PPS for analysis of immunogenicity is 10% or more, a second-line analysis based on the Full Analysis Set (FAS) for immunogenicity will be performed to complement the PPS analysis.

Table 12 Secondary Endpoints-Statistical Analyses

Endpoint	Statistical Analysis Methods
Secondary immunogenicity	For each study group with participants in Europe, for each sampling time point, and for each antigen*, the following statistics will be computed: • Unadjusted GMCs with 95% CI of anti-serotype specific IgG* before and 28 days after each study intervention administration as measured by in-house ELISA. • Unadjusted within-participant GMRs with 95% CI at 28 days after each study intervention administration compared to each study intervention administration baseline of anti-serotype specific IgG* as measured by in-house ELISA. • The number and percentage of participants with at least a 4-fold increase in Anti-serotype specific IgG* antibody concentration 28 days after each study intervention administration compared to first study intervention administration baseline, with 95% CI as measured by in-house ELISA. • The number and percentage of participants with Anti-*S.* Typhi Vi Ag IgG antibody concentrations equivalent to ≥4.3 µg/mL, before and 28 days after each study intervention administration, with 95% CI as measured by in-house ELISA. • 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*, visit, and administration. For each study group with participants in Africa, for each sampling time point, and for each antigen*, the following statistics will be computed: • Unadjusted GMCs with 95% CI of anti-serotype specific IgG* before and 28 days after each study intervention administration as measured by in-house ELISA. • Unadjusted within-participant GMRs with 95% CI at 28 days after each study intervention administration compared to each study intervention administration baseline of anti-serotype specific IgG* as measured by in-house ELISA.

Endpoint	Statistical Analysis Methods
	• The number and percentage of participants with at least a 4-fold increase in Anti-serotype specific IgG* antibody concentration 28 days after each study intervention administration compared to first study intervention administration baseline, with exact 95% CI as measured by in-house ELISA. • The number and percentage of participants with Anti-*S.* Typhi Vi Ag IgG antibody concentrations equivalent to ≥4.3 µg/mL, before and 28 days after each study intervention administration, with 95% CI as measured by in-house ELISA. • 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*, visit, and administration. * Anti-*S.* Typhi Vi Ag total IgG, Anti-*S.* Typhimurium O Ag total IgG, Anti-*S.* Enteritidis O Ag total will be tested. The GMCs, GMRs, and ratio of GMC along with 95% CIs will be obtained by exponentiating (base 10) the means and the lower and upper limits of the 95% CIs of the log-transformed values (base 10). For the between-group assessments, the ANOVA model will be fitted based on the participants having a result at both the baseline and the considered time point. 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 ANOVA model ≥0.10 (ie, 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 (ie, Europe + Africa) adjusted by center. ANOVA model will include both vaccine group and center group as fixed effects, and adjusted GMC, GMRs, and ratio of GMC will be derived by exponential transformation of the corresponding group contrast in the model. A sensitivity analysis will be performed pooling Europe and Africa data and adjusting treatment effect for center variable, regardless of the center*treatment associated p-value. A second sensitivity analysis will be performed pooling Europe and Africa and adjusting treatment effect for race variable. Finally, subgroup analysis will be performed by race.
Secondary Safety	The number and percentage of participants reporting SAEs from 28 days after third study intervention administration (Day 197) up to Day 337 will be tabulated by study intervention group in Stage 1/Stage 2. Number of participants with AEs/SAEs leading to withdrawal from the study, from 28 days after third study intervention administration (Day 197) up to Day 337, by study intervention group in Stage 1/Stage 2.

Abbreviations: Ag = Antigen; ANOVA = analysis of variance; CI = confidence intervals; ELISA = enzyme-linked immunosorbent assay; GMC = geometric mean concentrations; GMR = geometric mean ratios; iNTS-GMMA = invasive nontyphoidal Salmonella-generalized modules for membrane antigens; iNTS-TCV = invasive nontyphoidal Salmonella-typhoid conjugate vaccine; SAE = serious adverse event; *S.* Typhi = *Salmonella* Typhi; *S.* Typhimurium = *Salmonella* Typhimurium; TCV = typhoid conjugate vaccine

9.4.3 Tertiary Endpoints

The analysis on tertiary objective will be based on the PPS for immunogenicity, as described in Table 13. If, in any study group and at any time point, the percentage of vaccinated participants with serological results excluded from the PPS for analysis of immunogenicity is 10% or more, a second-line analysis based on the FAS for immunogenicity will be performed to complement the PPS analysis.

Table 13 Tertiary Endpoints-Statistical Analyses

CCI

9.5 Missing Data

Data from participants who withdraw from the study, including AEs and any follow-up, will be included in the analyses of primary, secondary, and tertiary outcomes. Missing data will not be imputed.

9.6 Interim Analyses

A group-unblinded interim analysis for immunogenicity will be performed 28 days after the second administration in all study participants in Stage 2 in order to support the preparation for future studies.

9.6.1 Sequence of Analyses

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

The sequence of interim and final analyses will be the following:

a. 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 statistician will be unblinded for the analysis (ie, will have access to individual participant treatment assignments). The remaining study personnel will stay blinded (ie, will not have access to the individual participant treatment assignment) until Day 197. It is possible however, due to limited sample size, that unblinding occurs for a few participants having as specific AE or SAE (eg, an AE/SAE 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).
b. 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. Data collected during the extended safety follow-up period will be analyzed after Day 337.
c. A final CSR will be produced after the analysis after Visit 9 in Stage 2 and the analysis after Day 337 will be included in an integrated CSR to be written after.

9.6.2 Statistical Considerations

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

9.7 Internal Safety Review Committee

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). The iSRC will include study-independent GSK members and an external, non-GSK clinical development expert to ensure an unbiased assessment.

Planned safety data reviews are specified in Figure 1 and in Table 14. After the reviews, if no safety signal is observed, the favorable outcome of the safety evaluations will be documented and provided in a written way, authorizing the Investigator to start the administration of the subsequent dose of study intervention to participants, as well as enrollment and study intervention administration to the remaining participants in the next step of the study, as described in the protocol. If a safety signal is observed during the safety evaluations or if any of the holding rules are met, the iSRC Chair (or his/her representative) is responsible for the urgent communication to GVGH PP, including the rationale for the decision to put the study intervention administration on hold or not.

The IQVIA study project lead will be accountable for notifying all investigators of the decision whether to suspend, modify or continue the conduct of the study on all groups or on selected groups.

In Stage 1/Step 1, there will be a sequential approach in which the 10 sentinel participants will receive the first low dose of the study interventions on consecutive days. The sentinel participants will receive a safety phone call for safety surveillance on the day following first study intervention administration (Day 2), before proceeding with administration of study intervention in subsequent participants. 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.

In Step 2, a second sentinel of 10 participants vaccinated on consecutive days. They will receive a phone call for safety surveillance on the day following the first study intervention administration (Day 2), before proceeding with study intervention administration in the subsequent participants. The remaining 30 participants will be vaccinated at least 60 minutes apart.

Likewise, in Stage 2, the first 21 participants will receive the study interventions sequentially, at least 60 minutes apart, with a safety phone call/home Visit the day after administration for safety surveillance.

All 155 participants in the study (Stage 1 and Stage 2) will be closely monitored at the site for at least 60 minutes post-administration for safety surveillance.

