Protocol Amendment 2

Study ID: 205480

Official Title of Study: A Phase 1, observer-blind, randomised, controlled, single-centre study to evaluate the safety, reactogenicity, and immune responses to an adjuvanted and non-adjuvanted conjugate vaccine against Salmonella Typhi and Salmonella Paratyphi A in healthy adults 18 to 50 years of age in Europe

NCT number: NCT05613205

Date of Document: 25-Aug-2023

CLINICAL STUDY PROTOCOL

SPONSOR:
GLAXOSMITHKLINE BIOLOGICALS SA (GSK)
RUE DE L'INSTITUT 89,
1330 RIXENSART, BELGIUM

Primary study intervention and number	• Vi-CRM_{197}+O:2-CRM_{197}, Typhoid and Paratyphoid A conjugate vaccine (Bivalent) (GSK3536867A) • ADJ+Vi-CRM_{197}+O:2-CRM_{197}, Adjuvanted Typhoid and Paratyphoid A conjugate vaccine (Bivalent)
Other study interventions	• Typhoid Vi polysaccharide vaccine (TYPHIM VI) • CCI [redacted]
eTrack study number and abbreviated title	205480 (TYPH-PARATYPH A CONJ VI-CRM O2-CRM GVGH-001 (H02_01TP))
EudraCT number	2021-002029-19
Date of protocol	Final: 23 August 2022
Date of protocol amendment	Amendment 1 Final: 25 May 2023 Amendment 2 Final: 21 August 2023
Title	A Phase 1, observer-blind, randomised, controlled, single-centre study to evaluate the safety, reactogenicity, and immune responses to an adjuvanted and non-adjuvanted conjugate vaccine against *Salmonella* Typhi and *Salmonella* Paratyphi A in healthy adults 18 to 50 years of age in Europe
Brief title	Safety and immunogenicity of a novel conjugate vaccine against *Salmonella* Typhi and *Salmonella* Paratyphi A in healthy adults

Based on GlaxoSmithKline Biologicals SA Protocol WS v17.1

Protocol Amendment 2 Sponsor Signatory Approval

eTrack study number and abbreviated title	205480 (TYPH-PARATYPH A CONJ VI-CRM O2-CRM GVGH-001 (H02_01TP))
EudraCT number	2021-002029-19
Date of protocol	Final: 23 August 2022
Date of protocol amendment	Amendment 1 Final: 25 May 2023 Amendment 2 Final: 21 August 2023
Title	A Phase 1, observer-blind, randomised, controlled, single-centre study to evaluate the safety, reactogenicity, and immune responses to an adjuvanted and non-adjuvanted conjugate vaccine against *Salmonella* Typhi and *Salmonella* Paratyphi A in healthy adults 18 to 50 years of age in Europe
Sponsor signatory	Ashwani Kumar Arora, GVGH Head of Clinical Development & Regulatory Affairs
Signature	_____
Date	_____

Note: Not applicable if an alternative signature process (e.g., electronic signature or email approval) is used to get the Sponsor approval

Protocol Amendment 2 Investigator Agreement

I agree:

- To conduct the study in compliance with this protocol, any future protocol amendments, or protocol administrative changes, with the terms of the clinical trial agreement and with any other study conduct procedures and/or study conduct documents provided by GlaxoSmithKline (GSK) Biologicals SA.
- To assume responsibility for the proper conduct of the study at this site.
- That I am aware of, and will comply with, 'Good Clinical Practice' (GCP) and all applicable regulatory requirements.
- That I will comply with the terms of the site agreement.
- To ensure that all persons assisting me with the study are adequately informed about the GSK study intervention and other study-related duties and functions as described in the protocol.
- To supervise any individual or party to whom I have delegated trial-related duties and functions conducted at the trial site.
- To ensure that any individual or party to whom I have delegated trial-related duties and functions conducted at the trial site are qualified to perform those trial-related duties and functions.
- To ensure that vaccine dilution and possibly necessary labelling of clinical study materials at the study site will be performed according to GSK Biologicals instructions only by trained site staff with appropriate qualifications as required by local laws and regulations.
- To acquire the reference ranges for laboratory tests performed locally and, if required by local regulations, obtain the laboratory's current certification or Quality Assurance procedure manual.
- To ensure that no clinical samples (including serum samples) are retained onsite or elsewhere without the approval of GSK and the express written informed consent of the participant and/or the participant's legally acceptable representative.
- To perform no biological assays on the clinical samples other than those described in the protocol or its amendment(s).
- To co-operate with representative(s) of GSK in the monitoring process of the study and in resolution of queries about the data.
- To have control of all essential documents and records generated under my responsibility before, during, and after the trial.
- That I have been informed that certain regulatory authorities require the Sponsor to obtain and supply, as necessary, details about the Investigator's ownership interest in the Sponsor or the investigational intervention(s), and more generally about his/her financial ties with the Sponsor. GSK will use and disclose the information solely for the purpose of complying with regulatory requirements.

Hence, I:

- Agree to supply GSK with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children).
- Agree to promptly update this information if any relevant changes occur during the study and for 1 year following completion of the study.
- Agree that GSK may disclose any information about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK with an updated Curriculum Vitae and all other documents required by regulatory agencies for this study.

eTrack study number and abbreviated title	205480 (TYPH-PARATYPH A CONJ VI-CRM O2-CRM GVGH-001 (H02_01TP))
EudraCT number	2021-002029-19
Date of protocol	Final: 23 August 2022
Date of protocol amendment	Amendment 1 Final: 25 May 2023 Amendment 2 Final: 21 August 2023
Title	A Phase 1, observer-blind, randomised, controlled, single-centre study to evaluate the safety, reactogenicity, and immune responses to an adjuvanted and non-adjuvanted conjugate vaccine against *Salmonella* Typhi and *Salmonella* Paratyphi A in healthy adults 18 to 50 years of age in Europe
Investigator name	_____
Signature	_____
Date	_____

SPONSOR INFORMATION

1. Sponsor

GlaxoSmithKline Biologicals SA (GSK),
Rue de l'Institut 89, 1330 Rixensart, Belgium.

2. Sponsor medical expert for the study

Refer to the local study contact information document.

3. Sponsor study monitor

Refer to IQVIA study contact list.

4. Sponsor study contact for reporting of a Serious Adverse Events (SAEs)

Refer to IQVIA study contact list.

5. Contact for emergency unblinding

Refer to IQVIA Study Plans.

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

Amendment 2 (21 August 2023):

This amendment is considered non-substantial based on the criteria defined in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall rationale for the current Amendment:

The main reasons for this amendment are to update the information on the IgG ELISA testing method and to add clarification regarding baseline samples for each corresponding post-vaccination laboratory evaluation in the primary endpoint table.

LIST OF MAIN CHANGES IN THE PROTOCOL AND THEIR RATIONALE:

Section # and title	Description of change	Brief rationale
Section 1 Synopsis, Section 3 (Objective and Endpoints), Table 3 (Study objectives and endpoints), Section 9.4(Statistical analyses), Sub-section 9.4.1 Primary endpoints (s), CCI [redacted]	CCI [redacted]	
	Clarification regarding the baseline for each post-vaccination laboratory estimation has been added.	This clarifies the baseline for each post vaccination laboratory estimation
Section 9.4 (Statistical analyses), Sub-section 9.4.2 Secondary endpoints (s)	"Number" has been added in the statistical analysis methods column for completeness, for the last endpoint calculating within-subject increase of at least 4-fold in Anti-O:2 IgG antibody concentrations, as measured by ELISA, per study group.	For completeness and harmonization with other statistical analysis methods.
Section 10.2 (Appendix 2: Clinical laboratory tests)	Deleted information related to VaccZyme Human anti-Vi IgG kit	As VaccZyme kit will no longer be used in the study, information regarding VaccZyme is replaced with a generalized description of an IgG ELISA assay

TABLE OF CONTENTS

PAGE

LIST OF TABLES

PAGE

LIST OF FIGURES

PAGE

1. PROTOCOL SUMMARY

1.1. Synopsis

Rationale:

A monovalent typhoid conjugate vaccine consisting of a fragmented Typhoid Vi antigen conjugated to Cross-Reacting Material 197 (fVi-CRM_{197}) was previously developed by the Novartis Vaccines Institute for Global Health (NVGH), now GSK Vaccines Institute for Global Health (GVGH). In 2013, this technology was transferred to Biological E Ltd (BioE, Hyderabad, India) who conducted several clinical studies using this formulation, which led to marketing approval as the BioE Typhoid Conjugate Vaccine (TYPHIBEV) in January 2020, by the Central Drugs Standard Control Organisation of the Government of India (MF/BIO/20/000001) and to WHO pre-qualification in Q4 2020.

A novel Typhoid and Paratyphoid A conjugate vaccine (bivalent), abbreviated hereinafter as Vi-CRM_{197}+O:2-CRM_{197}, aimed to prevent both typhoid and paratyphoid enteric fever in infants and older age groups, was developed recently by GVGH. This candidate vaccine is based on chemical conjugation of the Vi polysaccharide for *Salmonella* Typhi and the O:2 polysaccharide for *Salmonella* Paratyphi A, with the carrier protein *Corynebacterium diphtheriae* CRM_{197} widely used for production of several conjugate vaccines licensed worldwide. In 2013, the technology for this vaccine had been also out licensed to BioE for further development and commercialisation in certain endemic countries. GVGH is still responsible for the development of Vi-CRM_{197}+O:2-CRM_{197} to achieve proof of concept. This includes the conduct of toxicology studies and Phase 1/Phase 2 clinical studies.

The purpose of this first-time-in-human (FTIH) study is to evaluate the safety and immunogenicity profile of a low and a full dose of Vi-CRM_{197}+O:2-CRM_{197}, formulated with (ADJ+Vi-CRM_{197}+O:2-CRM_{197}) or without Aluminium adjuvant (Vi-CRM_{197}+O:2-CRM_{197}), administered in 2 doses, a priming dose and a booster dose, 24 weeks apart, in healthy adults 18 to 50 years of age in Europe. Subsequent studies are planned for endemic countries. The current study is sponsored by GSK and managed by GVGH.

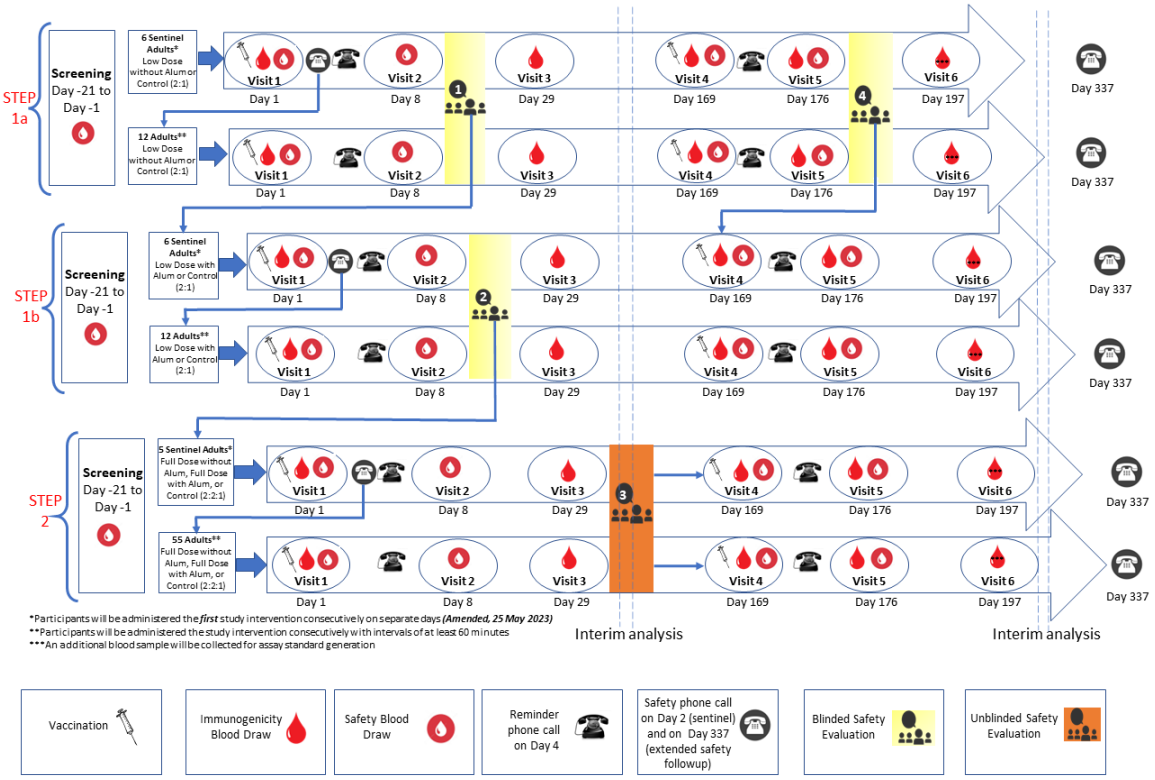
Objectives and endpoints:

Objectives	Endpoints
Primary	
Evaluate the safety profile of the Vi-CRM_{197}+O:2-CRM_{197} vaccine, with and without adjuvant.	• Percentage of participants with solicited administration-site events during 7 days after each vaccination, on the days of vaccination and the 6 subsequent days (study intervention administered on Day 1 and Day 169), per study group. • Percentage of participants with solicited systemic events during 7 days after each vaccination, on the days of vaccination and the 6 subsequent days (study intervention administered on Day 1 and Day 169), per study group. • Percentage of participants with unsolicited adverse events (AE) during 28 days after each vaccination, on the days of vaccination and 27 subsequent days (study intervention administered on Day 1 and Day 169), per study group. • Percentage of participants with any serious adverse event (SAE) from first vaccination until 28 days after second study intervention administration (Day 1 to Day 197), per study group. • Percentage of participants with AEs/SAEs leading to withdrawal from the study or withholding further study intervention administration, from first study intervention administration until 28 days after second study intervention administration (Day 1 to Day 197), per study group. • Percentage of participants with deviations from normal or baseline† values of haematological, renal, and hepatic panel test results at 7 days after each vaccination (Day 8 and Day 176), per study group.
Secondary	
Evaluate the long-term safety profile of the Vi-CRM_{197}+O:2-CRM_{197} vaccine, with and without adjuvant.	• Percentage of participants with any SAE from 28 days after second vaccination (Day 197) up to Day 337, per study group. • Percentage of participants with AEs/SAEs leading to withdrawal from the study from 28 days after second vaccination (Day 197) up to Day 337, per study group.
Evaluate the immunogenicity profile of the typhoid and paratyphoid A components of the Vi-CRM_{197}+O:2-CRM_{197} vaccine, with and without adjuvant, using enzyme-linked immunoassay (ELISA).	• Geometric mean concentration (GMC) of anti-Vi antigen Immunoglobulin G (IgG) antibody concentrations as measured by ELISA, before first vaccination (Day 1), 28 days after first vaccination (Day 29), before second vaccination (Day 169), 7 days after second vaccination (Day 176), and 28 days after second vaccination (Day 197), per study group. • GMC of Anti-O:2 IgG antibody concentrations, as measured by ELISA, before first vaccination (Day 1), 28 days after first vaccination (Day 29), before second vaccination (Day 169), 7 days after second vaccination (Day 176), and 28 days after second vaccination (Day 197), per study group.