Seven days after the first study intervention administration in the low dose cohort (Step 1) in Stage 1 is completed, an iSRC will receive a summary of all available safety data (solicited administration site events and systemic events, unsolicited AEs and SAEs) and listings of hematology and blood chemistry test values obtained following the first study intervention administration (baseline and 7 days after study intervention administration). Based on evaluation of the safety data (review #1, Table 14), the iSRC will make a recommendation, as to whether the next stage of the trial (Stage 1/Step 2), when the administration of the full dose of the study interventions to the study participants, should start.

Seven days after all participants in Stage 1/Step 1 have received their second study intervention, there will be an iSRC review of all safety data collected up to day 7 after second administration (Day 64) in Step 1 (review #2, Table 14). If there is no safety concern with any of the investigational groups, the second study intervention administration in Stage 1/Step 2 can commence.

There will be another iSRC data review 28 days after the second administration in Stage 1/Step 2 (review #3, Table 14). In the case of a favorable review, recruitment of participants in Stage 2 in Africa can commence.

All the participants in Stage 1 will complete the trial according to the schedule. A final safety evaluation of all data collected in Stage 1 will be performed once the study is completed.

The first 21 participants in Stage 2 will receive the study interventions sequentially, 60 minutes apart, with a follow-up safety phone call/home Visit conducted one day after the first administration to identify any safety concerns in the participants who received the study interventions. The Investigator will proceed with study interventions administration in the subsequent study participant only in the case that there is no safety concern in the previous participant who received the study interventions. 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.

Seven days after the first administration of the study interventions of the first 21 participants in Stage 2, there will be an iSRC to review all available safety data collected (review #4, Table 14). Following this, in the event of a positive safety review, the 84 remaining participants will receive the study interventions in parallel.

A last iSRC review analysis for safety will be performed 28 days after second administration in the first 21 participants in Stage 2 to allow the third study intervention administration of all participants in Stage 2 and to support preparation for future studies (review #5, Table 14).

A summary of the planned unblinded iSRC reviews for the trial are presented in Table 14. In case of any safety concerns, ad hoc iSRC reviews may be called.

Instream blinded monitoring will also be performed by the internal GSK Safety Review Team (SRT); details of these blinded data reviews for the trial are presented in Table 15.

Table 14 Summary of the iSRC Reviews*

iSRC #	Timing of Safety Evaluation	Subsequent Activities
1	7 days after first administration with low dose of 10 sentinel participants in Step 1 (Stage 1)	First administration with full dose of 40 participants in Step 2 (Stage 1)
2	7 days after second administration with low dose of 10 sentinel participants in Step 1 (Stage 1)	Second administration with full dose of 40 participants in Step 2 (Stage 1)
3	28 days after second administration with full dose of 40 participants in Step 2 (Stage 1)	First administration with full dose of first 21 participants in Stage 2
4	7 days after first administration of first 21 participants in Stage 2	First administration of remaining 84 participants in Stage 2
5	28 days after second administration in the first 21 participants in Stage 2	Third administration with full dose of all participants in Stage 2

Abbreviation: iSRC= Internal Safety Review Committee
* All available safety data will be cumulatively reviewed at each safety evaluation.

Table 15 Time points for Blinded Instream Monitoring

Stage #	Instream Monitoring
Stage 1 (Steps 1 and 2)	All cumulative data (all subjects) up to 7 days post-first vaccination
	All cumulative data (all subjects) up to 7 days post-second vaccination
	All cumulative data (all subjects) up to 7 days post-third vaccination
Stage 2	All cumulative data (all subjects) up to 7 days post-first vaccination of the additional 84 subjects
	All cumulative data (all subjects) up to 28 days post-first vaccination of the additional 84 subjects
	All cumulative data (all subjects) up to 7 days post-second vaccination of the first 21 subjects
	All cumulative data (all subjects) up to 28 days post-second vaccination of the additional 84 subjects

10.0 REFERENCES

Aldrich, C, Hartman H, Feasey N, et al. Emergence of phylogenetically diverse and fluoroquinolone resistant Salmonella Enteritidis as a cause of invasive nontyphoidal Salmonella disease in Ghana. PLoS Negl Trop Dis. 2019;13(6):e0007485.

Balasubramanian R, Im J, Lee JS, et al. The global burden and epidemiology of invasive non-typhoidal Salmonella infections. Hum Vaccin Immunother. 2019;15(6):1421-26.

Benedetto GD, Alfini R, Cescutti P, et al. Characterization of O-antigen delivered by Generalized Modules for Membrane Antigens (GMMA) vaccine candidates against nontyphoidal Salmonella', Vaccine. 2017;35(3): 419-26.

Butler NR, Voyce MA, Burland WL, Hilton MJ. Advantages of aluminium hydroxide adsorbed combined diphtheria, tetanus, and pertussis vaccines for the immunization of infants. Br Med J. 1969;1(5645):633-6.

Ekman P, Kirveskari J, Granfors K. Modification of disease outcome in *salmonella*-infected patients by HLA-B27. Arthritis Rheum. 2000; 43(7):1527-34.

Feasey NA, Dougan G, Kingsley RK, Heyderman RS, Gordon MA. Invasive non-typhoidal salmonella disease: an emerging and neglected tropical disease in Africa. Lancet. 2012;379(9835): 2489-99.

Feasey NA, Masesa C, Jassi C, et al. Three Epidemics of Invasive Multidrug-Resistant Salmonella Bloodstream Infection in Blantyre, Malawi, 1998-2014. Clin Infect Dis, 2015;61 Suppl 4(Suppl 4):S363-71.

Frenck Jr. RW, Conti V, Ferruzi P, et al. Efficacy, safety, and immunogenicity of the Shigella Sonnei 1790GAHB GMMA candidate vaccine: Results from a phase 2b randomized, placebo-controlled challenge study in adults. EClinicalMedicine. 2021 Aug 13;39:101076.

Garçon N, Stern PL, Cunningham AL. Understanding modern vaccines: perspectives in vaccinology. Amsterdam: Elsevier;2011.

GBD 2017 Non-typhoidal Salmonella Invasive Disease Collaborators. The global burden of non-typhoidal salmonella invasive disease: a systematic analysis for the Global Burden of Disease Study 2017. Lancet Infect Dis. 2019;19(12):1312-24.

Institute for Health Metrics and Evaluation (IHME) website Global Health Data Exchange (GHDx). Available from: http://ghdx.healthdata.org/gbd-results-tool?params=gbd-api-2019-permalink/1e5a4e3305d08fb898157bb92e1f3c1a. Accessed July 2021.

Kariuki S, Mbae C, Onsare R, et al. Multidrug-resistant Nontyphoidal Salmonella Hotspots as Targets for Vaccine Use in Management of Infections in Endemic Settings. Clin Infect Dis. 2019;68(Suppl 1): S10-S15.

Kawahara M, Kato-Negishi M. Link between Aluminum and the Pathogenesis of Alzheimer's Disease: The Integration of the Aluminum and Amyloid Cascade Hypotheses. Int J Alzheimers Dis. 2011:276393.

Lanzilao L, Stefanetti G, Saul A, MacLennan CA, Micoli , Rondini S. Strain Selection for Generation of O-Antigen-Based Glycoconjugate Vaccines against Invasive Nontyphoidal Salmonella Disease. PLoS One. 2015;10(10):e0139847.

Launay O, Lewis DJM, Anemona A, et al. Safety Profile and Immunologic Responses of a Novel Vaccine Against Shigella Sonnei Administered Intramuscularly, Intradermally and Intranasally: Results From Two Parallel Randomized Phase 1 Clinical Studies in Healthy Adult Volunteers in Europe. EBioMedicine. 2017;22:164-72.