Objectives	Endpoints
Evaluate different seroresponse rates to the typhoid and paratyphoid A component of the Vi-CRM_{197}+O:2-CRM_{197} vaccine, with and without adjuvant.	• Percentage of participants achieving anti-Vi antigen IgG antibody concentrations ≥4.3 µg/mL*, as measured by ELISA, before first vaccination (Day 1), 28 days after first vaccination (Day 29), before second vaccination (Day 169), 7 days after second vaccination (Day 176), and 28 days after second vaccination (Day 197), per study group. • Percentage of participants achieving anti-Vi antigen IgG antibody concentrations ≥2.0 µg/mL**, as measured by ELISA, before first vaccination (Day 1), 28 days after first vaccination (Day 29), before second vaccination (Day 169), 7 days after second vaccination (Day 176), and 28 days after second vaccination (Day 197), per study group. • Percentage of participants achieving at least 4-fold*** increase in Anti-O:2 IgG antibody concentrations, as measured by ELISA, at 28 days after first vaccination (Day 29), before second vaccination (Day 169), 7 days after second vaccination (Day 176), and 28 days after second vaccination (Day 197) compared to first vaccination baseline (Day 1), per study group. *This threshold, estimated to be protective against typhoid fever, was established in previous studies [Szu, 2013; WHO, 2020] and then used in the registration of Vi conjugated vaccine in India. **This threshold, estimated to be protective against typhoid fever, was defined as a short-term threshold in a previous study [Szu, 2014]. ***This threshold is chosen as a clinically meaningful threshold that, in the absence of an established correlate of protection, could allow quantitative decisions to be made for further development of this component of the vaccine.
CCI [redacted]	

†Baseline for post-first vaccination at Day 8 is Day 1 (can also be screening blood draw, if performed within 3 days of first vaccination), and baseline for post-second vaccination at Day 176 is Day 169.

1.2. Schema


STEP 1a
Screening Day -21 to Day -1
6 Sentinel Adults* Low Dose without Alum or Control (2:1)
12 Adults** Low Dose without Alum or Control (2:1)
STEP 1b
6 Sentinel Adults* Low Dose with Alum or Control (2:1)
12 Adults** Low Dose with Alum or Control (2:1)
STEP 2
5 Sentinel Adults* Full Dose without Alum, Full Dose with Alum, or Control (2:2:1)
55 Adults** Full Dose without Alum, Full Dose with Alum, or Control (2:2:1)
Visit 1 Day 1
Visit 2 Day 8
Visit 3 Day 29
Visit 4 Day 169
Visit 5 Day 176
Visit 6 Day 197
Day 337
1
2
3
4
*Participants will be administered the first study intervention consecutively on separate days (Amended, 25 May 2023)
**Participants will be administered the study intervention consecutively with intervals of at least 60 minutes
***An additional blood sample will be collected for assay standard generation
Interim analysis
Interim analysis
Vaccination
Immunogenicity Blood Draw
Safety Blood Draw
Reminder phone call on Day 4
Safety phone call on Day 2 (sentinel) and on Day 337 (extended safety followup)
Blinded Safety Evaluation
Unblinded Safety Evaluation

1.3. Schedule of Activities (SoA)

Table 1 Schedule of Activities (SoA)

Type of contact	Screening period	Visit 1 *(Priming Vacc)*	Sentinel participant safety phone contact	Reminder phone contact 1	Visit 2	Visit 3	Visit 4 *(Booster Vacc)*	Reminder phone contact 2	Visit 5	Visit 6	Follow-up safety phone contact
Time points	**Day -21 to Day -1**	**Day 1**	**Day 2**	**Day 4**	**Day 8**	**Day 29**	**Day 169**	**Day 172**	**Day 176**	**Day 197**	**Day 337**
Informed consent (Section 10.1.3)	●										
Check of inclusion/exclusion criteria (Sections 5.1 and 5.2)	●	●					●				
Collection of demographic data (Section 8.2.1.1)	●										
Medical history (Section 8.2.1.2)	●										
Physical examination (including vital sign assessment and body temperature measurement) (Section 8.2.1.3)	●	●					●				
Symptom-directed physical examination (Section 8.2.1.3)					○	○			○	○	
Height and weight measurement (Section 8.2.1.3)	●										
Randomisation (Section 6.3)		●									
Study intervention											
Check of contraindications and warnings, and precautions to vaccination (Sections 7.1.1 and 8.2.1.6)	○	○					○				
Check of criteria for temporary delay for enrolment and/or study intervention administration (Section 5.5)	○	○					○				

Type of contact	Screening period	Visit 1 *(Priming Vacc)*	Sentinel participant safety phone contact	Reminder phone contact 1	Visit 2	Visit 3	Visit 4 *(Booster Vacc)*	Reminder phone contact 2	Visit 5	Visit 6	Follow-up safety phone contact
Time points	**Day -21 to Day -1**	**Day 1**	**Day 2**	**Day 4**	**Day 8**	**Day 29**	**Day 169**	**Day 172**	**Day 176**	**Day 197**	**Day 337**
Pregnancy test (Section 8.2.1.4)	●[1]	●[2]					●[2]				
Study intervention allocation (Section 6.3)		●									
Administration of the Vi-CRM197+O:2-CRM_{197} vaccine (low or full dose, with or without Alum), or control		●[3]					●[4]				
Laboratory assessments											
Blood sampling for antibody determination (~10 mL)		●[5]				●	●[5]		●	●	
Blood collection for assay standard generation (~15 mL)										●	
Blood sampling for safety Screening laboratory assays (refer to Table 17) (~20 mL)	●										
Blood sampling for safety laboratory assays (haematological and clinical chemistry analyses) (~13.5 mL)		●[5,6]			●		●[5]		●		
Safety assessments											
Recording of any concomitant medication/vaccination (Section 6.8)	●	●	●[7]		●	●	●		●	●	
Recording of any intercurrent medical conditions (Section 9.3.1)		●	●[7]		●	●	●		●	●	

Type of contact	Screening period	Visit 1 *(Priming Vacc)*	Sentinel participant safety phone contact	Reminder phone contact 1	Visit 2	Visit 3	Visit 4 *(Booster Vacc)*	Reminder phone contact 2	Visit 5	Visit 6	Follow-up safety phone contact
Time points	**Day -21 to Day -1**	**Day 1**	**Day 2**	**Day 4**	**Day 8**	**Day 29**	**Day 169**	**Day 172**	**Day 176**	**Day 197**	**Day 337**
Recording of solicited events in the participant paper Diary (Days 1-7 post-vaccination) (Section 10.3.8)		○					○				
Recording of unsolicited AEs in the source document (Days 1-28 post-vaccination) (Section 10.3.8)		○	○[7]		○		○		○		
Transcription of unsolicited AEs in the eCRF by the Investigator or delegate		●	●		●	●	●		●	●	
Safety surveillance (including vital sign assessment and body temperature measurement) (60 minutes post-vaccination) (Section 10.3.8)		●					●				
Reporting of SAEs (Section 10.3.8)		●	●[7]		●	●	●		●	●	●
Reporting of SAEs related to study participation or concurrent GSK medication/ vaccine	●	●	●[7]		●	●	●		●	●	●
Reporting of pregnancies and pregnancy outcomes (Section 10.3.8)		●			●	●	●		●	●	
Recording of AEs/SAEs leading to withdrawal		●			●	●	●		●	●	●
Diary cards											
Distribution of diary cards		○					○				
Phone call for diary card completion reminder (Section 10.3.8)				●				●			

Type of contact	Screening period	Visit 1 *(Priming Vacc)*	Sentinel participant safety phone contact	Reminder phone contact 1	Visit 2	Visit 3	Visit 4 *(Booster Vacc)*	Reminder phone contact 2	Visit 5	Visit 6	Follow-up safety phone contact
Time points	**Day -21 to Day -1**	**Day 1**	**Day 2**	**Day 4**	**Day 8**	**Day 29**	**Day 169**	**Day 172**	**Day 176**	**Day 197**	**Day 337**
Safety phone call to sentinel participants 1-day post-vaccination to check for any holding rule events or SAEs (Section 8.2.2)			●								
Diary card transcription in the eCRF by Investigator or delegate					●				●		
Return of diary cards					●				●		
Participant study conclusion (Section 4.4)											●

[1]A blood pregnancy test will be performed.
[2]A urine pregnancy test will be performed.
[3]TYPHIM VI will be the control vaccination at Visit 1 (Day 1)
[4]CCI [redacted] will be the control vaccination at Visit 4 (Day 169)
[5]Blood collection will be performed prior to vaccination
[6]If a blood sample has been collected during Screening in the 3 days before the date of first vaccination, another safety blood sample does not need to be collected on Visit 1.
[7]All information needs to be verified at the site during an *ad hoc* Visit. Refer to Section 8.2.2 for details on safety monitoring.
AE=adverse event; eCRF=electronic case report form; SAE=serious adverse event; VACC=vaccination
Note: The double-line border following Day 29 and Day 197 indicates the interim analyses, which will be performed on all data obtained up to Day 29 *(*28 days after first vaccination in Step 2) and Day 197 (28 days after second vaccination in Step 2*)*. The double-line borders following Day 337 indicate the final analysis in these participants, which will be performed on all data obtained up to Day 337.
● is used to indicate a study procedure that requires documentation in the individual eCRF.
○ is used to indicate a study procedure that does not require documentation in the individual eCRF.

Table 2 Intervals between study visits

Interval	Planned Visit interval	Allowed interval range
Visit 1 → Visit 2	7 days	7 days – 10 days
Visit 1 → Visit 3	28 days	28 days – 33 days
Visit 1 → Visit 4	168 days	158 days – 178 days
Visit 4 → Visit 5	7 days	7 days – 10 days
Visit 4 → Reminder phone call 2	3 days	1 day – 3 days
Visit 4 → Visit 6	28 days	28 days – 33 days
Visit 4 → Follow-up safety phone contact	168 days	154 days – 182 days

2. INTRODUCTION

2.1. Study rationale

A monovalent typhoid conjugate vaccine consisting of a fragmented Typhoid Vi antigen conjugated to Cross-Reacting Material 197 (fVi-CRM_{197}) was previously developed by the Novartis Vaccines Institute for Global Health (NVGH), now GSK Vaccines Institute for Global Health (GVGH). In 2013, this technology was transferred to Biological E Ltd (BioE, Hyderabad, India) who conducted several clinical studies using this formulation, which led to marketing approval as the BioE Typhoid Conjugate Vaccine (TYPHIBEV) in January 2020, by the Central Drugs Standard Control Organisation of the Government of India (MF/BIO/20/000001) and to WHO pre-qualification in Q4 2020.

A novel Typhoid and Paratyphoid A conjugate vaccine (bivalent), abbreviated hereinafter as Vi-CRM_{197}+O:2-CRM_{197}, aimed to prevent both typhoid and paratyphoid enteric fever in infants and older age groups, was developed recently by GVGH. This candidate vaccine is based on chemical conjugation of the Vi polysaccharide for *Salmonella* Typhi and the O:2 polysaccharide for *Salmonella* Paratyphi A, with the carrier protein *Corynebacterium diphtheriae* CRM_{197} widely used for production of several conjugate vaccines licensed worldwide. In 2013, the technology for this vaccine had been also out licensed to BioE for further development and commercialisation in certain endemic countries. GVGH is still responsible for the development of Vi-CRM_{197}+O:2-CRM_{197} to achieve proof of concept. This includes the conduct of toxicology studies and Phase 1/Phase 2 clinical studies.

The purpose of this first-time-in-human (FTIH) study is to evaluate the safety and immunogenicity profile of a low and a full dose of Vi-CRM_{197}+O:2-CRM_{197}, formulated with (ADJ+Vi-CRM_{197}+O:2-CRM_{197}) or without Aluminium adjuvant (Vi-CRM_{197}+O:2-CRM_{197}), administered in 2 doses, a priming dose and a booster dose, 24 weeks apart, in healthy adults 18 to 50 years of age in Europe. Subsequent studies are planned for endemic countries. The current study is sponsored by GSK and managed by GVGH.

2.2. Background

Despite improved sociosanitary conditions in the last decade, enteric fever remains a major cause of disability and death, with billions of people likely to be exposed to *Salmonella enterica* pathogens causing typhoid and paratyphoid fever. In the 2017 Global Burden of Disease (GBD) study, approximately 14.3 million cases of enteric fever were reported, which caused approximately 135 900 deaths (116 800 due to typhoid fever and 19 100 due to paratyphoid fever) [GBD 2017 Typhoid and Paratyphoid Collaborators, 2019]. In 2017, paratyphoid fever was responsible for 23.7% of all cases of enteric fever, which was similar to an earlier 1990 GBD estimate of 21.3% [GBD 2017 Typhoid and Paratyphoid Collaborators, 2019]. High incidence countries for paratyphoid fever include Nepal [Zellweger, 2017], Bangladesh [Owais, 2010; Saha, 2018], Pakistan [Owais, 2010], and India [John, 2016]. Most blood cultures positive for *Salmonella* Typhi or *Salmonella* Paratyphi from clinical and laboratory records in Asian endemic countries are resistant to fluoroquinolones, with a high proportion also resistant to ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole [Barkume, 2018].

In this study, participants will be administered 2 vaccinations using a 0–6-month schedule (a priming dose and a booster dose) and a dose-escalation approach with 2 different doses (low and full), with or without adjuvant. TYPHIM VI (Typhoid Vi polysaccharide vaccine) will be used as control for the first vaccination, and [redacted] (booster immunisation vaccine against tetanus, diphtheria, and pertussis) as control for the second vaccination. Dose escalation will be performed by evaluating first a low dose formulated without adjuvant containing 5 µg of Vi-CRM_{197} (1/5 of the licensed vaccine) and 5 µg of O:2-CRM_{197} followed by an evaluation of a low dose formulated with adjuvant containing 5 µg of Vi-CRM_{197} (1/5 of the licensed vaccine) and 5 µg of O:2-CRM_{197}. Subsequently, a full dose formulated with and without adjuvant containing 25 µg of Vi-CRM_{197} (same as the licensed monovalent vaccine) and 25 µg of O:2-CRM_{197} will be evaluated. Depending on interim and final analyses results, additional studies will be planned in endemic countries for enteric fever.

Please refer to the current Investigator Brochure (IB) for information regarding preclinical studies of Vi-CRM_{197}+O:2-CRM_{197} and ADJ+Vi-CRM_{197}+O:2-CRM_{197}.

2.3. Benefit/Risk assessment

The safety and immunogenicity of the first generation monovalent Vi-CRM_{197} candidate vaccine was assessed in previous Phase 1 and 2 clinical studies in adults, children, and infants from *Salmonella* Typhi endemic and non-endemic countries [van Damme, 2011; Bhutta, 2014].

The second-generation fragmented Typhoid Vi antigen conjugated to CRM_{197} vaccine, which is the same component as in Vi-CRM_{197}+O:2-CRM_{197} without adjuvant, to be used in this study, was tested in Phase 1 (CTRI/2018/01/011500) and Phase 2/3 clinical studies (CTRI/2018/11/016419, CTRI/2019/07/020451, CTRI/2020/03/023712) sponsored by BioE. These completed studies led to licensing of the vaccine in India in January 2020 and to WHO pre-qualification in Q4-2020. There are no clinical studies with the use of the paratyphoid A component of the investigational vaccine.

Aluminium Hydroxide (Alum) is a well-known, safe, and widely used adjuvant in licensed vaccines. It has been added to the Vi-CRM_{197}+O:2-CRM_{197} vaccine to enhance the immune response to the O:2-CRM_{197} component, with the possibility that it can lead to antigen sparing and eventually achieve a single-dose licensed vaccine.

Intramuscular vaccination commonly precipitates a transient and self-limiting local inflammatory reaction. This may typically include pain at the injection site, redness, and swelling. As with all injectable vaccines, appropriate medical treatment and supervision will be readily available in case of a rare anaphylactic event following administration of the vaccine.