Launay O, Ndiaye AGW, Conti V, et al. Booster Vaccination With GVGH Shigella Sonnei 1790GAHB GMMA Vaccine Compared to Single Vaccination in Unvaccinated Healthy European Adults: Results From a Phase 1 Clinical Trial. Front Immunol. 2019;10:335.

Maggiore L, Yu L, Omasits U, et al. Quantitative proteomic analysis of Shigella flexneri and Shigella Sonnei Generalized Modules for Membrane Antigens (GMMA) reveals highly pure preparations. Int J Med Microbiol. 2016;306(2):99-108.

Marks F, Kalckreuth VV, Aaby P, et al. Incidence of invasive *salmonella* disease in sub-Saharan Africa: a multicentre population-based surveillance study. Lancet Glob Health. 2017;5(3):e310-e23.

McColl GJ, Diviney MB, Holdsworth RF, et al. HLA-B27 expression and reactive arthritis susceptibility in two patient cohorts infected with *Salmonella Typhimurium*. Aust NZ J Med 2000;30: 28-32.

Obiero CW, Ndiaye AGW, Scire AS, et al. A Phase 2a Randomized Study to Evaluate the Safety and Immunogenicity of the 1790GAHB Generalized Modules for Membrane Antigen Vaccine against Shigella Sonnei Administered Intramuscularly to Adults from a Shigellosis-Endemic Country. Front Immunol. 2017;8:1884.

Pasquale AD, Preiss S, Da Silva FT, Garcon N. Vaccine Adjuvants: from 1920 to 2015 and Beyond. Vaccines (Basel). 2015;3(2):320-43.

Petrovsky N, Aguilar JC. Vaccine adjuvants: current state and future trends. Immunol Cell Biol. 2004;82(5):488-96.

Puyvelde SV, Pickard D, Vandelannoote K, et al. An African Salmonella Typhimurium ST313 sublineage with extensive drug-resistance and signatures of host adaptation. Nat Commun. 2019;10(1):4280.

Reddy EA, Shaw AV, Crump JA. Community-acquired bloodstream infections in Africa: a systematic review and meta-analysis. Lancet Infect Dis. 2010;10(6):417-32.

Robert WF, Valentino C, Pietro F, et al. Efficacy, safety, and immunogenicity of the Shigella Sonnei 1790GAHB GMMA candidate vaccine: Results from a phase 2b randomized, placebo-controlled challenge study in adults. EClinicalMedicine. 2021;39:101076.

Uche IV, MacLennan CA, Saul A. A Systematic Review of the Incidence, Risk Factors and Case Fatality Rates of Invasive Nontyphoidal Salmonella (iNTS) Disease in Africa (1966 to 2014). PLoS Negl Trop Dis. 2017;11(1):e0005118.

US Department of Health and Human Services. Food and Drug Administration (FDA) Center for Biologics Evaluation and Research. Guidance for Industry-Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials; 2007. Available from https://www.fda.gov/media/73679/download.

US Department of Health and Human Services. Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events; 2017. Available from https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf.

WHO COVID-19: Case Definitions, published 16 Dec 2020. WHO reference https://www.who.int/publications/i/item/WHO-2019-nCoV-Surveillance_Case_Definition-2022.1

Wills MR, Savory J. Aluminum and chronic renal failure: sources, absorption, transport, and toxicity. Crit Rev Clin Lab Sci. 1989;27(1):59-107.

Zeidler H, Hudson AP. Reactive Arthritis Update: Spotlight on New and Rare Infectious Agents Implicated as Pathogens. Curr Rheumatol Rep. 2021;23(7):53.

11.0 APPENDICES

Appendix 1 Abbreviations

Abbreviation	Definition
ADE	Adverse device effect
AE	Adverse event
Ag	Antigen
AMR	Antimicrobial resistance
CFR	Code of Federal Regulations
CI	Confidence interval
COVID-19	Coronavirus disease 2019
eCRF	Electronic case report form
DAIDS	Division of AIDS
EoS	End of study
ES	Exposed Set
FAS	Full Analysis Set
FIH	First-in-human
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GMMA	Generalized modules for membrane antigens
GSK	GlaxoSmithKline Biologicals SA
GVGH	GSK Vaccines Institute for Global Health
HLA-B27	Human leukocyte antigen B27
HRT	Hormonal replacement therapy
IB	Investigator’s Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IM	Intramuscular

Abbreviation	Definition
iNTS	Invasive nontyphoidal Salmonella
IRB	Institutional Review Boards
iSRC	Internal Safety Review Committee
LPS	Lipopolysaccharides
LSLV	Last subject last visit
PPS	Per Protocol Set
S. Enteritidis	*Salmonella* Enteritidis
S. Typhi	*Salmonella* Typhi
S. Typhimurium	*Salmonella* Typhimurium
SADE	Serious adverse device effect
SAE	Serious adverse event
SmPC	Summary of Product Characteristics
SoA	Schedule of Activities
SRT	Safety Review Team
sSA	Sub-Saharan Africa
SUSAR	Suspected Unexpected Serious Adverse Reactions
TCV	Typhoid conjugate vaccine
Typhim Vi	Typhoid Vi polysaccharide vaccine
USADE	Unanticipated serious adverse device effect
WHO	World Health Organization
WOCBP	Woman of childbearing potential

Glossary of Terms

Adverse event:	Any untoward medical occurrence in a patient or clinical investigation participant, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (ie, lack of efficacy), abuse or misuse.
Blinding:	A procedure in which 1 or more parties to the trial are kept unaware of the intervention assignment in order to reduce the risk of biased study outcomes. The level of blinding is maintained throughout the conduct of the trial, and only when the data are cleaned to an acceptable level of quality will appropriate personnel be unblinded or when required in case of a serious adverse event In an observer-blind study, the participant, the site, and Sponsor personnel involved in the clinical evaluation of the participants are blinded while other study personnel may be aware of the treatment assignment.
Certified copy:	A copy (irrespective of the type of media used) of the original record that has been verified (ie, by a dated signature or by generation through a validated process) to have the same information, including data that describe the context, content, and structure, as the original.
Combination product:	Combination product comprises any combination of – drug – device – biological product Each drug, device and biological product included in a combination product is a constituent part.
Eligible:	Qualified for enrollment into the study based upon strict adherence to inclusion/exclusion criteria.
Enrollment:	The process of registering a participant into a clinical study by assigning participant identification number after signing the informed consent form.

Essential documents:	Documents which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced.
Evaluable:	Meeting all eligibility criteria, complying with the procedures defined in the protocol, and, therefore, included in the per protocol analysis.
First act of recruitment:	The study start date is the date on which the clinical study will be open for recruitment of participants and the first participant will sign the informed consent form.
GSK Vaccines Institute for Global Health (GVGH):	A GSK-owned company, part of the GSK Global Health Program, committed to develop vaccines for major neglected diseases of impoverished communities.
Intervention:	Term used throughout the clinical study to denote a set of investigational product(s) or marketed product(s) or placebo intended to be administered to a participant.
Intervention number:	A number identifying an intervention to a participant, according to intervention allocation.
Invasive medical device:	A device which, in whole or in part, penetrates inside the body, either through a body orifice or through the surface of the body.
Investigational vaccine/product:	A pharmaceutical form of an active ingredient being tested in a clinical trial, including a product with a marketing authorization when used in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use. Synonym: Investigational Medicinal Product
Investigator:	A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the Investigator is the responsible leader of the team and may be called the Principal Investigator. The Investigator can delegate trial-related duties and functions conducted at the trial site to qualified individual or party to perform those trial-related duties and functions.
Medical device deficiency:	A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Device deficiencies include malfunctions, use errors and information supplied by the manufacturer.