Blood sampling procedures planned in the study may result in bruising at the sampling site. There is also a rare possibility of bleeding, fainting, infection, or nerve injury. Safe sampling procedures will be applied by appropriately trained and qualified site staff to minimise distress and sampling errors. The amount of blood to be taken for sampling is within the locally accepted range for the study age group and is not expected to be harmful to the participant's health.

By taking part in the study, 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 its potential ability to provide clinical protection. Administration of control vaccines can also provide some benefits to the participants such as protection against tetanus, diphtheria, and pertussis CCI and prevention of typhoid fever (TYPHIM VI). Participants can gain medical advice about their health status through the medical evaluations and laboratory assessments done during the study.

Detailed information about the known and expected benefits and risks and expected AEs of Vi-CRM_{197}+O:2-CRM_{197} and ADJ+Vi-CRM_{197}+O:2-CRM_{197} can be found in the IB. Detailed information about the known and expected benefits and risks and expected AEs of CCI and TYPHIM VI can be found in the Prescribing information/Summary of Product Characteristics (SmPC).

3. OBJECTIVES AND ENDPOINTS

Table 3 Study objectives and endpoints (*Amended*, 21 August 2023)

Objectives	Endpoints
Primary	
Evaluate the safety profile of the Vi-CRM_{197}+O:2-CRM_{197} vaccine, with and without adjuvant.	• Percentage of participants with solicited administration-site events during 7 days after each vaccination, on the days of vaccination and the 6 subsequent days (study intervention administered on Day 1 and Day 169), per study group. • Percentage of participants with solicited systemic events during 7 days after each vaccination, on the days of vaccination and the 6 subsequent days (study intervention administered on Day 1 and Day 169), per study group. • Percentage of participants with unsolicited adverse events (AE) during 28 days after each vaccination, on the days of vaccination and 27 subsequent days (study intervention administered on Day 1 and Day 169), per study group. • Percentage of participants with any serious adverse event (SAE) from first vaccination until 28 days after second study intervention administration (Day 1 to Day 197), per study group. • Percentage of participants with AEs/SAEs leading to withdrawal from the study or withholding further study intervention administration, from first study intervention administration until 28 days after second study intervention administration (Day 1 to Day 197), per study group. • Percentage of participants with deviations from normal or baseline† values of haematological, renal, and hepatic panel test results at 7 days after each vaccination (Day 8 and Day 176), per study group.
Secondary	
Evaluate the long-term safety profile of the Vi-CRM_{197}+O:2-CRM_{197} vaccine, with and without adjuvant.	• Percentage of participants with any SAE from 28 days after second vaccination (Day 197) up to Day 337, per study group. • Percentage of participants with AEs/SAEs leading to withdrawal from the study from 28 days after second vaccination (Day 197) up to Day 337, per study group.
Evaluate the immunogenicity profile of the typhoid and paratyphoid A components of the Vi-CRM_{197}+O:2-CRM_{197} vaccine, with and without adjuvant, using enzyme-linked immunoassay (ELISA).	• Geometric mean concentration (GMC) of anti-Vi antigen Immunoglobulin G (IgG) antibody concentrations as measured by ELISA, before first vaccination (Day 1), 28 days after first vaccination (Day 29), before second vaccination (Day 169), 7 days after second vaccination (Day 176), and 28 days after second vaccination (Day 197), per study group. • GMC of Anti-O:2 IgG antibody concentrations, as measured by ELISA, before first vaccination (Day 1), 28 days after first vaccination (Day 29), before second vaccination (Day 169), 7 days after second vaccination

Objectives	Endpoints
	(Day 176), and 28 days after second vaccination (Day 197), per study group.
Evaluate different seroresponse rates to the typhoid and paratyphoid A component of the Vi-CRM_{197}+O:2-CRM_{197} vaccine, with and without adjuvant.	• Percentage of participants achieving anti-Vi antigen IgG antibody concentrations ≥4.3 µg/mL*, as measured by ELISA, before first vaccination (Day 1), 28 days after first vaccination (Day 29), before second vaccination (Day 169), 7 days after second vaccination (Day 176), and 28 days after second vaccination (Day 197), per study group. • Percentage of participants achieving anti-Vi antigen IgG antibody concentrations ≥2.0 µg/mL**, as measured by ELISA, before first vaccination (Day 1), 28 days after first vaccination (Day 29), before second vaccination (Day 169), 7 days after second vaccination (Day 176), and 28 days after second vaccination (Day 197), per study group. • Percentage of participants achieving at least 4-fold*** increase in Anti-O:2 IgG antibody concentrations, as measured by ELISA, at 28 days after first vaccination (Day 29), before second vaccination (Day 169), 7 days after second vaccination (Day 176), and 28 days after second vaccination (Day 197) compared to first vaccination baseline (Day 1), per study group. *This threshold, estimated to be protective against typhoid fever, was established in previous studies [Szu, 2013; WHO, 2020] and then used in the registration of Vi conjugated vaccine in India. **This threshold, estimated to be protective against typhoid fever, was defined as a short-term threshold in a previous study [Szu, 2014]. ***This threshold is chosen as a clinically meaningful threshold that, in the absence of an established correlate of protection, could allow quantitative decisions to be made for further development of this component of the vaccine.
CCI [redacted]	

†Baseline for post-first vaccination at Day 8 is Day 1 (can also be screening blood draw, if performed within 3 days of first vaccination), and baseline for post-second vaccination at Day 176 is Day 169.

4. STUDY DESIGN

4.1. Overall design

This is a Phase 1 observer-blind, controlled, self-contained, randomised, single-centre, dose-escalation study with 3 Steps (Step 1a, Step 1b, and Step 2). A total of 96 participants in 7 study groups, including 17 sentinel participants, are planned to be enrolled in the study. Figure 1 shows a visual representation of the study design and Table 4 shows a description of the study intervention groups.

An electronic case report form (eCRF) and a paper Diary will be used for data collection, which will include biological sampling (blood) and safety follow-ups.

The study design, the enrolment, and the monitoring procedures will follow GSK safety standards for FTIH clinical studies (Refer to Sections 8.2.2 and 10.1.5 for details on staggered vaccination, safety monitoring, and holding rules).

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

Figure 1 Study design overview

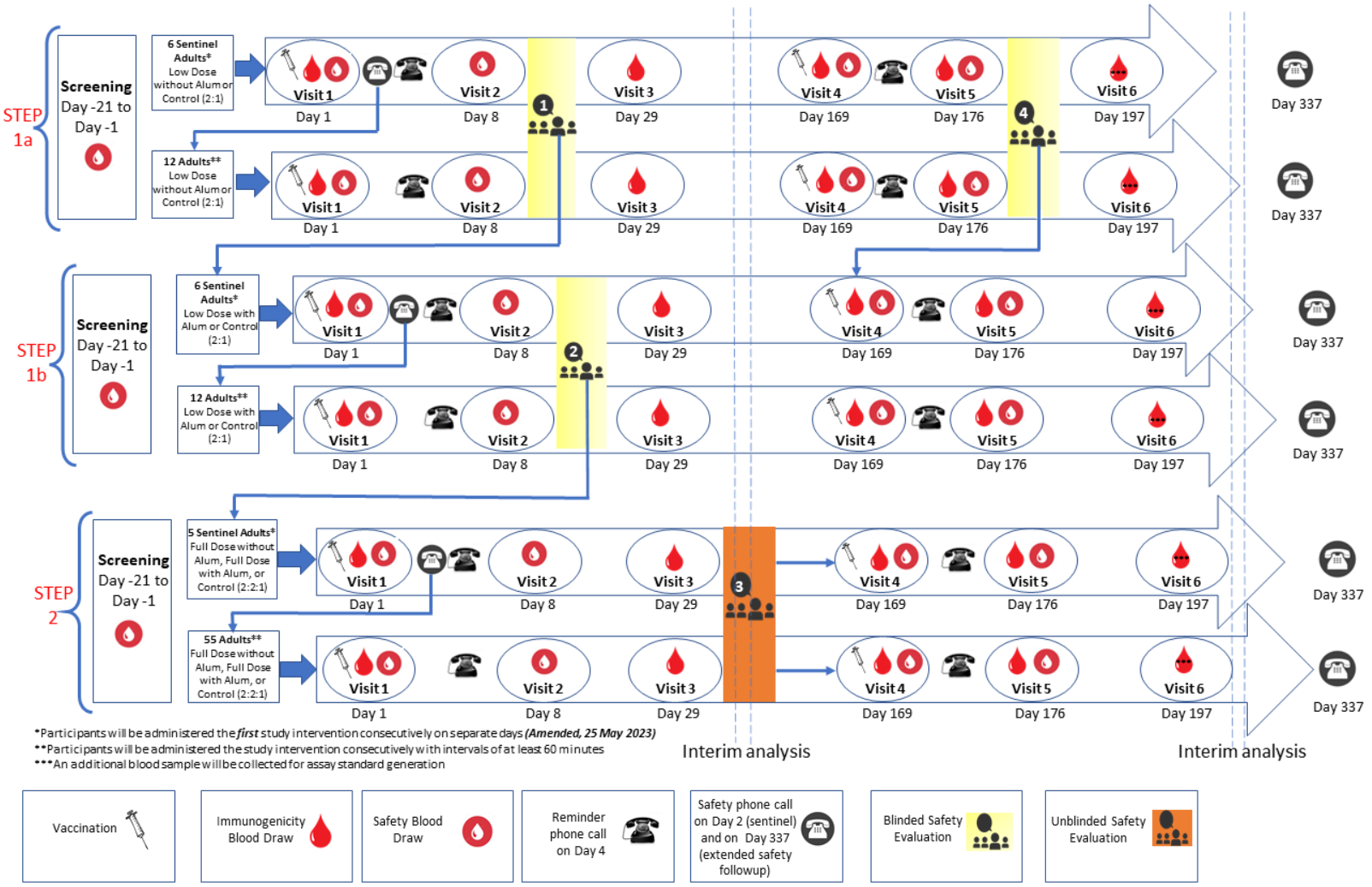


Table 4 Study groups, intervention, and blinding

Study groups	Number of participants	Age (Min-Max)	Study intervention(s)	Blinding	
				FSFV → IA 1*	IA 1* → LSLV)
Step 1a low dose without Alum	12	18 – 50 years	2 intramuscular vaccinations (Day 1 and Day 169) with low dose of Vi-CRM_{197}+O:2-CRM_{197} without Alum	Observer-blind	Single-blind*
Step 1a control	6		1 intramuscular vaccination (Day 1) with TYPHIM VI and 1 intramuscular vaccination (Day 169) with CCI		
Step 1b low dose with Alum	12		2 intramuscular vaccinations (Day 1 and Day 169) with low dose of ADJ+Vi-CRM_{197}+O:2-CRM_{197} with Alum		
Step 1b control	6		1 intramuscular vaccination (Day 1) with TYPHIM VI and 1 intramuscular vaccination (Day 169) with CCI		
Step 2 full dose without Alum	24		2 intramuscular vaccinations (Day 1 and Day 169) with full dose of Vi-CRM_{197}+O:2-CRM_{197} without Alum		
Step 2 full dose with Alum	24		2 intramuscular vaccinations (Day 1 and Day 169) with full dose of ADJ+Vi-CRM_{197}+O:2-CRM_{197} with Alum		
Step 2 control	12		1 intramuscular vaccination (Day 1) with TYHPIM VI and 1 intramuscular vaccination (Day 169) with CCI		

FSFV = first subject first visit; IA = interim analysis; LSLV = last subject last visit
*Refer to Sections 6.3.4 and 9.5.1 for additional details on change of blinding during the interim analysis

4.2. Scientific rationale for study design

4.2.1. Rationale for choice of vaccination route and schedule

Previous clinical studies (CTRI/2018/11/016419, CTRI/2019/07/020451, CTRI/2020/03/023712) with the typhoid component of the Vi-CRM_{197}+O:2-CRM_{197} vaccine have shown sufficient immunogenicity and an acceptable safety profile with a single intramuscular injection, which led to the licensing of the vaccine in India.

According to results from preclinical studies in mice [Micoli, 2012; Micoli, 2020] with each component of the Vi-CRM_{197}+O:2-CRM_{197} vaccine, 2 injections may be needed in clinical studies to achieve optimal immunogenicity of the paratyphoid A component. An interval of 6 months between 2 vaccinations is expected to boost the immune response from the second vaccination. The selected schedule is considered appropriate for this FTIH study.

4.2.2. Rationale for choice of follow-up period

No adverse events of special interest are planned to be collected in this study; the investigational vaccine does not contain any novel adjuvant and the Vi-CRM_{197} component is already registered in India with no particular safety concern observed during its development (refer to the IB). No particular safety concerns have been identified in other licensed Vi-based vaccines against typhoid fever.

A 6-month follow-up period after the first study intervention administration will allow the identification of any possible late-occurring AEs. A follow-up of 28 days after the second study intervention administration will allow collection of unsolicited AEs and any other event as indicated in Table 12. An extended 6-month safety follow-up after the second study intervention administration will collect any late-occurring SAE and AEs/SAEs leading to withdrawal or study discontinuation.

4.2.3. Rationale for choice of study population

Healthy adults in Europe have been chosen since enteric fever caused by typhoid and paratyphoid A is not endemic in this population. Therefore, it is expected that participants will not have pre-existing antibodies, which may interfere with the immunogenicity evaluation of the candidate vaccine. This study population has also been chosen on the basis of being a low-risk population for the assessment of safety of a FTIH vaccine. The age of participants selected for this study is consistent with planned clinical development of the vaccine.

4.2.4. Rationale for choice of active comparator

The safety profiles of both TYPHIM VI and CCI [redacted] are well characterised. Additionally, both comparator vaccines are not likely to be part of the routine vaccination schedule of study participants, hence, all participants may receive benefit of vaccination by participation in the study.

TYPHIM VI, which is licensed in Europe, has been chosen as a comparator, rather than the TYPHIBEV vaccine (not licensed in Europe) or any other conjugated typhoid vaccines. This is consistent with the primary objective being safety in this FTIH clinical study.

4.3. Justification for dose

The full dose for the typhoid, Vi-CRM_{197} component, to be used in this study is the same as the dose of the monovalent vaccine licensed for protection against typhoid fever among individuals aged 6 months to 45 years in 2020 in India and WHO pre-qualified in the same year. That dose was shown in a Phase 2/3 clinical study (CTRI/2018/11/016419) to be comparable in terms of safety and immunogenicity to a licensed Typhoid Vi-Tetanus Toxoid conjugate vaccine (Typbar-TCV, Bharat Biotech) when administered to healthy adults, children, and infants.

Two injections with the highest dose of the paratyphoid A, O:2-CRM_{197} component to be used in this study have shown a robust immune response in mice, rats, and rabbits. Results from a repeat-dose toxicology study in rabbits are available in the IB to confirm the safety of the highest antigen doses. There are no clinical safety data with the use of the paratyphoid A component of the vaccine in humans.

Although a 4-fold decrease in antigen was preferred from the full dose to the low dose, a 5-fold decrease has been chosen instead for reasons of practical feasibility of the volume to be administered. Fractional dosing will be used for administration of the low dose due to the lack of a commercially available diluent.

Aluminium Hydroxide (Alum) has been added to this vaccine as an adjuvant to enhance the immune response to the O:2-CRM_{197} component, with the expectation that it will lead to antigen sparing and the use of an effective single-dose vaccine in humans. Adjuvant effects have been shown in animal studies but still need to be confirmed in human studies.