Participant:	Term used throughout the protocol to denote an individual who has been contacted to participate or who participates in the clinical study as a recipient of the study intervention (vaccine(s)/product(s)/control). Synonym: subject
Participant number:	A unique identification number assigned to each participant who consents to participate in the study.
Primary completion date:	The date that the final participant was examined or received an intervention for the purpose of final collection of data for all primary outcomes, whether the clinical trial was concluded according to the prespecified protocol or was terminated.
Protocol amendment:	The ICH defines a protocol amendment as: 'A written description of a change(s) to or formal clarification of a protocol.' GSK further details this to include a change to an approved protocol that affects the safety of participants, scope of the investigation, study design, or scientific integrity of the study.
Randomization:	Process of random attribution of intervention to participants to reduce selection bias.
Remote visit:	This term refers to the visit conducted in the place other than the study site.
Safety Review Team:	This team lead by safety comprises of core representatives from GSK Global Safety, clinical, epidemiology, regulatory, and statistics departments, who are also part of the study team. For this study, the team is responsible for reviewing observed safety concerns based on blinded safety data.
Solicited event:	Events to be recorded as endpoints in the clinical study. The presence/occurrence/intensity of these events is actively solicited from the participant or an observer during a specified follow-up period following study intervention administration.
Source data:	All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).
Source documents:	Original legible documents, data, and records (eg, hospital records, clinical and office charts, laboratory notes, memoranda, participants' diaries or evaluation checklists, pharmacy dispensing records, recorded data

	from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, participant files, and records kept at the pharmacy, laboratories and at medico-technical departments involved in the clinical trial).
Study intervention:	Any investigational or marketed product(s) or placebo intended to be administered to a participant during the study.
Study monitor:	An individual assigned by the Sponsor and responsible for assuring proper conduct of clinical studies at 1 or more investigational sites.
Unsolicited adverse event:	Any AE reported in addition to those solicited during the clinical study. Also, any 'solicited' symptom with onset outside the specified period of follow-up for solicited symptoms will be reported as an unsolicited adverse event.

Appendix 2 Regulatory, Ethical, and Study Oversight Considerations

Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines.
  - Applicable ICH GCP Guidelines.
  - Applicable laws and regulations.
- The protocol, protocol amendments, informed consent form (ICF), IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC and regulatory authority approval, when applicable, before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to participants.
- The Investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
  - Providing oversight of the conduct of the study at the study center and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.
- After reading the protocol, each Investigator will sign the protocol signature page and send a copy of the signed page to the Sponsor or representative (Appendix 9). The study will not start at any study center at which the Investigator has not signed the protocol.

Adequate Resources

The Investigator is responsible for supervising any individual or party to whom the Investigator delegates study-related duties and functions conducted at the study center.

If the Investigator/institution retains the services of any individual or party to perform study-related duties and functions, the Investigator/institution should ensure this individual, or party is qualified to perform those study-related duties and functions and

should implement procedures to ensure the integrity of the study-related duties and functions performed and any data generated.

Financial Disclosure

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

Informed Consent Process

- The Investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was entered in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

For participants who are rescreened, participants are required to sign a new ICF, only if there are changes to the original ICF. If there are no changes to the original ICF, participants should confirm that they still agree to be part of the study. This information should be captured in the participant source document.

Data Protection

The Sponsor must keep coded data from clinical studies for a minimum of 30 years after the end of the study to ensure the validity of the research. This will also be the case if a participant stopped study participation prematurely. The Sponsor will also keep coded data, where needed because of legal action or an investigation involving the Sponsor.

The contract between Sponsor and study sites specifies responsibilities of the parties related data protection, including handling of data security breaches and respective communication and cooperation of the parties.

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access. Sponsor or Sponsor's delegate are contractually bound to protect participant coded data. GSK will protect participant coded data and will only share it as described in the ICF.

Participants will be assigned a unique identifier by the Sponsor or Sponsor's delegate. Any participant records or datasets transferred to the Sponsor or Sponsor's delegate will contain only the identifier. Name and any other information which would identify the participant will not be transferred.

The participants must be informed that:

- Their personal study-related data will be used by the Sponsor in accordance with local data protection law.
- Their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- Sponsor or Sponsor's delegate will ensure protection of the personal data of the Investigator and site staff which is collected within the framework of and for the purpose of the study, in accordance with the Data Privacy Notice that will be sent to the site staff.

The participants must be notified about their rights regarding the use of their personal data in accordance with the data privacy section of the ICF.

Administrative Structure

The details of administrative structure are provided in Table 16.

Table 16 Study Administrative Structure

Function	Responsible Organization
Clinical Supply Management, Quality Assurance Auditing	GSK
Laboratory Assessments	GSK
Randomization, Blinding, unblinding	IQVIA
Study Operations Management, Medical Monitoring, Study Master File	IQVIA
Biostatistics, Medical Writing	IQVIA

Medical Monitor

Refer to Study Reference Manual

Dissemination of Clinical Study Data

The key design elements of this protocol and results summaries will be posted on www.ClinicalTrials.gov, https://pactr.samrc.ac.za, and/or GSK Clinical Study Register in compliance with applicable regulations/GSK policy. GSK will aim to register protocols summaries prior to study start and target results summaries submission within 12 months of primary/study completion date. Where external regulations require earlier disclosure, GSK will follow those timelines.

Where required by regulation, summaries will also be posted on applicable national or regional clinical study registers.

Where required by applicable regulatory requirements, an Investigator signatory will be identified for the approval of the study report, and provided reasonable access to statistical tables, figures, and relevant reports. GSK will also provide the Investigator with the full summary of the study results. The Investigator is encouraged to share the summary results with the study participants, as appropriate.

Sponsor or Sponsor's delegate will provide the Investigator with the randomization codes for their site only after completion of the full statistical analysis.

GSK intends to make anonymized patient-level data from this study available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient care. This helps ensure the data provided by study participants are used to maximum effect in the creation of knowledge and understanding.

Data Quality Assurance

The Investigator should maintain a record of the location(s) of their respective essential documents, including source documents (refer to Appendix 1 for definitions of essential and source documents). The document storage system used during the study and for archiving (irrespective of the type of media used) should provide for document identification, version history, search, and retrieval.

Essential study documents may be added or removed where justified (in advance of study initiation) based on their importance and relevance to the study. When a copy is used to replace an original document (eg, source documents, eCRF), the copy should fulfill the requirements for certified copies (refer to Appendix 1 for the definition of a certified copy).

All participant data related to the study will be recorded on printed or eCRF unless transmitted to GSK/IQVIA electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.

The Investigator must maintain adequate and accurate source documents and study records that include all pertinent observations on each of the site's study participants (refer to Appendix 1 for the definition of source documents) that supports information entered in the eCRF.

The Investigator must permit study-related monitoring, audits, IRB review, and regulatory agency inspections and provide direct access to source documents or certified copies for such review and inspection.

IQVIA is responsible for the data management of this study including quality checking of the source data (refer to Appendix 1 for the definition of source data).

Study monitors will perform ongoing source data verification to confirm that data entered in the eCRF by authorized site personnel are attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data must be traceable, not obscure the original entry, and be fully explained if necessary (eg, via an audit trail). The safety and rights of participants must be protected, and the study conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Quality tolerance limits will be predefined to identify systematic issues that can impact participant safety and/or the reliability of study results.