4.4. End of Study definition

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

End of Study (EoS): Last Subject Last Visit (safety phone contact, Day 337).

5. STUDY POPULATION

Adherence to the inclusion and exclusion criteria specified in the protocol is essential. Deviations from these criteria are not allowed because they can jeopardise the scientific integrity, regulatory acceptability of the study or safety of the participant.

5.1. Inclusion criteria

All participants must satisfy ALL the following criteria at study entry:

- Participants who, in the opinion of the Investigator, can and will comply with the requirements of the Protocol (e.g., completion of the diary cards, return for follow-up visits).
- Written informed consent obtained from the participant prior to performance of any study specific procedure.
- Healthy participants as established by medical history, clinical examination, and Screening laboratory investigations.
- Participant satisfying Screening requirements.
- Participant seronegative for human immunodeficiency virus, hepatitis B, and hepatitis C at Screening.

- A male or female participant between, and including, 18 and 50 years of age at the time of the first study intervention administration.
- Female participants of non-childbearing potential may be enrolled in the study. Non-childbearing potential is defined as pre-menarche, current bilateral tubal ligation or occlusion, hysterectomy, bilateral ovariectomy or post-menopause. Refer to Section 10.4.1 for definitions of women of childbearing potential, menarche, and menopause.
- Female participants of childbearing potential may be enrolled in the study if the participant:
  - has practiced adequate contraception 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.

5.2. Exclusion criteria

The following criteria should be checked at the time of study entry. The potential participant MUST NOT be included in the study if ANY exclusion criterion applies:

5.2.1. Medical conditions

- Progressive, unstable, or uncontrolled clinical conditions.
- History of any reaction or hypersensitivity likely to be exacerbated by any component of the vaccine.
- Hypersensitivity, including allergy, to medicinal products or medical equipment whose use is foreseen in this study.
- Clinical conditions representing a contraindication to intramuscular vaccination and blood draws.
- Any confirmed or suspected immunosuppressive or immunodeficient condition, based on medical history and physical examination (no laboratory testing required).
- Any behavioural 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.
- Acute* or chronic illness, clinically significant pulmonary, cardiovascular, hepatic, or renal functional abnormality, as determined by physical examination or laboratory screening tests.

  *Participants with a minor illness (such as mild diarrhoea or mild upper respiratory infection) without fever may be enrolled at the discretion of the Investigator.

- Any clinically significant* haematological (haemoglobin level, white blood cell, lymphocyte, neutrophil, eosinophil, platelet, red blood cell count and erythrocyte mean corpuscular volume) and/or biochemical (alanine aminotransferase [ALT], aspartate aminotransferase [AST], creatinine, and total protein) laboratory abnormality.

  *The Investigator should use his/her clinical judgement to decide which abnormalities are clinically significant.

- Confirmed positive COVID-19 test during the period starting 14 days before the first administration of study vaccines (Day -14 to Day 1).
- Any other clinical condition that, in the opinion of the Investigator, might pose additional risk to the participant due to participation in the study.
- Confirmed or suspected autoimmune diseases (e.g., vitiligo, autoimmune thyroiditis).

5.2.2. Prior/Concomitant therapy

- Previous administration of any type of Typhoid vaccine (Ty21a, Vi-PS, or Typhoid conjugate vaccine).
- Use of any investigational or non-registered product (drug, vaccine, or medical device) other than the study interventions during the period starting 30 days before the first administration of study vaccines (Day -30 to Day 1), or 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 (-21 days in the case of live vaccines) and ending 28 days after the last dose of study intervention administration*, with the exception of flu and COVID-19 vaccines, administered during the period starting at 7 days before and 7 days after each dose (14 days before and 14 days after in case of live vaccines).

  *In case emergency mass vaccination for an unforeseen public health threat (e.g., a pandemic) is recommended and/or organised by public health authorities outside the routine authorisation programme, 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 (e.g., 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 intervention 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. 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 study, at any time during the study period, in which the participant has been or will be exposed to an investigational or a non-investigational vaccine/product (drug/invasive medical device).

5.2.4. Other exclusions

- History of travel to countries of Asia that are considered endemic* for enteric fever in the last 3 years.

  *Refer to Section 10.8 for the list of countries; this also includes travel during the study duration.

- Pregnant or lactating female.
- Female participants planning to become pregnant or planning to discontinue contraceptive precautions.
- History of or current chronic* alcohol consumption and/or drug abuse.

  *Chronic alcohol consumption is defined as one or more of the following: a) a prolonged period of frequent and heavy alcohol use, b) the inability to control drinking once it has begun, c) physical dependence manifested by withdrawal symptoms when the individual stops using alcohol, d) tolerance or the need to use increasing amounts of alcohol to achieve the same effects, e) and a variety of social and/or legal problems arising from alcohol use.

- Any study personnel or immediate dependents, family, or household member.

5.3. Lifestyle considerations

Not applicable

5.4. Screen failures

A screening failure is an individual who consents to participate in this study but is not entered in the study (was not randomised, did not receive a study intervention, and did not undergo a post-screening procedure).

The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for the screening failure. No laboratory data will be retained in the eCRF for participants identified as screening failures.

5.5. Criteria for temporarily delaying study intervention administration

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

- Participants with haematological/biochemical values out of normal range which are expected to be temporary may be rescreened/re-vaccinated at a later date, within the allowed time interval.
- Acute disease and/or fever at the time and/or study intervention administration. Refer to the SoA (Section 1.3) for definition of fever and preferred location for measuring temperature in this study.
- Participants with a minor illness (such as mild diarrhoea, mild upper respiratory infection) without fever may be dosed at the discretion of the Investigator.
- Participants with a positive COVID-19 test before a planned study intervention administration will be allowed to receive the study intervention only if at least 14 days have passed since the first positive test.
- Participants receiving flu and COVID-19 vaccines, administered during the period starting at 7 days before and 7 days after each planned dose (14 days before and 14 days after in case of live vaccines).
- Use of antipyretics and/or analgesics and/or antibiotics within 3 days prior to study intervention administration.

6. STUDY INTERVENTION AND CONCOMITANT THERAPY

Refer to the Glossary of terms for the definition of study intervention.

6.1. Study interventions administered

Table 5 shows the study vaccines that will be administered in the study. The investigational vaccines, Vi-CRM_{197}+O:2-CRM_{197} and ADJ+Vi-CRM_{197}+O:2-CRM_{197}, will be administered in 2 different doses depending on Step. The low dose will be administered by fractional dosing (0.1 mL) retrieved from the same 0.5 mL vial presentation as the full dose. The licensed vaccines, TYPHIM VI and [redacted] will be administered as per their SmPC.

Table 5 Study interventions administered

Study intervention name:	TYP04A (Low Dose Vi-CRM_{197}+O:2-CRM_{197})	TYP04B (Full Dose Vi-CRM_{197}+O:2-CRM_{197})	TYP03A (Low Dose ADJ+Vi-CRM_{197}+O:2-CRM_{197})	TYP03B (Full Dose ADJ+Vi-CRM_{197}+O:2-CRM_{197})	TYPHIM VI (Sanofi Pasteur)	DTP01A (CCI [redacted]
Study intervention formulation:	CCI [redacted]					
Presentation:	vial, solution for injection	vial, solution for injection	vial, solution for injection	vial, solution for injection	pre-filled syringe, solution for injection	pre-filled syringe, suspension for injection
Type:	Investigational	Investigational	Investigational	Investigational	Comparator	Comparator
Product category:	Biologic	Biologic	Biologic	Biologic	Combination Product	Combination product
Route of administration:	intramuscular					
Administration site:						
• **Location**	Deltoid					
• **Directionality**	Upper					
• **Laterality***	Non-dominant					
Number of doses to be administered:	2 per participant	2 per participant	2 per participant	2 per participant	1 per participant	1 per participant
Volume to be administered:	0.1 mL	0.5 mL	0.1 mL	0.5 mL	0.5 mL	0.5 mL
Packaging and labelling:	Refer to the Study Procedures Manual for more details					
Responsible for manufacture:	CCI [redacted]					

*The non-dominant arm is the preferred arm of injection. In case it is not possible to administer the study intervention in the non-dominant arm, an injection in the dominant arm may be performed

Study participants must be observed closely for at least 60 minutes after the administration of the study interventions. Appropriate medical treatment must be readily available during the observation period in case of anaphylaxis or syncope.

6.2. Preparation/Handling/Storage/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 authorised study personnel should be allowed access to the study interventions. Storage conditions will be assessed by a IQVIA Clinical Research Associate during pre-study activities. Refer to the Study Procedures Manual for more details on storage and handling of the study interventions.

6.3. Measures to minimise bias: randomisation and blinding

6.3.1. Participant identification

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

6.3.2. Intervention allocation to the participant

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

The target will be to enrol approximately 96 eligible participants, 18 to 50 years of age, who will be randomly assigned to the different study groups, according to Step:

Step 1a: 18 adults will be assigned in a 2:1 ratio to the following study groups

- "Step 1a low dose without Alum" (approximately 12 participants)
- "Step 1a control" (approximately 6 participants)

Step 1b: 18 adults will be assigned in a 2:1 ratio to the following study groups

- "Step 1b low dose with Alum" (approximately 12 participants)
- "Step 1b control" (approximately 6 participants)

Step 2: 60 adults will be assigned in a 2:2:1 ratio to the following study groups

- "Step 2 full dose without Alum" (approximately 24 participants)
- "Step 2 full dose with Alum" (approximately 24 participants)

- "Step 2 control" (approximately 12 participants)

Refer to the IQVIA Lab Manual and Pharmacy Manual for additional information about the study intervention number allocation.

6.3.3. Allocation of participants to assay subsets

CCI

[redacted]

6.3.4. Blinding and unblinding

Data will be collected in an observer-blind manner until the first interim analysis (to be performed 28 days after first study intervention administration in Step 2). From the first interim analysis (refer to Section 9.5.1) until EoS, the study will be considered single-blind, with the participant and Investigator remaining blinded. Study interventions will be prepared and administered by qualified study personnel who will not participate in data collection, evaluation, review, or the entry of any study endpoint (i.e., reactogenicity, safety, immunogenicity).

Investigators will remain blinded to each participant's assigned study intervention throughout the course of the study. All activities involving vaccine handling (e.g., re-labelling of clinical study materials at the study site) and vaccine administration will be performed by unblinded site staff according to instructions and training provided by GSK or delegated contract research organisation staff before study start. The site staff responsible for these activities will be personnel who are respectively qualified according to applicable local laws and regulations. Preparation and administration of the vaccine(s) should be performed at a location different from the location where clinical assessment and evaluation is performed. The participant will be instructed not to look at the injection syringe while the study intervention is administered. The unblinded site staff will be also responsible for completing the Vaccine Administration Log and Vaccine Accountability Log to ensure final accountability. Refer to the IQVIA Pharmacy Manual for further details on blinding procedures and management.

In case a participant's intervention assignment is unblinded, the participant's continuation in the study will be evaluated on a case-by-case basis between the Investigator and GSK. The participant should still be followed up for safety if a study intervention has been performed.

The laboratory in charge of sample testing will be blinded to the study intervention assignment. Codes will be used to link the participant and study to each sample. There will be no link between the study intervention group and the identity of the participant.

6.3.4.1. Emergency unblinding

Unblinding a participant's individual study intervention 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 unblinding envelopes.

A physician other than the Investigator (e.g., an emergency room physician) or participant/care giver/family member may also request emergency unblinding via the Investigator. The participant card provides contact information for the Investigator and his/her back up.

6.3.4.2. 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 interventions, prior to regulatory reporting. Global Safety (GS) is responsible for unblinding the study intervention assignment within the timeframes defined for expedited reporting of SAEs (refer to the Section 10.3.10.1).

In addition, GSK GS 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

Participants will receive the study interventions directly from the Investigator or designee, under medical supervision. The date and time of administration of each study intervention dose in the clinic will be recorded in the source documents.

6.5. Dose modification

Not applicable.

6.6. Continued access to study intervention after the end of the study

During the study conclusion Visit/Contact, 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.

6.7. Treatment of overdose

Not applicable.

6.8. Concomitant therapy

At each study Visit, 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 medications/products, except vitamins and dietary supplements, administered during the period of 28 days post-vaccination.
- Relevant medications/products such as vaccines, immunoglobulin, blood products, immunosuppressors, and immunomodulators, administered during the period starting from the administration of the first dose of the study intervention and ending on Visit 6 (Day 197).
- Any vaccination administered in the period starting 30 days before the first dose of study vaccine and ending on Visit 6 (Day -30 to Day 197).
- Prophylactic medication (i.e., medication administered in the absence of ANY symptom and in anticipation of a reaction to the vaccination).
- All concomitant medication associated with an adverse event, 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 (refer to Sections 5.2.2 and 9.3.1 for further details).
- All concomitant medication which may explain/cause/be used to treat an SAE including vaccines/products, as defined in Sections 8.3.1 and 10.3.8.2. These must also be recorded in the Expedited Adverse Event Report.

The IQVIA Clinical Research Associate should be contacted if there are any questions regarding concomitant or prior therapy.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of study intervention

‘Discontinuation’ of study intervention refers to any participant who has not received all planned doses of study intervention. A participant who discontinued study intervention may continue other study procedures (e.g., safety or immunogenicity), planned in the study protocol at the discretion of the Investigator.

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

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

Participants who discontinue study intervention will not be replaced.

7.1.1. 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 study intervention. Such participants should be encouraged to continue other study procedures, at the investigators' discretion (Section 10.3.8.2). 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.
- Any condition that in the judgement of the Investigator would make intramuscular injection unsafe.

7.2. Participant discontinuation/withdrawal from the study

A participant is considered to have withdrawn from the study if no new study procedure has been performed or no new information has been collected for him/her since the date of withdrawal/last contact.

From an analysis perspective, a study 'withdrawal' refers to any participant who did not return for the concluding Visit/Contact planned in the protocol.

Investigators will attempt to contact participants who do not return for scheduled visits or follow-up.

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.

The primary reason for study withdrawal will be documented in the eCRF, based on the list below:

- AEs requiring expedited reporting to GSK (refer to Section 10.3.10.1 for more details)
- 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)

*If a participant is withdrawn from the study because he/she 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 (see Section 10.3.8.2).

7.3. Lost to follow-up

A participant will be considered ‘lost to follow-up’ if he/she fails to return for scheduled visits and cannot be contacted by the study site.

Please refer to the IQVIA Lab Manual and Pharmacy Manual for a description of actions to be taken before considering the participant lost to follow-up.

8. 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 summarised in the SoA (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.

Procedures conducted as part of routine clinical management (e.g. haematologic profiles), and obtained before the participant signed the informed consent form (ICF), may be used for Screening and/or for establishing a clinical baseline (provided the procedure met protocol specified criteria and was performed within the time frame defined in the SoA) (Section 1.3).

The SPM provides the Investigator and site personnel with detailed administrative and technical information that does not impact participant safety.

During special circumstances (e.g., COVID-19 pandemic), if local regulations allow, and quality of study procedures is maintained, participant(s) can be offered remote visits (e.g., telemedicine, home visits) for the collection of biological samples and/or safety data/safety assessment(s)/study intervention administration. These remote visits must be performed by qualified study staff. Refer to the SoA for the timing of these visits. Details of how these visits will be conducted are outlined in the SPM.