Study records and source documents pertaining to the conduct of this study, including signed ICFs, must be retained by the Investigator for 25 years from issuance of the final CSR/equivalent summary unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of GSK. No records may be transferred to another location or party without written notification to GSK.

Source Documents

Source documents provide evidence to establish the existence of the participant and substantiate the integrity of collected data. The Investigator should maintain a record of the location(s) of their source documents.

Data transcribed into the eCRF from source documents must be consistent with those source documents; any discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

The Sponsor or designee will perform monitoring to confirm that data entered in the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the

study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Definitions of what constitutes source data and documents can be found in Appendix 1.

Study and Study Center Closure

The first act of recruitment is the date of the first participant enrollment and is considered the study start date.

GSK/IQVIA reserves the right to close the study center or terminate the study at any time for any reason. Study centers will be closed upon study completion. A study center is considered closed when all required documents and study supplies have been collected and a study center closure visit has been performed.

The Investigator may initiate study center closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study center may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB or local health authorities, GSK's procedures, or GCP guidelines
- Inadequate recruitment of participants by the Investigator
- Discontinuation of further study intervention development
- Total number of participants included earlier than expected

If the study is prematurely terminated or suspended, GSK/IQVIA shall promptly inform the investigators, the IRBs, and the regulatory authorities of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participants and should assure appropriate participant therapy and/or follow-up.

Publication Policy

GSK aims to submit for publication the results of the study in searchable, peer reviewed scientific literature within 18 months from LSLV studies and follows authorship and other guidance from the International Committee of Medical Journal Editors.

Appendix 3 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or participant, temporally associated with the use of study treatment, whether or not considered related to the study treatment. Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study treatment.

Events <u>Meeting</u> the AE Definition
• Significant or unexpected worsening or exacerbation of the condition/indication under study. • Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, electrocardiogram, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug, disease or other interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • Signs or symptoms temporally associated with administration of the study intervention. • Signs, symptoms that require medical attention (eg, hospital stays, physician visits and emergency room visits). • Significant failure of an expected pharmacologic or biological action. • Pre- or post- intervention events that occur as a result of protocol-mandated procedures (ie, invasive procedures, modification of participant's previous therapeutic regimen). • The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition. • Pre-existing conditions or signs and/or symptoms present in a participant before the first dose of study intervention. These events will be recorded in the medical history section of the eCRF. • Situations in which an untoward medical occurrence did not occur (eg, social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen. • Hospitalization for elective treatment of a pre-existing condition (known or diagnosed before signing the informed consent) that did not worsen from baseline.

Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose:
a) Results in death
b) Is life-threatening The term 'life-threatening' in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c) Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d) Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e) Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy)

f) Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious.

  Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Solicited Events

Events to be recorded as endpoints in the clinical study. The presence/occurrence/intensity of these events is actively solicited from the participant or an observer during a specified follow-up period following study intervention administration.

Table 17 Solicited Events to be Collected

Solicited administration site events	Pain at administration site
	Redness at administration site
	Swelling at administration site
Solicited systemic events	Fever
	Headache
	Myalgia
	Arthralgia
	Fatigue

Participants will be instructed to measure and record the axilla temperature in the evening. If additional temperature measurements are taken at other times of the day, participants will be instructed to record the highest temperature in the pDiary card.

Unsolicited Events

Any AE reported in addition to those solicited during the clinical study. Also, any 'solicited' symptom with onset outside the specified period of follow-up for solicited symptoms will be reported as unsolicited AEs. Unsolicited events will be collected for 28 days after each study intervention administration (ie, Day 1 to Day 28, Day 57 to Day 84 and Day 169 to Day 196).

An unsolicited AEs is an AEs that was not included in a list of solicited events using a Participant pDiary. Unsolicited events must have been spontaneously communicated by a

participant who has signed the informed consent. Unsolicited AEs include both serious and non-serious AEs.

Potential unsolicited AEs may be medically attended (ie, symptoms or illnesses requiring a hospitalization, or an emergency room visit, or visit to/by a health care provider). The participants will be instructed to contact the site as soon as possible to report medically attended event(s), as well as any events that, though not medically attended, are of participant's concern. Detailed information about reported unsolicited AEs will be collected by qualified site personnel and documented in the participant's records.

Unsolicited AEs that are not medically attended or perceived as a concern by the participant will be collected during an interview with the participants and by review of available medical records at the next visit.

COVID-19 Cases

Diagnosis of COVID-19 should be made in accordance with the WHO COVID-19 Case Definitions [WHO, 2020]. Cases should be categorized as AEs (unsolicited or AEs leading to withdrawal) or SAEs, and routine procedures for recording, evaluation, follow-up, and reporting of AEs and SAEs should be followed in accordance with the time period set out in the protocol.

Assessment of Intensity

The intensity of the following solicited events will be assessed as described:

Table 18 Intensity Scales for Solicited Events

Event	Intensity grade	Parameter
Pain at administration site	0	None
	1 (Mild)	Mild: Any pain neither interfering with nor preventing normal everyday activities.
	2 (Moderate)	Moderate: Painful when limb is moved and interferes with everyday activities.
	3 (Severe)	Severe: Significant pain at rest. Prevents normal everyday activities.
Redness and swelling at administration site (Greatest surface diameter in mm)	0	<20 mm
	1 (Mild)	≥20 mm to ≤50 mm
	2 (Moderate)	>50 mm to ≤100 mm
	3 (Severe)	>100 mm
Temperature* in °C	0	<38.0°C
	1 (Mild)	≥38.0°C to <39.0°C
	2 (Moderate)	≥39.0°C to ≤40.0°C

Event	Intensity grade	Parameter
	3 (Severe)	>40.0°C
Headache	0	None
	1 (Mild)	Headache that is easily tolerated
	2 (Moderate)	Headache that interferes with normal activity
	3 (Severe)	Headache that prevents normal activity
Myalgia	0	None
	1 (Mild)	Myalgia present but does not interfere with activity
	2 (Moderate)	Myalgia that interferes with normal activity
	3 (Severe)	Myalgia that prevents normal activity
Arthralgia	0	None
	1 (Mild)	Arthralgia present but does not interfere with activity
	2 (Moderate)	Arthralgia that interferes with normal activity
	3 (Severe)	Arthralgia that prevents normal activity
Fatigue	0	Normal
	1 (Mild)	Fatigue that is easily tolerated
	2 (Moderate)	Fatigue that interferes with normal activity
	3 (Severe)	Fatigue that prevents normal activity

*Refer to the Schedule of Activities (Table 1) for the definition of fever and the preferred location for temperature measurement.

The Investigator will assess the maximum intensity that occurred over the duration of the event for all unsolicited AEs (including SAEs) recorded during the study. The assessment will be based on the Investigator's clinical judgment.

The intensity should be assigned to one of the following categories:

1 (mild)	=	An AE which is easily tolerated by the participant, causing minimal discomfort, and not interfering with everyday activities.
2 (moderate)	=	An AE which is sufficiently discomforting to interfere with normal everyday activities.
3 (severe)	=	An AE which prevents normal, everyday activities

An AE that is assessed as Grade 3 (severe) should not be confused with an SAE. Grade 3 is a category used for rating the intensity of an event; and both AEs and SAEs can be assessed as Grade 3.

Assessment of Causality

The Investigator must assess the relationship between study intervention and the occurrence of each unsolicited AE/SAE using clinical judgment. Where several different

interventions were administered, the Investigator should specify, when possible, if the unsolicited AE/SAE could be causally related to a specific intervention. When a causal relationship to a specific study intervention cannot be determined, the Investigator should indicate the unsolicited AE/SAE to be related to all interventions.

Alternative possible causes, such as the natural history of underlying disease, concomitant therapy, other risk factors, and the temporal relationship of the event to the study intervention will be considered and investigated. The Investigator will also consult the IB and/or SmPC to assist in making his/her assessment.

Causality should be assessed by the Investigator using the following question:

Is there a reasonable possibility that the unsolicited AE may have been caused by the study intervention?

YES	There is a reasonable possibility that the study intervention contributed to the AE.
NO	There is no reasonable possibility that the AE is causally related to the administration of the study intervention. There is other, more likely causes and administration of the study intervention is not suspected to have contributed to the AE.

If an event meets the criteria to be determined 'serious', additional examinations/tests will be performed by the Investigator to determine ALL possible contributing factors for each SAE.

Possible contributing factors include:

- Medical history.
- Other medication.
- Protocol required procedure.
- Other procedure not required by the protocol.
- Lack of efficacy of the study intervention, if applicable.
- An error in study intervention administration.
- Other cause (specify).

There may be situations when an SAE has occurred, and the Investigator has minimal information to include in the initial report to GSK. However, it is very important to record an assessment of causality for every event before submitting the Expedited AEs Report to GSK.

The causality assessment is 1 of the criteria used when determining regulatory reporting requirements. The Investigator may change his/her opinion of causality after receiving additional information and update the SAE information accordingly.

Assessment of Outcomes

The Investigator will assess the outcome of all unsolicited AEs (including SAEs) recorded during the study as:

- Recovered/resolved.
- Recovering/resolving.
- Not recovered/not resolved.
- Recovered with sequelae/resolved with sequelae.
- Fatal (SAEs only)

Medically Attended Visits

For each solicited and unsolicited AE the participant experiences, the participant will be asked if the participant received medical attention (defined as hospitalization, or an otherwise unscheduled visit to or from medical personnel for any reason, including emergency room visits). This information will be recorded in the in the pDiary/source documents and in the eCRF/Expedited Adverse Events Report as applicable.

Reporting, Follow-up, and Assessments of AE and/or SAE

AE and SAE Recording
All AEs and SAEs should be recorded into the appropriate section of the eCRF, irrespective of intensity or whether or not they are considered intervention-related. The participant will be instructed to contact the Investigator immediately should the participants manifest any signs or symptoms they perceive as serious. When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) relative to the event. The Investigator will then record all relevant information regarding an AE/SAE in the eCRF. The Investigator is not allowed to send photocopies of the participant's medical records to either the Sponsor or IQVIA instead of appropriately completing the eCRF. However, there may be instances when copies of medical records for certain cases are requested by the Sponsor or IQVIA. In this instance, all participant identifiers will be blinded on the copies of the medical records prior to submission to the Sponsor or IQVIA. The Investigator will attempt to establish a diagnosis pertaining to the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE/SAE and not the individual signs/symptoms.

Follow-up of AEs and SAEs
After the initial AE/SAE or any other event of interest for the study, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until the event is resolved, stabilized, or otherwise explained or the participant is lost to follow-up. Other non-serious AEs must be followed until the last contact or until the participant is lost to follow-up. **Follow-up During the Study** AEs documented at a previous visit/contact and defined as not recovered/not resolved or recovering/resolving will be reviewed at subsequent visits/contacts until the last visit/contact of the participant. If the participant dies during participation in the study or during a recognized follow-up period, IQVIA will be provided with any available post-mortem findings, including histopathology. **Follow-up After the Participant is Discharged from the Study** The Investigator will provide any new or updated relevant information on previously reported SAE to IQVIA using electronic Expedited AE Report as applicable. The Investigator is obliged to perform or

arrange for the conduct of supplemental clinical examinations/tests and/or evaluations to elucidate the nature and/or causality of the AE or SAE as fully as possible.

Updating of SAE Information After Removal of Write Access to the Participant's eCRF

When additional SAE information is received after removal of write access to the participant's eCRF, new or updated information should be recorded on the appropriate paper report, with all changes signed and dated by the Investigator.

Events Requiring Expedited Reporting to Sponsor's Delegate

- Once an Investigator becomes aware that an SAE has occurred in a study participant, the Investigator or Investigator's designee must complete information in the electronic Expedited AE Report WITHIN 24 HOURS. The report will always be completed as thoroughly as possible with all available details of the event. The report allows to specify that the event is serious or non-serious.
- Even if the Investigator does not have all information regarding an SAE, the report should still be completed within 24 hours. Once additional relevant information is received, the report should be updated WITHIN 24 HOURS. The Investigator will always provide an assessment of causality at the time of the initial report.
- The Investigator will be required to confirm the review of the SAE causality by ticking the "reviewed" box in the electronic Expedited AE Report within 72 hours of submission of the SAE.

SAE Reporting to IQVIA via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to IQVIA will be the electronic data collection tool.
- If the electronic system is unavailable for more than 24 hours, then the study center will use paper Expedited AE Report.
- The study center will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given study center, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a study center receives a report of a new SAE from a participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the study center can report this information on a paper Expedited AE Report or by phone.
- Contacts of SAE reporting can be found in the Study Reference Manual.

Appendix 4 Contraceptive Guidance and Collection of Pregnancy Information

Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with 1 of the following:
   a) Documented hysterectomy.
   b) Documented bilateral salpingectomy.
   c) Documented bilateral oophorectomy.
   Note: Documentation can come from the study center personnel's: review of the participant's medical records, medical examination, or medical history interview.
3. Postmenopausal female:
   a) A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
   b) Females on HRT and whose menopausal status is in doubt will be required to use 1 of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance

Female participants

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in the table below.

Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent[a] Failure rate of <1% per year when used consistently and correctly.
Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation • Oral. • Intravaginal. • Transdermal.
Progestogen only hormonal contraception associated with inhibition of ovulation • Oral. • Injectable.
Highly Effective Methods That Are User Independent[a]
• Implantable progestogen only hormonal contraception associated with inhibition of ovulation • Intrauterine device (IUD). • Intrauterine hormone-releasing system (IUS). • Bilateral tubal occlusion. Male partner sterilization prior to the female participant's entry into the study, and this male is the sole partner for that participant, (The information on the male sterility can come from the site personnel's review of the participant's medical records; medical examination and/or semen analysis, or medical history interview provided by her or her partner).
Vasectomized partner A vasectomized partner is a highly effective birth control method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
Sexual abstinence Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
NOTES: [a] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for subjects participating in clinical studies.

Collection of Pregnancy Information

Female Participants who Become Pregnant

- The Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the Sponsor's delegate within 24 hours of learning of a participant's pregnancy. The participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any post-study pregnancy related SAE considered reasonably related to the study treatment by the Investigator will be reported to the Sponsor as described in Section 8.3.3. While the Investigator is not obligated to actively seek this information in former participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention or be withdrawn from the study.

Appendix 5 Genetics

In Stage 1 only, genetic testing for HLA-B27 will be performed at Screening and only participants with a negative result will be allowed to participate in the study. The assay will be performed by the local site laboratory, or a laboratory designated by the site. ***In case of participant rescreening, this test should not be repeated since the result is not expected to change in the participant lifetime.***

Appendix 6 Definition of Medical Device AE, Adverse Device Effect (ADE), Serious Adverse Device Effect (SADE) and Unanticipated SADE (USADE)

Definitions of a Medical Device AE

- Medical device AE is any untoward medical occurrence, in a clinical study participant, users, or other persons, temporally associated with the use of study intervention whether considered related to a medical device or not. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medical device. This definition includes events related to the medical device or comparator and events related to the procedures involved.
- An ADE is an AE related to the use of a medical device. This definition includes any AE resulting from:
  - insufficient or inadequate instructions for use (ie, user error), or
  - any malfunction of a medical device, or
  - intentional misuse of the medical device.