The following procedures can be performed remotely/virtually (refer to the Glossary of terms for the definitions of telemedicine, remote and virtual visits) for the duration of such special circumstances:

- Safety follow-up may be performed by telemedicine, which will use secure video conferences, phone calls, and a web portal and/or mobile application as a way of communicating with the participant and monitoring the participant's progress. In addition, qualified study staff may also identify AEs and report them to the Investigator for evaluation.
- Biological samples may be collected by qualified study staff in a different location other than the study site or at participant's home. Biological samples should be collected only if they can be processed in a timely manner and appropriately stored until the intended use.
- Administration of study intervention can be performed in a different location other than the study site or at participant's home by qualified study staff if appropriate storage conditions for the study intervention can be ensured. Furthermore, appropriate medical treatment must be readily available during 60 minutes after dosing in case of anaphylaxis or syncope.
- If despite best efforts it is not possible to perform the visits within the interval predefined in the protocol (see Table 2), then the interval may be extended for the specified visits up to a maximum length of days as presented in Table 6.

Table 6 Intervals between study visits under special circumstances (e.g., COVID-19 pandemic)

Interval	Planned Visit interval	Allowed interval range
Visit 1 → Visit 2	7 days	7 days – 10 days
Visit 1 → Visit 3	28 days	28 days – 38 days
Visit 1 → Visit 4	168 days	154 days – 182 days
Visit 4 → Visit 5	7 days	7 days – 10 days
Visit 4 → Visit 6	28 days	28 days – 38 days
Visit 4 → Follow-up safety phone contact	168 days	154 days – 182 days

8.1. Immunogenicity assessments

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.

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 subject to prior IEC/IRB 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.

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.

8.1.1. Biological samples

Table 7 summarises the collection of blood in the study. The maximum amount of blood to be collected in the study is ~140 mL per participant.

Table 7 Biological samples

Sample type	Quantity	Unit	Timepoint	Participants sampled
Blood for serum preparation	~10 mL/Visit for antibody determination, ~15 mL for assay standard generation, ~20 mL for safety Screening laboratory assays, ~13.5 mL/Visit for pre/post-vaccination visits safety laboratory assays	mL	As scheduled (refer to Table 1 and Figure 1)	All participants in Step 1 and Step 2

8.1.2. Laboratory assays

Table 8 Laboratory assays

Assay type	System	Component	Method	Laboratory*
Humoral Immunity (Antibody determination)	Serum	Anti-Vi antigen IgG (*Salmonella* Typhi)	ELISA	GVGH or GVGH-delegated lab
		Anti-O antigen IgG (*Salmonella* Paratyphi A)		
		CCI [redacted]		

*Refer to the list of clinical laboratories for details.
ELISA=enzyme-linked immunoassay; GVGH=GSK Vaccines Institute for Global Health; IgG=Immunoglobulin G; CCI [redacted]

Exploratory systems serology analysis assays will be performed by the GVGH laboratory, or a laboratory designated by GVGH.

Please refer to the Section 10.2 for a brief description of the assays performed in the study.

The addresses of clinical laboratories used for sample analysis are provided in a separate document accompanying this study protocol.

GSK clinical laboratories *(GVGH)* have established a Quality System supported by procedures. The activities of GSK clinical laboratories are audited regularly for quality assessment by an internal (Sponsor-dependent) but laboratory-independent Quality Department.

8.1.3. Immunological read-outs

Table 9 Immunological read-outs

Blood sampling timepoint		No. participants	Component
Type of contact and timepoint	**Sampling timepoint**		
Visit 1 (Day 1)	Pre-1st vaccination	96	Anti-Vi antigen IgG
			Anti-O:2 IgG
			CCI [redacted]
Visit 3 (Day 29)	Post-1st vaccination	96	Anti-Vi antigen IgG
			Anti-O:2 IgG
			CCI [redacted]
Visit 4 (Day 169)	Pre-2nd vaccination	96	Anti-Vi antigen IgG
			Anti-O:2 IgG
			CCI [redacted]
Visit 5 (Day 176)	Post-2nd vaccination 1	96	Anti-Vi antigen IgG
			Anti-O:2 IgG
			CCI [redacted]
Visit 6 (Day 197)	Post-2nd vaccination 2	96	Anti-Vi antigen IgG
			Anti-O:2 IgG
			CCI [redacted]

8.1.4. Cytology

Not applicable

8.1.5. Clinical safety laboratory assessments

Refer to the Section 10.2.1 for the list of clinical laboratory safety assessments required by the protocol. These assessments must be conducted according to the clinical laboratory manual and the SoA.

8.1.6. Immunological correlates of protection

No generally accepted immunological correlate of protection has been demonstrated so far for the typhoid or paratyphoid A component used in the candidate vaccine.

No antigen measurement that can assess immunological correlates of protection are planned in this study for the comparator vaccines. An antigen threshold for anti-Vi IgG of >4.3 µg/mL (similar to the endpoint threshold used in this study) was defined as criteria of sustained protection for at least 4 years during licensing of TYPHIBEV [Kasi, 2021]. An anti-Vi IgG of >2.0 µg/mL was estimated to be predictive of short-term protection in a previous paediatric study [Szu, 2014].

8.2. Safety assessments

The Investigator and his/her designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE. This includes the assessment of COVID-19 cases as per the WHO definition [WHO, 2022]. The Investigator and designees are responsible for following up AEs that are serious, considered related to the study intervention or the study, or that caused the participant's withdrawal from the study intervention or the study.

The safety measures in this study have been planned considering the nature of the existing knowledge on the investigational vaccine components (Vi, O:2, CRM_{197}, Alum). The Vi component is licensed in India and WHO-prequalified; it is similar to the Bharat Biotech Typbar-TCV vaccine and the Sanofi Pasteur TYPHIM VI, both of which have been administered to millions of people worldwide with an acceptable safety profile and without particular risks. CRM_{197} and Alum are well-known vaccine components with a well-characterised safety profile.

8.2.1. Pre-vaccination procedures

8.2.1.1. Collection of demographic data

Record demographic data such as month and year of birth, sex, and race in the participant's eCRF.

8.2.1.2. Medical history

Obtain the participant's medical history by interviewing the participant and/or review of the participant's medical records. Record any pre-existing conditions, signs and/or symptoms present in the last 3 years prior to the first study intervention in the eCRF.

8.2.1.3. Physical examination

A complete physical examination will be performed at screening and on each vaccination visits (Day 1 and Day 169). The physical examination will be performed by the Investigator and clinically relevant findings should be recorded in the participant source documents and in eCRF (only for enrolled participants). Physical examination includes assessment of body temperature (axillary is preferred location) and resting vital signs (systolic/diastolic blood pressure, pulse rate, and respiratory rate). On days of vaccination, body temperature and vital signs will be measured immediately prior to (maximum 60 minutes before) and 60 minutes after vaccination. Height and weight measurements will be performed during screening only. If the Investigator determines that the participant's health on the days of vaccination temporarily precludes vaccination, the visit will be rescheduled as possible by the study site.

A symptom-directed physical examination will be performed on visits where no vaccination is administered. The nature of the physical examination will be driven by any specific symptoms identified by the Investigator. The symptom-directed physical examination will not be recorded in the eCRF. However, any abnormalities detected that meet the definition of AE (refer to Section 10.3) will be recorded as such in the eCRF.

Treatment of any abnormalities observed during any physical examinations must be performed according to local medical practice outside this study or by referral to an appropriate health care provider.

8.2.1.4. Pregnancy test

Female participants of childbearing potential must take a blood pregnancy test at screening and a urine pregnancy test before the administration of any dose of study intervention. Pregnancy testing must be done even if the participant is menstruating at the time of the study visit. The study intervention may only be administered if the pregnancy test is negative.

Refer to the Section 10.4.3.1 for the information on study continuation for participants who become pregnant during the study.

8.2.1.5. Pre-vaccination body temperature

The axillary temperature of each participant needs to be measured prior to (maximum 60 minutes before) administration of any study vaccine. If the participant has fever [fever is defined as temperature ≥38.0°C regardless of the location of measurement] on the day of vaccination, the vaccination visit will be rescheduled within the allowed interval for this visit (refer to Table 2).

8.2.1.6. Warnings and precautions to vaccination

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

For contraindications to the administered marketed study vaccines, refer to their SmPC and/or Prescribing Information.

8.2.2. Study holding rules and safety monitoring

Study holding rules (refer to Table 11) are introduced to ensure careful exposure to the investigational candidate vaccine and to prevent participants from being exposed to any unnecessary safety risks. The holding rules will serve as criteria to point attention to potential safety concerns and indicate requirements for additional formal committee reviews that will decide whether additional participants can be exposed to the vaccine. If the Investigator becomes aware of a holding rule threshold being met, he/she must suspend administration of the study intervention and inform IQVIA immediately. Refer to the IQVIA study contact list for contact information and Section 8.2.2.3 for additional information.

Safety during the study will be monitored on an ongoing basis by the Safety Review Team (SRT), a cross-functional internal GSK committee that will evaluate safety data in a blinded manner. In addition, a GSK project-independent internal Safety Review Committee (iSRC) will be established to monitor safety at predefined timepoints and, more specifically, to recommend continuation of vaccine administration based on the unblinded safety results (refer to Section 8.2.2.1). The iSRC Chair together with the SRT will also perform blinded reviews at predefined timepoints (refer to Section 8.2.2.1), which will assess the need for full committee unblinded reviews by iSRC based on assessment of safety signals/concerns. Ad hoc safety evaluations by the iSRC may be called at any time if there are any suspected safety concerns.

The iSRC will also include an external expert (non-GSK employee); the organisation of the iSRC, the specific roles of its members, how reviews will be conducted, and how blinding will be maintained, will be outlined in the iSRC Charter.

8.2.2.1. Staggered vaccination

Participants will always be vaccinated sequentially. At Visit 1 (Day 1), sentinel participants should receive the first vaccination each 1 day apart and non-sentinel participants should receive it at least 60 minutes apart. At Visit 4 (Day 169), all participants, should receive the second vaccination at least 60 minutes apart. All participants will be closely observed for at least 60 minutes after vaccination.

The Investigator is not permitted to begin dosing study participants in Step 1b or Step 2 until the receipt of favourable written documentation of safety evaluations (iSRC/SRT). Screening procedures may continue, to facilitate the enrolment of remaining participants.

<u>Step 1a:</u>

A “Step 1a low dose without Alum” subgroup comprises 2 study groups (2:1 randomisation [Step 1a low dose without Alum: Step 1a control]) will receive either 2 vaccinations with the candidate low dose Vi-CRM_{197}+O:2-CRM_{197} vaccine without Alum

or 1 vaccination with the TYPHIM VI vaccine (as control for the first vaccination) and 1 vaccination with the CCI [redacted] vaccine (as control for the second vaccination).

First, 6 sentinel participants will receive, on consecutive days, either the low dose of the Vi-CRM_{197}+O:2-CRM_{197} or the TYPHIM VI vaccine (2:1 randomisation). Each sentinel participant will be followed up with a safety phone call approximately 1 day after vaccination. If there are any safety concerns, the sentinel participant will be asked to visit the site to assess any potential SAEs or to assess if any holding rules have been met. If no holding rules have been met nor SAEs reported by any of the sentinel participants, 12 additional participants will receive sequentially (at least 60 minutes apart) either the low dose of the Vi-CRM_{197}+O:2-CRM_{197} or the TYPHIM VI vaccine, maintaining the 2:1 randomisation.

All available safety data (including laboratory test results) collected until 7 days after first vaccination in Step 1a will be reviewed blindly by the iSRC Chair together with the SRT (Safety evaluation #1; refer to Table 10). The iSRC Chair and SRT will decide whether an unblinded review by the full iSRC is needed, before initiating the first vaccination in Step 1b (administration of the low dose of the candidate vaccine with Alum or control vaccine to sentinel participants). A positive outcome will also allow the 18 participants in Step 1a to receive further vaccinations as per the SoA.

All available safety data (including laboratory test results) collected until 7 days after second vaccination in Step 1a will be reviewed blindly by the iSRC Chair together with the SRT (Safety evaluation #4; refer to Table 10). The iSRC Chair and SRT will decide whether an unblinded review by the full iSRC is needed, before initiating the second vaccination in Step 1b (administration of the low dose of the candidate vaccine with Alum or control vaccine to sentinel participants).

Step 1b

A "Step 1b low dose with Alum" subgroup comprises 2 study groups (2:1 randomisation [Step 1b low dose with Alum: Step 1b control]) will receive either 2 vaccinations with the low dose Vi-CRM_{197}+O:2-CRM_{197} vaccine with Alum or 1 vaccination with the TYPHIM VI vaccine (as control for the first vaccination) and 1 vaccination with the CCI [redacted] vaccine (as control for the second vaccination).

Upon approval from the iSRC/SRT (Safety evaluation #1), 6 sentinel participants will receive on consecutive days the first vaccination with either the low dose Vi-CRM_{197}+O:2-CRM_{197} vaccine with Alum or the TYPHIM VI vaccine (2:1 randomisation). Each sentinel participant will be followed up with a safety phone call approximately 1 day after vaccination. If there are any safety concerns, the sentinel participant will be asked to visit the site to assess any potential SAEs or if any holding rules have been met. If no holding rules have been met nor SAEs reported by any of the sentinel participants, a further 12 participants will receive sequentially (at least 60 minutes apart) either the low dose Vi-CRM_{197}+O:2-CRM_{197} vaccine with Alum or the TYPHIM VI vaccine and CCI [redacted] vaccine, maintaining the 2:1 randomisation ratio.

All available safety data (including laboratory test results) collected until 7 days after first vaccination in Step 1b will be reviewed blindly by the iSRC Chair together with the SRT

(Safety evaluation #2; refer to Table 10). The iSRC Chair and SRT will decide whether unblinded data review by the full iSRC is needed, before initiating the first vaccination in Step 2 (administration of the full dose of the candidate vaccine with Alum, full dose of the candidate vaccine without Alum, or control vaccines to sentinel participants).

Step 2:

A "full dose with and without Alum" subgroup comprises 3 study groups (2:2:1 randomisation [Step 2 full dose without Alum: Step 2 full dose with Alum: Step 2 control]) will receive either 2 vaccinations with the full dose Vi-CRM_{197}+O:2-CRM_{197} vaccine without Alum or the full dose Vi-CRM197+O:2-CRM_{197} vaccine with Alum or 1 vaccination with the TYPHIM VI vaccine (as control for the first vaccination) and 1 vaccination with the [redacted] vaccine (as control for the second vaccination).

Upon approval from the iSRC/SRT (Safety evaluation #2), 5 sentinel participants will receive on consecutive days the first vaccination with either the full dose Vi-CRM_{197}+O:2-CRM_{197} vaccine without Alum, the full dose Vi-CRM_{197}+O:2-CRM_{197} vaccine with Alum, or the TYPHIM VI vaccine (2:2:1 randomisation). Each sentinel participant will be followed up with a safety phone call approximately 1 day after vaccination. If there are any safety concerns, the sentinel participant will be asked to visit the site to assess any potential SAEs or if any holding rules have been met. If no holding rules have been met nor SAEs reported by any of the sentinel participants, a further 55 participants will receive sequentially (at least 60 minutes apart) either the full dose Vi-CRM_{197}+O:2-CRM_{197} vaccine without Alum, the full dose Vi-CRM_{197}+O:2-CRM_{197} vaccine with Alum, or the TYPHIM VI vaccine, maintaining the 2:2:1 randomisation ratio.

All available safety data (including laboratory test results) collected until 28 days after first vaccination in Step 2 will be reviewed in an unblinded manner by the iSRC (Safety evaluation #3). The iSRC will recommend whether to proceed with second vaccination in Step 2 and allow the participants in Step 2 to complete the study as per the SoA.