Definition of Medical Device SAE, SADE and USADE

A medical device SAE is any serious adverse event that:
Led to death
Led to serious deterioration in the health of the participant, that either resulted in: • A life-threatening illness or injury. The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe. • A permanent impairment of a body structure or a body function. • Inpatient or prolonged hospitalization. Planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered an SAE. • Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.
Led to fetal distress, fetal death or a congenital abnormality or birth defect
Is a suspected transmission of any infectious agent via a medicinal product
Serious Adverse Device Effect (SADE) definition
A SADE is defined as an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event. Any device deficiency that might have led to an SAE if appropriate action had not been taken or circumstances had been less fortunate.

Unanticipated SADE (USADE) definition
An USADE (also identified as UADE in US Regulations 21 CFR 813.3), is a serious adverse device effect that by its nature, incidence, severity, or outcome has not been identified in the current version of the IB.

Recording and Reporting of Medical Device AE, ADEs, SADEs, and USADE

- Any device deficiency must be reported to Sponsor or Sponsor's delegate within 24 hours after the Investigator determines that the event meets the definition of a device deficiency.
- Refer to paper 'Medical device or combination product with device deficiency/incident report form' for details on transmission of this information to the Sponsor.
- Sponsor or Sponsor's delegate will review all device deficiencies, determine, and document in writing whether they could have led to an SAE. These device deficiencies will be reported to the regulatory authorities and IRBs/IECs as required by national regulations.
- If required or in case of any issues refer to the general safety contacts for SAE/AE reporting.

Reporting of Medical Device Deficiencies for Associated Person

- If an Associated Person (eg, spouse, caregiver, site staff etc.) experiences a device deficiency, the medical device deficiency information, and any associated AE/SAE information will be reported to GSK. The associated person will be provided with the safety reporting information and authorization to contact physician letter.
- If follow-up information is required, authorization to contact physician (or other licensed medical practitioner) must be signed to obtain consent.
- Medical device deficiencies should be reported using the medical device deficiency report form.
- Sponsor will review all device deficiencies and determine and document in writing whether they could have led to an SAE. These device deficiencies will be reported to the regulatory authorities and IRBs/IECs as required by national regulations.
- Contacts for Medical Device Deficiency reporting can be found in the medical device deficiency report form.

Appendix 7 Grading Scales for Hematology and Biochemistry Safety Laboratory Assessments

The details of grading scales are provided in Table 19 and Table 20.

Table 19 Stage 1 – Adults (Europe)

Laboratory test	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially life--threatening (Grade 4)
Creatinine – mg/dL (male)	>1.17 – 1.7	>1.7 – 2.0	>2.0 – 2.5	>2.5 or requires dialysis
Creatinine – mg/dL (female)	>0.96 – 1.7	>1.7 – 2.0	>2.0 – 2.5	>2.5 or requires dialysis
Liver Function Tests –ALT, AST increase by factor	≥1.1 – 2.5 × ULN	>2.5 – 5.0 × ULN	>5.0 – 10 × ULN	>10 × ULN
Hemoglobin (female) - g/dL	11.0 – <11.8	9.5 – <11.0	8.0 – <9.5	<8.0
Hemoglobin (female/male) change from baseline value - g/dL	Any decrease – 1.5	>1.5 – 2.0	>2.0 – 5.0	>5.0
Hemoglobin (male) - g/dL	12.5 – <12.9	10.5 – <12.5	8.5 – <10.5	<8.5
WBC Increase - cell/mm^3	>9300 – 15000	>15000 – 20000	>20000 – 25000	>25000
WBC Decrease - cell/mm^3	2500 – <3650	1500 – <2500	1000 – <1500	<1000
Platelets Decreased - cell/mm^3 (male)	125000 – <149000	100000 – <125000	25000 – <100000	<25000
Platelets Decreased – cell/mm^3 (female)	125000 – <171000	100000 – <125000	25000 – <100000	<25000
Neutrophils Decrease - cell/mm^3	1500 – <1573	1000 – <1500	500 – <1000	<500
Lymphocytes decrease cell/mm^3	750 - <1133	500 - <750	250 - <500	<250
Eosinophils Cell/mm^3	>273 - 1500	>1500 - 5000	>5000	Hypereosinophilic

Abbreviations: ALT=alanine aminotransferase; AST = aspartate aminotransferase; ULN=upper limit of normal; WBC=white blood cell

The grading scale has been adapted from the Food and Drug Administration (FDA) Guidance for Industry-Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials [US Department of Health and Human Services, 2007] and adjusted considering local reference ranges provided by the site. Parameters not included in the FDA grading scales will not be graded; their assessment will be based on laboratory reference ranges and medical judgment.

Table 20 Stage 2 – Adults (Africa)

Laboratory test	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially life-threatening (Grade 4)
Creatinine	≥1.1 – 1.3 x ULN	>1.3 – 1.8 x ULN OR Increase to 1.3 to <1.5 x participant's baseline	>1.8 – <3.5 x ULN OR Increase to 1.5 to <2.0 x participant's baseline	≥3.5 x ULN OR Increase of ≥2.0 x participant's baseline
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 – <11.4	8.5 – <9.5	6.5 – < 8.5	<6.5
Hemoglobin (male) - g/dL	10.0 – <11.4	9.0 – <10.0	7.0 – <9.0	<7.0
WBC Decrease - cell/mm^3 (male/female)	2000 – <2400	1500 – <2000	1000 – <1500	<1000
Platelets Decreased - cell/mm^3 (male/female)	100000 – <117000	50000 – <100000	25000 – <50000	<25000
Neutrophils Decrease - cell/mm^3 (male/female)	700 – <750	600 – <700	400 – <600	<400
Lymphocytes decrease cell/mm^3 (male/female)	600 – <830	500 – <600	350 – <500	<350

Abbreviations: 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 [US Department of Health and Human Services, 2017] and adjusted considering local normal ranges provided by the site. Parameters not included in the DAIDS grading scales will not be graded and their assessment will be based on laboratory normal ranges and medical judgment.

Appendix 8 Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

Amendment 1 (12 August 2022)
This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

The original protocol has been amended to include the suggestions from the Belgium site Ethics Committee, and remove exploratory tertiary endpoints related to Stage 2 blood sampling that can no longer be performed and as such are no longer applicable and to correct inconsistencies in the protocol.

Section # and Name	Description of Change	Brief Rationale
Throughout	Minor editorial and document formatting revisions	Minor, therefore, have not been summarized
Section 1.0 Protocol Synopsis, Section 3.0 Objectives and Endpoints, Section 1.3 Schedule of Activities Table 1 Schedule of Activities, Section 8.1.2 Laboratory Assays, Section 9.4.1 Primary Endpoints, Table 11 Primary Endpoints-Statistical Analyses	The primary endpoints were updated. In the Original Protocol, the reporting duration of AEs/SAEs leading to withdrawal from the study and/or withholding doses of study intervention was mentioned up to the study end (Day 1 to Day 337). This duration was updated to 28 days after third study intervention administration (Day 1 to Day 197) in Protocol Amendment 1.	To differentiate between the active follow-up duration from Day 1 to Day 197 and long-term safety follow-up duration from Day 197 to Day 337.
Section 1.0 Protocol Synopsis, Section 3.0 Objectives and Endpoints, Section 1.3 Schedule of Activities Table 1 Schedule of Activities, Section 8.1.2 Laboratory Assays, Section 9.4.1 Primary Endpoints, Section 9.4.2 Secondary Endpoints Table 12 Secondary Endpoints-Statistical Analyses	In the Protocol Amendment 1, a new secondary endpoint was added to include number of participants with AEs/SAEs leading to withdrawal from the study from 28 days after third study intervention administration (Day 197) up to Day 337.	To differentiate between the active follow-up duration from Day 1 to Day 197 and long-term safety follow-up duration from Day 197 to Day 337.
Section 1.0 Protocol Synopsis, Section 3.0 Objectives and Endpoints, Section 1.3 Schedule of Activities Table 1 Schedule of Activities, Section 8.1.2 Laboratory Assays Table 9 Laboratory Assays, Section 9.4.3 Tertiary	Tertiary endpoints were updated to reflect the subset of visits from each group instead of subset of randomly selected participants from each group. It was clarified that immunogenicity samples from different groups will be considered for different antibody components.	To maximize the number of samples to be tested for functionality of antibodies, by sampling all participants but limiting the time

Section # and Name	Description of Change	Brief Rationale
Endpoints Table 13 Tertiary Endpoints-Statistical Analyses	CCI [redacted]	points to the most relevant ones
Section 1.0 Protocol Synopsis, Section 3.0 Objectives and Endpoints, Section 1.3 Schedule of Activities Table 1 Schedule of Activities, Section 4.1.2 Stage 2, Section 8.1.1 Biological Samples Table 8 Biological Sample, Section 9.4.3 Tertiary Endpoints, Appendix 5 Genetics	Flow cytometry, cytokines and gene expression for Stage 2 have been removed. The following endpoints or information related to these endpoints were deleted: • *S.* Typhimurium-specific lymphocyte populations in randomly selected participants from each group in Africa/Stage 2 before each study intervention administration (Day 1, Day 57, and Day 169), 7 days after each study intervention administration (Day 8, Day 64, and Day 176) and 28 days after each study intervention administration (Day 29, Day 85, and Day 197) • Quantify cytokines produced following vaccination using a Luminex multiplex cytokine assay before each study intervention administration (Day 1, Day 57, and Day 169) and 7 days after each study intervention administration (Day 8, Day 64, and Day 176) • Characterize gene expression with ribonucleic acid-sequencing in all participants in Stage 2 before each study intervention administration (Day 1, Day 57, and Day 169) and 7 days after each study intervention administration (Day 8, Day 64, and Day 176)	The specified analysis is no longer feasible at the site as earlier planned
Section 1.0 Synopsis, Section 1.3 Schedule of Activities Table 1 Schedule of Activities, Section 4.1.2 Stage 2	Statement about safety follow-up call in Stage 2 was added.	To clarify that the sentinels in Stage 2 will also be followed up with a safety phone call, similar to Stage 1 participants.
Section 1.3 Schedule of Activities Table 1 Schedule of Activities, Section 4.1.2 Stage 2	Statement about 7-day post-dose sample for antibody determination was deleted.	To correct an error which was introduced in the Original Protocol.

Section # and Name	Description of Change	Brief Rationale
Section 1.3 Schedule of Assessments Table 2 Intervals Between Study Visits	The last study interval was updated from Visit 9 (Day 197) → Visit 10 (Day 337) to Visit 7 (Day 169) → Visit 10 (Day 337).	For consistency and relevancy.
Section 1.3 Schedule of Activities Table 1 Schedule of Activities	Information about Home visit was added.	To clarify that a home visit may be performed in Stage 2 to assist illiterate participants in completing the diary cards and same will be included in the eCRFs.
Section 1.3 Schedule of Activities Table 1 Schedule of Activities, Section 4.1.2 Stage 2, Section 5.1 Inclusion Criteria, Section 8.6 Genetic Testing, Appendix 5 Genetics	It was clarified that HLA-B27 testing will be done in Stage 1 only.	The HLA test was added in the Original Protocol based on advice from Belgian authorities. This is removed for Stage 2 now due to unavailability of HLA-B27 test in Malawi and based on the feedback from Malawi PI that genetic testing is not favored by Malawi EC.
Section 1.1 Synopsis, Section 4.1.2 Stage 2	It was clarified that, if the participants have any complaints, they will be invited to the study site for an evaluation of the possible 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.	To provide further details and ensure that holding rules are applied promptly, if needed.
Section 4.1.2 Stage 2 Table 4 Study groups, Intervention, and Blinding	It was clarified that the Sponsor representatives are unblinded after Visit 9 are completed for all subjects.	For clarity
Section 4.4 End of Study Definition	The end of study information (in case where the end of study would be the date of last testing results revealed) was updated to be achieved no later than 8 months after last subject last visit instead of 6 months after third study intervention administration.	To adhere to the applicable guidelines, since these guidelines consider last subject last visit as the criteria for the end of study
Section 6.0 Study Intervention	The title was updated from Study Intervention to Study Intervention and Concomitant	To reflect that this section also includes

Section # and Name	Description of Change	Brief Rationale
and Concomitant Therapy	Therapy.	information about concomitant medications
Section 6.1 Study Intervention(s) Administered Table 7 Study Interventions Administered (Comparator and Control Vaccines)	The presentation for Saline was updated to “ampoule” from “vial”	To rectify an earlier error
Section 6.3.3.1 Emergency Unblinding	Sponsor helpdesk contact is removed, because CRO’s (IQVIA) randomization system will be used in the study.	To facilitate prompt access by the Investigator in case emergency unblinding is required
Section 8.6 Genetic Testing	It was clarified that based on advice from Belgian CA (FAHMP), to minimize any risk of autoimmune reactions, and spondyloses specifically, blood samples collected for safety during Screening in Stage 1 will undergo sampling for HLA-B27 genetic marker and only prospective participants who are found to be negative for HLA-B27 will be included in the study.	Rationale added for rationale for including only participants negative for HLA B27, in Stage 1
Section 10.0 references	New references have been added.	To provide the background for newly added information in the document
Appendix 2 Regulatory, Ethical, and Study Oversight Considerations	It was added that the Sponsor must keep coded data from clinical studies for a minimum of 30 years after the end of the study to ensure the validity of the research. This will also be the case if a participant stopped study participation prematurely. The Sponsor will also keep coded data, where needed because of legal action or an investigation involving the Sponsor.	Based on the request for Belgian site Ethics Committee
Throughout	Minor editorial and document formatting revisions	To improve the quality of the document

Appendix 9 Signature of Investigator

PROTOCOL TITLE: 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

PROTOCOL NO: 216152 (INTS-GMMA GVGH-002) (H08_01TP)

VERSION: Protocol Amendment 2 Final

This protocol is a confidential communication of Sponsor. I confirm that I have read this protocol, I understand it, and I will work according to this protocol. I will also work consistently with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices and the applicable laws and regulations. Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior written approval from the Sponsor.

Instructions to the Investigator: Please SIGN and DATE this signature page. PRINT your name, title, and the name of the study center in which the study will be conducted. Return the signed copy to IQVIA.

I have read this protocol in its entirety and agree to conduct the study accordingly:

Signature of Investigator: _____ Date: _____

Printed Name: _____

Investigator Title: _____

Name/Address of Center: _____

_____

_____

Signature Page for 216152 TMF-16201956 v1.0

Reason for signing: Approved	Name: PPD Role: Approver Date of signature: 09-Jun-2023 14:09:40 GMT+0000

Signature Page for TMF-16201956 v1.0