Table 10 Safety evaluation schedule

Safety evaluation	Safety data reviewed	Approval to proceed to
#1: Blinded*	Up to 7 days after 1st vaccination in Step 1a	Administration of 1st study intervention to sentinel participants in Step 1b and subsequent administrations to participants in Step 1a
#2: Blinded*	Up to 7 days after 1st vaccination in Step 1b	Administration of 1st study intervention to sentinel participants in Step 2
#3: Unblinded	Up to 28 days after 1st vaccination in Step 2	Administration of 2nd vaccination in Step 2
#4: Blinded*	Up to 7 days after 2nd vaccination in Step 1a	Administration of 2nd vaccination in Step 1b

*During blinded safety evaluations, if there are any concerns that would require the evaluation of unblinded safety data, an iSRC evaluation will occur that will decide on the succeeding administration of the vaccine or to begin the next Step of the study.
Notes: All available safety data will be cumulatively reviewed at each safety evaluation (e.g., safety data after the first vaccination will be reviewed before the administration of the second vaccination). In case the safety evaluations #3 and #4 could become scheduled to occur close together, they may be combined in a single unblinded iSRC evaluation.

8.2.2.2. Outcome of safety evaluation

- If no safety concern is observed during the blinded or unblinded data review, the favourable outcome of the safety evaluations will be documented and provided in writing, authorising the Investigator to start vaccination of participants with the subsequent dose as well as enrolment and vaccination of the remaining participants of the next step of the study.
- In case the Investigator becomes aware of one or more holding rules (refer to Section 8.2.2.3), he/she should immediately inform IQVIA of the event (refer to the IQVIA study contact list for contact information).
- If a safety issue is observed during the unblinded data review or if any of the holding rules (e.g. 2a or 2b; Refer to Table 11) is met, the iSRC Chair (or his/her representative) is responsible for the urgent communication to the GVGH PP, including any rationale for a decision to put the vaccination on hold or not. The GVGH PP will be accountable for notifying all investigators (through IQVIA) of the decision whether to suspend, modify, or continue the conduct of the study on all groups or on selected groups.
- If a safety issue is observed during the blinded data review or a holding rule threshold is met (not known in which study group events occurred), an ad hoc iSRC safety evaluation meeting will be called.

8.2.2.3. Study holding rules

Table 11 shows the holding rules to be implemented for this study. These holding rules have been written under the assumption that the safety data from all participants will be available. If the data from all participants are not available (e.g., in case a participant is lost to follow-up), then the holding rules will be assessed on a pro-rata basis.

Holding rules 1a-d in all steps of the study and holding rule 2c in Step 1a and 1b will be monitored by the Investigator on a continuous basis (threshold ≥1, refer to Table 11). Meeting any of these holding rules will trigger a hold of study intervention administration irrespective of number of participants enrolled and/or timing of the event.

For holding rules 2a-b in all steps of the study and holding rule 2c in Step 2, the Investigator will inform IQVIA immediately if a threshold is suspected to be met, without pausing administration of the study intervention (threshold ≥2-6, refer to Table 11). IQVIA will provide a report to the GVGH PP who will then confirm if the threshold has been met and advise whether to pause the study intervention administration.

If the Investigator becomes aware that a holding rule threshold has been met (either directly or via IQVIA), the following communication sequence must be followed:

- The concerned site staff must 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 by IQVIA project lead.

Table 11 Study holding rules

Holding rule	Event	Number of participants needed to pause vaccination in the study and trigger further evaluation by the iSRC		
		Step 1a	Step 1b	Step 2
1a	Death or any life-threatening SAE regardless of causality	≥1	≥1	≥1
1b	Any non-life-threatening SAE that cannot be reasonably attributed to a cause other than vaccination as per Investigator or Sponsor assessment	≥1	≥1	≥1
1c	Any withdrawal from the study (by Investigator or participant request) following a Grade 3 AE	≥1	≥1	≥1
1d	Any solicited administration-site event or solicited systemic event leading to hospitalisation, OR Necrosis at the injection site, Each with an event onset within the 7-day post-vaccination period	≥1	≥1	≥1
2a	Any Grade 3 solicited administration-site events (lasting 48h or more as Grade 3), with an event onset within each 7-day post-vaccination period	≥3	≥3	≥6
2b	Any Grade 3 solicited systemic events (lasting 48h or more as Grade 3), with an event onset within each 7-day post-vaccination period	≥2	≥2	≥3
2c	Any Grade 3 unsolicited AE, which can be reasonably attributed to the vaccination as per Investigator or Sponsor assessment, with an event onset within each 7-day post-vaccination period OR Any Grade 3 or above abnormality* in pre-specified haematological or biochemical laboratory parameters collected at 7 days post-vaccination period	≥1**	≥1**	≥2

AE=adverse event, SAE=serious adverse event
*Refer to Section 10.9 for the grading scales to the pre-specified laboratory parameters
**The Investigator should inform IQVIA CRA and Medical Monitor immediately if an event occurs and should follow instruction as applicable to holding rules 1a-1d.

8.3. AEs, SAEs, and other safety reporting

8.3.1. Time period and frequency for collecting AE, SAE, and other safety information

Table 12 Timeframes for collecting and reporting of safety information

	SCR* D-21 to D-1	VAC 1 D1	D8	D29	VAC 2 D169	D176	D197	SFU D337
Administration-site and systemic solicited events		D1 to D7			D169 to D175			
Unsolicited AEs**		D1 to D28			D169 to D196			
AEs/SAEs leading to withdrawal from the study		D1 to D337						
SAEs**		D1 to D337						
SAEs related to the study intervention		D1 to D337						
SAEs related to study participation or concurrent GSK medication/ vaccine***	D-21 to D337							
Pregnancy		D1 to D197						
Any other event of interest for the study		D1 to D197						

*Consent obtained
**Unsolicited AEs/SAEs due to COVID-19 will be recorded according to the WHO case definition [WHO, 2022].
*** Any SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a participant consents to participate in the study.
D=Day; SFU=safety follow-up; SCR=Screening; VAC=Vaccination

The Investigator or designee will record and immediately report all SAEs in 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, as indicated in Section 10.3.10. The Investigator will submit any updated SAE data to the Sponsor or designee within 24 hours of it being available. SAEs

related to study participation or to a concurrent GSK medication/vaccine will be collected from the time consent is obtained until the participant is discharged from the study.

During the extended safety follow-up period (Day 197 to Day 337), participants will be encouraged to inform the Investigator in a timely manner if they have any event meeting the description of an SAE. Any SAE reported during this period will qualify for expedited reporting according to Section 10.3.10. Any SAEs discovered retrospectively during the safety phone call on Day 337 will also be reported accordingly.

A post-study AE/SAE is defined as any event that occurs outside of the AE/SAE reporting periods defined in Table 12. Investigators are not obligated to actively seek AEs or SAEs from former study participants. 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 intervention, the Investigator will promptly notify the study contact for reporting SAEs mentioned in the IQVIA study contact list.

8.3.2. Method of detecting AEs and SAEs, pregnancies, and other events

Detection and recording of AE/SAE/pregnancies are detailed in Section 10.3.8.

Assessment of AE/SAE intensity, causality and outcome are described in Section 10.3.9.

Open-ended and non-leading verbal questioning of participants is the preferred method of acquiring information related to an AE/SAE/pregnancy.

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 laboratory tests with clinically significant abnormal values reported during the study should be repeated until the values return to normal/baseline, or until they are no longer considered significantly abnormal by the Investigator. Refer to Section 10.3.6 for more information on clinically abnormal laboratory assessments that qualify as an AE or SAE.
- In case abnormal values are not considered clinically significant by the Investigator, additional evaluations could be requested by the GVGH PP.
- If abnormal values do not return to normal/baseline after an interval judged reasonable by the Investigator, the aetiology of the abnormal value should be identified, and the Sponsor notified.

8.3.3. Regulatory reporting requirements for SAEs, pregnancies, and other events

Once the Investigator or designee becomes aware that a study participant has experienced an SAE, they or designated study staff must report it to the 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 Section 10.3.9.2. 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.

Refer to the IQVIA study contact list for the Medical Monitor's name and contact information.

Table 13 Timeframes for submitting SAE and pregnancy reports

Type of Event	Initial Reports		Follow-up of Relevant Information on a Previous Report	
	Timeframe	Documents	Timeframe	Documents
SAEs	24 hours*‡	electronic Expedited Adverse Events Report	24 hours*	electronic Expedited Adverse Events Report
Pregnancies	24 hours*	electronic pregnancy report	24 hours*	electronic pregnancy report

* Timeframe allowed after receipt or awareness of the information by the Investigator/site staff.
‡ For each SAE, the Investigator(s) must document in the medical notes that they have reviewed the SAE and have provided an assessment of causality.

8.3.4. Treatment of expedited AEs

Any medication administered for the treatment of an SAE should be recorded in the Expedited Adverse Event Report of the participant's eCRF screen (refer to the Section 10.3.10.1).

8.3.5. Participant card

The Investigator (or designee) must provide the participant with a "participant card" containing information about the clinical study. The participant must be instructed to always keep the participant card in his/her/their possession for the duration of the study. In an emergency, this card serves to inform the responsible attending physician that the participant is in a clinical study and that relevant information may be obtained by contacting the Investigator or his/her back up.

8.3.6. Medical device deficiencies

The comparator vaccines used in this study are combination products constituted of a biologic product in a medical device (pre-filled syringes). Refer to the Glossary of terms for the definition of combination product and medical device deficiency.

8.3.6.1. 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 GSK. This applies to any medical device provided for the conduct of the study.

Device deficiencies will be reported to GSK within 24 hours after the Investigator determines that the event meets the protocol definition of a device deficiency. Refer to Section 10.6 for definitions and details on recording and reporting of these events.

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 GSK within 24 hours.

Medical device deficiencies and any associated AE/SAE for Associated Person (i.e., spouse, caregiver, site staff) will also be collected. The Associated Person will be provided with a safety reporting information and authorisation letter.

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

8.3.6.2. 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 GSK. GSK has a legal responsibility to notify appropriate regulatory authorities and other entities about safety information linked to medical devices being used in clinical studies. Refer to section 10.6.3 for details of reporting.

The Investigator, or responsible person according to local requirements (e.g., 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

Not applicable

8.5. Genetics and/or Pharmacogenomics

Not applicable

8.6. Biomarkers

Not applicable

8.7. Immunogenicity

Not applicable

8.8. Health outcomes

Not applicable

9. STATISTICAL CONSIDERATIONS

9.1. Statistical hypotheses

No specific statistical hypotheses will be tested in this study. All analyses of safety and immunogenicity will be descriptive. Results of this study will inform the planning of subsequent studies and selection of candidate vaccine formulation.

9.2. Sample size determination

Approximately 96 participants will be randomised to achieve 82 evaluable participants. Participants who withdraw from the study will not be replaced.

Since no confirmatory objectives are being evaluated in this study, the sample size selected for this study is not driven by statistical considerations. The sample size has been determined to allow an adequate assessment of the investigational doses and an evaluation of the holding rules as detailed in Section 8.2.2.3.

9.2.1. Statistical consideration for safety assessment

Table 14 shows the probability to observe at least one AE for different sample sizes and AE rate. In Steps 1a and 1b, a sample size of 12 participants receiving the investigational vaccine would provide a probability of at least 80% to observe at least one AE, if the true AE rate is equal to or greater than 15%. In Step 2, a sample size of 24 participants receiving the investigational vaccine would provide a probability of at least 80% to observe at least one AE, if the true AE rate is equal to or greater than 7.5%.

Table 14 Probability to observe at least 1 AE according to sample size and AE rate

Number of participants receiving investigational vaccine	True AE rate	Probability to observe at least one AE
12	1.0%	11.4%
	2.5%	26.2%
	5.0%	46.0%
	7.5%	60.8%
	10.0%	71.8%
	12.5%	79.9%
	15.0%	85.8%
	17.5%	90.1%
	20.0%	93.1%
24	1.0%	21.4%
	2.5%	45.5%
	5.0%	70.8%
	7.5%	84.6%
	10.0%	92.0%
	12.5%	95.9%
	15.0%	98.0%
	17.5%	99.0%
	20.0%	99.5%

Probability to observe at least one AE was estimated with the PROBBNML function from SAS 9.4

9.2.2. Statistical considerations on immunogenicity assessment

The percentage of participants with 4-fold increases among the O:2 component has been defined as a measure of a seroresponse. Results on both full dose groups (adjuvanted and not adjuvanted) will be used to make decisions for the planning of subsequent studies and the clinical development programme. Assuming a 12% participant dropout rate in 24 participants from each of full dose group, 21 participants will be considered evaluable. Table 15 shows the precision in terms of 95% confidence interval on the 4-fold increase in these participants.

Table 15 95% confidence intervals for seroresponse in participants receiving the full dose of the vaccine

Number of participants with 4-fold increases in anti-O:2 IgG	Percentage of participants with 4-fold increases	95% confidence interval
10	47.6%	25.7% - 70.2%
11	52.4%	29.8% - 74.3%
12	57.1%	34% - 78.2%
13	61.9%	38.4% - 81.9%
14	66.7%	43% - 85.4%
15	71.4%	47.8% - 88.7%
16	76.2%	52.8% - 91.8%
17	81.0%	58.1% - 94.6%
18	85.7%	63.7% - 97%

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

9.3. Analysis sets

The first-line analysis population set for immunogenicity analysis will be the Per-Protocol Set (PPS). If, in any study group at any timepoint, the percentage of vaccinated participants with serological results excluded from the PPS for analysis of immunogenicity is 10% or more of the Full Analysis Set (FAS), a second-line analysis based on the FAS for immunogenicity will be performed to complement the PPS analysis.

For the purposes of this study, the following analysis sets will be defined:

Table 16 Analysis sets

Analysis set	Description
Enrolled	All participants who entered the study (who were randomised, or received study intervention, or underwent a post-Screening study procedure). Note: participants who never passed Screening even if rescreened (Screening failures) and participants screened but never enrolled into the study (met eligibility but not needed for the study) are excluded from the Enrolled analysis set.
Exposed	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	All participants who received at least 1 dose of the study intervention and have post-vaccination immunogenicity data. The allocation in a group is done in function of the randomised intervention. The Full Analysis Set (FAS) for immunogenicity will be defined by time point.
Per-Protocol	All eligible participants who received each dose 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 Per-Protocol Set (PPS) for immunogenicity will be defined by time point.
Unsolicited Safety	All participants who received at least 1 dose of the study intervention (Exposed Set) that report unsolicited AEs/report not having unsolicited AEs. The allocation in a group is based on the administered intervention.
Solicited Safety	All participants who received at least 1 dose of the study intervention (Exposed Set) who have solicited safety data. The allocation in a group is based on the administered intervention.

9.3.1. Criteria for elimination from analysis

If the participant meets one of the criteria mentioned below or ones listed in the Section 7.1.1, 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 (i.e., 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 (e.g., infliximab) administered at any time during the study period.
- Use of any immunoglobulins and/or any blood products administered during the study period.
- Use of any vaccine not foreseen by the Study Protocol administered during the entire period of participant's study participation.
- Use of foreseen vaccines outside the recommended time window.
- Unblinding after any study intervention has been administered.

Other criteria for elimination from analyses will be reported in the Statistical Analysis Plan (SAP) and in the Protocol Deviation Management Plan.

9.3.1.1. Intercurrent medical conditions

The following intercurrent medical conditions must be recorded in the eCRF and may lead to elimination from the per-protocol analysis:

- Occurrence of a condition that has the capability of altering their immune response (i.e., varicella, COVID-19) or are confirmed to have an alteration of their initial immune status
- Occurrence of a serious chronic or progressive disease according to judgement of the Investigator (e.g., 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
- Any drug and/or alcohol abuse

9.4. Statistical analyses

9.4.1. Primary endpoint(s) (*Amended*, 21 August 2023)

Endpoint description	Analysis set	Statistical analysis methods
• Percentage of participants with solicited administration-site events during 7 days after each vaccination, on the days of vaccination and the 6 subsequent days (study intervention administered on Day 1 and Day 169), per study group	Solicited Safety Set	• Number and percentages of participants with at least one, any, and Grade 3 administration-site solicited AEs
• Percentage of participants with solicited systemic events during 7 days after each vaccination, on the days of vaccination and the 6 subsequent days (study intervention administered on Day 1 and Day 169), per study group	Solicited Safety Set	• Number and percentages of participants with at least one, any, and Grade 3 systemic solicited AEs
• Percentage of participants with unsolicited AEs during 28 days after each vaccination, on the days of vaccination and 27 subsequent days (study intervention administered on Day 1 and Day 169), per study group	Unsolicited Safety Set	• Number and percentages of participants with unsolicited AEs
• Percentage of participants with any SAEs from first vaccination until 28 days after second study intervention administration (Day 1 to Day 197), per study group	Exposed Set	• Number and percentages of participants with SAEs
• Percentage of participants with AEs leading to withdrawal from the study or withholding further study intervention administration, from first study intervention administration until 28 days after second study intervention administration (Day 1 to Day 197), per study group	Exposed Set	• Number and percentage of participants with AEs/SAEs leading to withdrawal from the study or withholding further study intervention administration
• Percentage of participants with deviations from normal or baseline † values of haematological, renal, and hepatic panel test results at 7 days after each vaccination Day 8 and Day 176 per study group*	Exposed Set	• Number and percentages of participants having haematological, renal, and hepatic abnormalities

†Baseline for post-first vaccination at Day 8 is Day 1 (can also be screening blood draw, if performed within 3 days of first vaccination), and baseline for post-second vaccination at Day 176 is Day 169.

9.4.2. Secondary endpoint(s)

Endpoint description	Analysis set	Statistical analysis methods
• Percentage of participants with any SAE from 28 days after second vaccination (Day 197) up to Day 337, per study group	Exposed Set	• Number and percentages of participants with SAEs
• Percentage of participants with AEs/SAEs leading to withdrawal from the study from 28 days after second vaccination (Day 197) up to Day 337, per study group	Exposed Set	• Number and percentage of participants with AEs/SAEs leading to withdrawal from the study
• Anti-Vi antigen IgG antibody concentrations as measured by ELISA, at selected timepoints, per study group • Anti-O:2 IgG antibody concentrations, as measured by ELISA, at selected timepoints, per study group	PPS, FAS (only if number of participants differs more than 10%)	• Geometric Mean Concentrations (with 95% CI) at Day 1, Day 29, Day 169, Day 176, and Day 197 • Within-subject geometric mean ratios (with 95% CI) at Day 29, Day 169, Day 176, and Day 197 versus Day 1 baseline, and at Day 176 and Day 197 versus Day 169 baseline
• Anti-Vi antigen IgG antibody concentrations ≥ 4.3 µg/mL, as measured by ELISA, per study group • Anti-Vi antigen IgG antibody concentrations ≥ 2.0 µg/mL, as measured by ELISA, per study group • Within-subject increase of at least 4-fold in Anti-O:2 IgG antibody concentrations, as measured by ELISA, per study group	PPS, FAS (only if number of participants differs more than 10%)	• Number and percentage (with 95% CI) of participants with Anti-Vi antigen IgG antibody concentrations ≥ 4.3 µg/mL at Day 1, Day 29, Day 169, Day 176, and Day 197 • Number and percentage (with 95% CI) of participants with Anti-Vi antigen IgG antibody concentrations ≥ 2.0 µg/mL at Day 1, Day 29, Day 169, Day 176, and Day 197 • ***Number and*** percentage (with 95% CI) of participants with at least 4 fold Anti-O:2 IgG antibody concentrations at, Day 29, Day 169, Day 176, and Day 197 compared to Day 1 baseline

CCI

[redacted]

9.5. Interim analyses

To accelerate evaluation of vaccine immunogenicity in the target population and facilitate planning of future studies, interim and final analyses will be performed as described in Section 9.5.1.

9.5.1. Sequence of analyses

A first interim analysis on safety and immunogenicity will be performed by a Sponsor's delegate unblinded statistician on data collected from all participants until 28 days after the first vaccination in Step 2 (Visit 3, Day 29). An interim CSR will be produced but no individual listings will be generated. Results will not impact the continuation of the study itself but will inform further development of the candidate vaccine in other studies. Since some treatment groups of specific participants may be revealed during the interim analysis, the study will be considered single-blind from this point and onwards with the Investigator, site staff and participants remaining blinded up to EoS.

A second interim analysis on safety and immunogenicity may be performed by a Sponsor's delegate unblinded statistician on data collected from all participants until 28 days after the second vaccination in Step 2 (Visit 6, Day 197). No individual listings will be generated.

The final analysis will include all data for at least primary and secondary endpoints up to and including follow-up safety phone contact (Day 337). CCI [redacted] A final CSR containing all available data will be written and made available to the investigators.

9.5.2. Statistical consideration for interim analysis

No statistical adjustment will be performed since analyses are descriptive without any confirmatory objectives.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, ethical, and study oversight considerations

10.1.1. Regulatory and ethical considerations

- This study will be conducted in accordance with the protocol and with:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organisations of Medical Sciences International Ethical Guidelines
  - Applicable International Council of Harmonisation (ICH) GCP Guidelines

  - Applicable laws and regulations

- The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the Investigator for review and approval. These documents will be signed and dated by the Investigator before the study is initiated.
- Any protocol amendments will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- GSK/IQVIA will provide full details of the above procedures to the Investigator, either verbally, in writing, or both.
- 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/EC.
  - Notifying the IRB/IEC of SAE(s) or other significant safety findings as required by IRB/IEC procedures.
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

10.1.2. Financial disclosure

Investigators and sub-investigators must 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 study and for 1 year after completion of the study.

10.1.3. Informed consent process

The Investigator or his/her representative must fully explain the nature of the study to the participant and answer all questions regarding the study.

Participants must be informed that their participation is voluntary.

Freely given and written informed consent must be obtained from each participant, as appropriate, prior to participation in the study.

The content of the ICF must meet 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 centre.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the consent was obtained. The authorised person obtaining the informed consent must also sign the ICF.

Participants must be re-consented if a new version of the ICF(s) or an ICF addendum is released during their participation in the study.

A copy of the signed and dated ICF(s) must be provided to the participants.

Participants who are rescreened 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.

10.1.4. Data protection

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:

- His/her personal study-related data will be used by the Sponsor in accordance with local data protection law.
- His/her medical records may be examined by Clinical Quality Assurance auditors or other authorised 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.

10.1.5. Committee structure

The iSRC will consist of study-independent GSK clinician, safety representative, statistician and at least 1 external (non-GSK employee) member with expertise in clinical trials. All members' roles and responsibilities will be defined in the iSRC Charter.

The SRT is a cross-functional internal GSK committee responsible for ongoing safety assessment of the entire project.

10.1.6. Dissemination of clinical study data

The key design elements of this protocol and results summaries will be posted on www.ClinicalTrials.gov 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 trial 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 randomisation codes for their site only after completion of the full statistical analysis.

GSK intends to make anonymised patient-level data from this trial 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 trial participants are used to maximum effect in the creation of knowledge and understanding.

10.1.7. Data quality assurance

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 Investigator should maintain a record of the location(s) of their respective essential documents, including source documents (see Glossary of terms for the exact definition of essential and source documents). The document storage system used during the trial and for archiving (irrespective of the type of media used) should provide for document identification, version history, search, and retrieval.

Essential trial documents may be added or removed where justified (in advance of trial initiation) based on their importance and relevance to the trial. When a copy is used to replace an original document (e.g., source documents, case report form), the copy should fulfil the requirements for certified copies (see Glossary of terms for the exact definition of certified copies).

All participant data related to the study will be recorded on printed or eCRF unless transmitted to the GSK/IQVIA electronically (e.g., 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 trial records that include all pertinent observations on each of the site's trial participants (see Glossary of terms for the exact definition of source documents) that supports information entered in the eCRF.

The Investigator must permit study-related monitoring, audits, IRB/IEC 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 (see Glossary of terms for the exact definition of source data).

Study monitors will perform ongoing source data verification to confirm that data entered in the eCRF by authorised 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 (e.g., 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 (QTLs) will be predefined in the Risk Management Plan Study Risk Register (GVGH Study Risk-Based Quality Assessment Template) to identify systematic issues that can impact participant safety and/or the reliability of study results. These predefined parameters will be monitored during the study. Important deviations from the QTLs and remedial actions taken will be summarised in the clinical study report (CSR).

Trial 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 the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.8. 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.

Definitions of what constitutes source data and documents can be found in the Glossary of terms.

10.1.9. Study and site start and closure

First act of recruitment

The first act of recruitment, defined by either the date of first contact with a potential study participant or date of publication of an advertisement for this specific study (whichever is earlier), will signify the official start of the study.

Study/Site termination

GSK or its designee reserves the right to close the study site or terminate the study at any time for any reason at its sole discretion, provided there is sufficient notice given to account for all participants safe exit from study.

Regular closure of study sites will occur upon study completion. A study site is considered closed when all required data/documents and study supplies have been collected and a study site closure visit has been performed.

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

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor'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 IECs/IRBs, the regulatory authorities, and any contract research organisation(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

At the end of the study, the Investigator will:

- Review data collected to ensure accuracy and completeness
- Complete the Study Conclusion screen in the eCRF.

10.1.10. Publication policy

GSK aims to submit the results of the study for publication in searchable, peer reviewed scientific literature within 18 months from the Last Subject Last Visit (safety phone contact, Day 337) for interventional studies and follows the guidance from the International Committee of Medical Journal Editors.

10.2. Appendix 2: Clinical laboratory tests (*Amended*, 21 August 2023)

Anti-Vi antigen IgG determination from serum

Anti-Vi specific IgG antibodies will be measured by a ***qualified, fit for purpose (Amended 21 August 2023),*** anti-Vi IgG ELISA ***assay.*** The assay ***setup, qualification, and serology testing*** will be performed in a laboratory designated by GVGH.

Anti-O antigen IgG determination from serum

Anti-O:2 IgG antibodies in serum will be measured by an ELISA assay, which uses a standard curve with an assigned value of ELISA units/mL. This assay, developed by GVGH, is based on a method previously reported [Launay, 2017] and will be performed in a laboratory designated by GVGH. The ELISA is performed using *S.* Paratyphi A O antigen as coating antigen. For this assay, a standard curve is run in duplicate on each plate. Results are expressed in ELISA units (EU)/mL of serum. One unit equals the reciprocal of the dilution to give an optical density of 1.

CCI

10.2.1. Protocol-required safety laboratory assessments

Table 17 shows the protocol-required safety assays, which will be performed by the local laboratory.

Table 17 Protocol-required safety laboratory assessments

Laboratory assessments	Parameters
Safety Screening laboratory assays	
Haematology	• Leukocytes (white blood cells [WBC]) • Erythrocytes (red blood cells [RBC]) • Haemoglobin • Haematocrit • Platelets • Eosinophils • Basophils • Neutrophils • Monocytes • Lymphocytes
Clinical chemistry	• Total bilirubin • Aspartic aminotransferase (AST) • Alanine aminotransferase (ALT) • γ-Glutamyl transferase (γ-GT) • Lactic dehydrogenase (LDH) • Alkaline phosphatase (AP) • Total proteins • Glucose (random glucose) • Blood urea (BU)* • Creatinine • Sodium • Potassium
Other Screening tests	• Hepatitis B surface antigen antibodies • Hepatitis C virus antibodies • HIV antibodies • Prothrombin time • Blood human chorionic gonadotropin (hCG) pregnancy test (for women of childbearing potential)
Pre/Post-vaccination safety laboratory assays (Visit 1, Visit 2, Visit 4, and Visit 5)	
Haematology	• Leukocytes (WBC) • Erythrocytes (RBC) • Haemoglobin • Haematocrit • Platelets • Eosinophils • Basophils • Neutrophils • Monocytes • Lymphocytes
Clinical chemistry	• Creatinine • AST • ALT • BU*
Other tests	• Urine hCG pregnancy test (as needed for women of childbearing potential; required at Visit 1 and Visit 4)

*BU will be converted to blood urea nitrogen for grading purposes. Refer to Section 10.9.
ALT=alanine aminotransferase; AST=aspartate aminotransferase; BU=blood urea; hCG=human chorionic gonadotropin; RBC=red blood cell; SAE=serious adverse event; ULN=upper limit of normal; WBC=white blood cell
NOTES:
All haematology assay outputs should be reported in absolute values.
All events of ALT ≥3 × upper limit of normal (ULN) and bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT ≥3 × ULN, which may indicate severe liver injury (possible Hy's Law), must be reported as an SAE.

10.3. Appendix 3: Adverse Events: definitions and procedures for recording, evaluating, follow-up, and reporting Definition of AE

10.3.1. Definition of an AE

An AE is any untoward medical occurrence (an unfavourable/unintended sign – including an abnormal laboratory finding), symptom, or disease (new or exacerbated) in a clinical study participant that is temporally associated with the study intervention. The AE may or may not be considered related to the study intervention.

10.3.1.1. Events Meeting the AE Definition

- Significant or unexpected worsening or exacerbation of the condition/indication under study.
- 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 administration of the study intervention even though they may have been present before study start.
- 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 the study intervention or a concurrent medication.
- Signs or symptoms temporally associated with administration of the study intervention.
- Signs, symptoms that require medical attention (e.g., 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 (i.e., invasive procedures, modification of participant's previous therapeutic regimen).
- Clinically significant abnormal laboratory findings or other abnormal assessments that are present at baseline and significantly worsen following the start of the study will also be reported as AEs or SAEs.

- AEs to be recorded as solicited AEs are described in the Section 10.3.3. All other AEs will be recorded as UNSOLICITED AEs.

10.3.1.2. Events NOT Meeting the AE Definition

- Situations where an untoward medical occurrence did not occur (e.g., social and/or convenience admission to a hospital, admission for routine examination).
- 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.
- 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.
- Hospitalisation for elective treatment of a pre-existing condition (known or diagnosed before signing the informed consent) that did not worsen from baseline.
- Any clinically significant abnormal laboratory findings or other abnormal safety assessments associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.

10.3.2. Definition of an SAE

An SAE is any untoward medical occurrence that:
a. Results in death.
b. Is life threatening Note: 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, had it been more severe.
c. Requires hospitalisation or prolongation of existing hospitalisation Note: In general, hospitalisation signifies that the participant has been admitted at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or in an out-patient setting. Complications that occur during hospitalisation are also considered AEs. The event will also be considered serious if a complication prolongs hospitalisation or fulfils any other serious criteria. When in doubt as to whether 'hospitalisation' occurred or was necessary, the AE should be considered serious.
d. Results in disability/incapacity Note: 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, diarrhoea, influenza like illness, and accidental trauma (e.g., sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

e.	Is a congenital anomaly/birth defect in the offspring of a study participant
f.	Abnormal pregnancy outcomes (e.g., spontaneous abortion, foetal death, stillbirth, congenital anomalies, ectopic pregnancy)
g.	Other situations Medical or scientific judgement must be exercised in deciding whether reporting is appropriate in other situations. Important medical events that may not be immediately life threatening or result in death or hospitalisation but may jeopardise the participant or require medical or surgical intervention to prevent one of the other outcomes listed in the above definition should be considered serious. Examples of such events are invasive or malignant cancers; intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias; and convulsions that do not result in hospitalisation.

10.3.3. Solicited events

a. Solicited administration-site events

The following administration-site events will be solicited:

Table 18 Solicited administration-site events

All participants
Pain at administration site
Redness at administration site
Swelling at administration site

b. Solicited systemic events

The following systemic events will be solicited:

Table 19 Solicited systemic events

All participants
Fever
Headache
Myalgia (muscle pain)
Arthralgia (joint pain)
Fatigue (tiredness)

Note: participants will be instructed to measure and record the axillary 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 diary card.

10.3.4. Unsolicited AEs

An unsolicited adverse event is an adverse event that was either not included in the list of solicited events or could be included in the list of solicited events but with an onset outside the specified period of follow-up for solicited events. Unsolicited AEs 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 (i.e., symptoms or illnesses requiring a hospitalisation, 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 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.

10.3.5. Adverse events of special interest

Not applicable

10.3.6. Clinical laboratory parameters and other abnormal assessments qualifying as AEs or SAEs

In the absence of a diagnosis, abnormal laboratory findings assessments (e.g. clinical chemistry, haematology, or other tests) or other abnormal results the Investigator considers clinically significant will be recorded as an AE or SAE, if they meet the definition of an AE or SAE (refer to the Sections 10.3.1 and 10.3.2).

The Investigator must exercise his or her medical and scientific judgement in deciding whether an abnormal laboratory finding, or other abnormal assessment is clinically significant.

All events of ALT ≥3 × upper limit of normal (ULN) and bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT ≥3 × ULN, which may indicate severe liver injury (possible Hy's Law), must be reported as an SAE.

10.3.7. Events or outcomes not qualifying as AEs or SAEs

10.3.7.1. Pregnancy

Female participants who become pregnant after the first study intervention dose must not receive subsequent doses of the study intervention but may continue other study procedures at the discretion of the Investigator.

While pregnancy itself is not considered an AE or SAE, any abnormal pregnancy outcome or complication or elective termination of a pregnancy for medical reasons will be recorded and reported as an SAE. Please refer to the Section 10.3.2 for definition of SAE.

10.3.8. Recording and follow-up of AEs, SAEs, and pregnancies

The participants will be instructed to contact the Investigator immediately should they experience any signs or symptoms they perceive as serious.

When an AE/SAE occurs, it is the Investigator's responsibility to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) related to the event. This includes the assessment of COVID-19 cases as per the WHO definition [WHO, 2022]. The Investigator will then record all relevant information regarding an AE/SAE on the eCRF. The Investigator may not send photocopies of the participant's medical records to GSK instead of appropriately completing the eCRF.

There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all participant identifiers will be blinded on copies of the medical records prior to submission to GSK.

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 instead of individual signs/symptoms.

A pDiary, hereafter referred to as Participant Diary, will be used in this study to capture solicited administration-site or systemic events. The participant should be trained on how and when to complete the Participant Diary.

Anyone who measures administration-site or systemic events and who will record the event in the Participant Diary should be trained on using the Diary. This training must be documented in the participant's source record. If any individual other than the participant is making entries in the Participant Diary, their identity must be documented in the Participant Diary/participant's source record.

The Investigator or delegate will transcribe the required information into the eCRF in English.

10.3.8.1. Time period for collecting and recording AEs, SAEs, and pregnancies

All AEs that occur during the 28 days following administration of each dose of study intervention (Day 1 to Day 28 and Day 169 to Day 196) must be recorded onto the appropriate section of the eCRF, irrespective of their intensity or whether they are considered related to the study intervention.

All SAEs and pregnancies will be collected as specified in Table 12 and Section 10.3.10.

10.3.8.2. Follow-up of AEs, SAEs, pregnancies, or any other events of interest

After the initial AE/SAE/pregnancy or any other event of interest, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed up until the event is resolved, stabilised, otherwise explained, or the participant is lost to follow-up.

Other non-serious AEs must be followed until resolution or until the participant is lost to follow-up.

10.3.8.2.1. 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 30 days after the last vaccination.

If a participant dies during their participation in the study or during a recognised follow-up period, GSK will be provided with any available post-mortem findings, including histopathology.

10.3.8.2.2. Follow-up after the participant is discharged from the study

The Investigator will provide any new or updated relevant information to GSK on a previously reported SAE using an electronic Expedited Adverse Events Report and/or pregnancy 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 SAE as fully as possible.

10.3.8.2.3. Follow-up of pregnancies

Pregnant participants will be followed to determine the outcome of the pregnancy. At the end of the pregnancy, whether full-term or premature, information on the status of the mother and child will be forwarded to GSK using the electronic pregnancy report and the Expedited Adverse Events Report if applicable. Generally, the follow-up period does not need to be longer than 6 to 8 weeks after the estimated date of delivery.

Regardless of the reporting period for SAEs in this study, if the pregnancy outcome is an SAE, it should always be reported as such.

Furthermore, if the Investigator becomes aware of any SAE occurring as a result of a post-study pregnancy AND it is considered by the Investigator to be reasonably related to the study intervention, he/she must report this information to Sponsor or Sponsor's delegate as described in the Section 10.3.10.

10.3.8.3. Updating of SAE and pregnancy information after removal of write access to the participant's eCRF

When additional SAE or pregnancy information is received after write access to the participant's eCRF is removed, new or updated information should be recorded on the appropriate paper report, with all changes signed and dated by the Investigator. The updated report should be faxed to the Study contact for reporting SAEs (refer to the IQVIA study contact list) within the defined reporting time frames specified in the Table 13.

10.3.9. Assessment of intensity and toxicity

10.3.9.1. Assessment of intensity

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

Table 20 Intensity scales for solicited events in adults

Adult		
Event	**Intensity grade**	**Parameter**
Pain at administration site	0	None
	1	Mild: Any pain neither interfering with nor preventing normal everyday activities.
	2	Moderate: Painful when limb is moved and interferes with everyday activities.
	3	Severe: Significant pain at rest. Prevents normal everyday activities.
Redness at administration site		Greatest surface diameter in mm
Swelling at administration site		Greatest surface diameter in mm
Temperature*		Temperature in °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
Fatigue (tiredness)	0	Normal
	1	Mild: Fatigue that is easily tolerated
	2	Moderate: Fatigue that interferes with normal activity
	3	Severe: Fatigue that prevents normal activity
Myalgia (muscle pain)	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 (joint pain)	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

*Refer to the SoA (Section 1.3) for the definition of fever and the preferred location for temperature measurement.

The maximum intensity of administration site redness/swelling will be scored as follows (based on the US Food & Drug Administration [FDA] grading scale [U.S. Department of Health and Human Services, 2007]):

Redness/Swelling			
Grade 0 Absent	**Grade 1 Mild**	**Grade 2 Moderate**	**Grade 3 Severe**
<25 mm	≥25 – ≤50 mm	>50 – ≤100 mm	>100 mm

The maximum intensity of fever will be scored as follows (based on the US FDA grading scale [U.S. Department of Health and Human Services, 2007]):

Fever			
Grade 0 Absent	**Grade 1 Mild**	**Grade 2 Moderate**	**Grade 3 Severe**
<38.0°C	≥38.0°C – <38.5°C	≥38.5°C – <39.0°C	≥39.0°C

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 judgement.

The intensity should be assigned to 1 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 (such an AE would, for example, prevent attendance at work and would necessitate the administration of corrective therapy).

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. An event is defined as 'serious' when it meets 1 of the predefined outcomes as described in the Section 10.3.2.

10.3.9.2. Assessment of causality

The Investigator must assess the relationship between study intervention and the occurrence of each unsolicited AE/SAE using clinical judgement. 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 and/or Prescribing Information for marketed products 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 are 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' (see Section 10.3.2), 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 Sponsor or designee. However, it is very important to record an assessment of causality for every event before submitting the Expedited Adverse Events Report to Sponsor or designee.

The causality assessment is one 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.

10.3.9.3. Medically attended visits

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

10.3.9.4. 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).

10.3.10. Reporting of SAEs, pregnancies, and other events

10.3.10.1. Events requiring expedited reporting to Sponsor or designee

Once an Investigator becomes aware that an SAE has occurred in an enrolled participant, the Investigator (or designee) must complete information in the electronic Expedited Adverse Events Report WITHIN 24 HOURS, even if the Investigator does not have complete information on the SAE. It must be completed as thoroughly as possible, with all available details of the event. The report must be dated and signed by the Investigator (or designee).

The SAE report must be updated WITHIN 24 HOURS of the receipt of updated information on the SAE. The Investigator will always provide an assessment of causality at the time of the initial report.

Refer to the Table 13 for the details on timeframes for reporting of SAEs and pregnancies.

Refer to the Section 10.3.10.2 for information on backup systems in case the electronic reporting system does not work.

10.3.10.2. Backup system in case the electronic reporting system does not work

If the electronic reporting system does not work, the Investigator (or designee) must fax or email a completed, dated and signed paper Expedited Adverse Events Report to the study contact for reporting SAEs (refer to the Sponsor Information or IQVIA study contact list) within 24 hours of becoming aware of the SAE.

Investigator (or designee) must complete the electronic Expedited Adverse Events Report within 24 hours after the electronic reporting system is working again. The information reported through the electronic SAE reporting system will be considered valid for regulatory reporting purposes.

10.4. Appendix 4: Contraceptive guidance and collection of pregnancy information

10.4.1. Definitions

10.4.1.1. Woman of childbearing potential (WOCBP)

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

10.4.1.1.1. Women not considered as women of childbearing potential

- Premenarchal

  Menarche is the first onset of menses in a young female. Menarche is normally preceded by several changes associated with puberty including breast development and pubic hair growth.

  Additional evaluation should be considered if a participant's fertility status is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention.

- Premenopausal female with ONE of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy
  - Current bilateral tubal ligation or occlusion

Note: Documentation can come from the site personnel's: review of participant's medical records, medical examination, or medical history interview.

- Postmenopausal female

  A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (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.

- Females on HRT and whose menopausal status is in doubt will be required to use a non-hormonal, highly effective contraception method if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrolment.

10.4.2. Contraception guidance

- Female participants of childbearing potential are eligible to participate if they agree to use a highly effective contraceptive method consistently and correctly according to the methods listed in GSK's list of highly effective contraceptive methods (Table 21).

Table 21 Highly effective contraceptive methods

Highly effective contraceptive methods that are user dependent ***Failure rate of <1% per year when used consistently and correctly***
Combined (oestrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation • Oral • Intravaginal • Transdermal
Progestogen-only hormonal contraception associated with inhibition of ovulation • Injectable • Oral
Highly effective methods that are user independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation • Intrauterine device • Intrauterine hormone-releasing system • Bilateral tubal occlusion
Vasectomised partner *(A vasectomised partner is a highly effective contraception 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.)*
Male partner sterilisation 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.)*
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 drug. 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.)*

10.4.3. Collection of pregnancy information

10.4.3.1. Female participants who become pregnant

Refer to the Sections 8.3.1, 8.3.2, 10.3.8.1 and 10.3.8.3 for further information on detection, recording, reporting and follow-up of pregnancies.

Any female participant who becomes pregnant during the study will discontinue study intervention or be withdrawn from the study.

10.5. Appendix 5: Genetics

Not applicable

10.6. Appendix 6: Definition of medical device AE, adverse device effect (ADE), serious adverse device effect (SADE) and unanticipated SADE (USADE)

10.6.1. Definition of medical device AE and ADE

- 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 unfavourable 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 (i.e., user error), or
  - any malfunction of a medical device, or
  - intentional misuse of the medical device.

10.6.2. Definition of medical device SAE, SADE and USADE

A medical device SAE is any serious adverse event that:
a. Led to death
b. 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 hospitalisation. Planned hospitalisation 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.
c. Led to foetal distress, foetal death or a congenital abnormality or birth defect
d. Is a suspected transmission of any infectious agent via a medicinal product
Serious Adverse Device Effect (SADE) definition
• A SADE is defined as an ADE that has resulted in any of the consequences characteristic of a SAE. • 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.

10.6.3. 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.
- Email/Facsimile transmission of the paper 'Medical device or combination product with device deficiency/incident report form' is the preferred method to transmit this information to the Sponsor.
- Contacts for reporting can be found in the IQVIA study contact list.
- GSK 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.

10.6.4. Reporting of medical device deficiencies for Associated Person

If an Associated Person (i.e., e.g., spouse, caregiver, site staff) experiences a device deficiency, the medical device deficiency information, and any associated AE/SAE information will be reported to Sponsor or Sponsor's delegate. The Associated Person will be provided with the safety reporting information and authorisation to contact physician letter.

If follow-up information is required, authorisation 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.
- GSK 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.

10.7. Appendix 7 Country-specific requirements

Not applicable

10.8. Appendix 8: List of Asian countries considered endemic for typhoid fever

- Bangladesh
- Cambodia
- China
- India
- Lao People's Democratic Republic
- Myanmar
- Nepal
- Pakistan
- Sri Lanka
- Thailand
- Vietnam

10.9. Appendix 9: Toxicity grading scale for safety laboratory assessment

Laboratory test	Grade 1	Grade 2	Grade 3	Grade 4
BUN – mg/dL	<23 – 26	>26 – 31	>31	Requires dialysis
Creatinine – mg/dL (female)	>1.1 – 1.7	>1.7 – 2.0	>2.0 – 2.5	>2.5 or requires dialysis
Creatinine – mg/dL (male)	>1.3 – 1.7	>1.7 – 2.0	>2.0 – 2.5	>2.5 or requires dialysis
Eosinophils – cell/mm^3	>500 – 1500	>1500 – 5000	>5000	Hypereosinophilic
Haemoglobin (female) – gm/dL	11.0 – <11.6	9.5 – <11	8.0 – <9.5	<8.0
Haemoglobin (female/male) – change from baseline value – gm/dL	Any decrease – 1.5	>1.5 – 2.0	>2.0 – 5.0	>5.0
Haemoglobin (male) – gm/dL	12.5 – <12.9	10.5 – <12.5	8.5 – <10.5	<8.5
Liver function tests – ALT, AST increase by factor	≥1.1 – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 10 x ULN	>10 x ULN
Lymphocyte decrease – cell/mm^3	750 - <800	500 - <750	250 - <500	<250
Neutrophil decrease – cell/mm^3	1340	1000 - <1340	500 - <1000	<500
Platelet decrease – cell/mm^3	125 000 – <150 000	100 000 – <125 000	25 000 – <100 000	<25 000
WBC decrease – cell/mm^3	2500 – <3700	1500 – <2500	1000 – <1500	<1000
WBC Increase – cell/mm^3	>10 000 – 15 000	>15 000 – 20 000	>20 000 – 25 000	>25 000

Toxicity Grading scale for safety laboratory test results have been based on the US FDA Guidance for Industry [U.S. Department of Health and Human Services, 2007] and adjusted in consideration of local normal ranges provided by the site. Parameters not included in the FDA grading scales will not be graded; their assessment will be based on laboratory normal ranges and medical judgement.
ALT=alanine aminotransferase; AST=aspartate aminotransferase, BUN=blood urea nitrogen; ULN=upper limit of normal, WBC=white blood cells

10.10. Appendix 10: Abbreviations and Glossary of terms

10.10.1. List of abbreviations

ADE: adverse device effect

AE: adverse event

ALT: alanine aminotransferase

ANOVA: analysis of variance

AST: aspartate aminotransferase

BioE: Biological E Ltd

BU: blood urea

BUN:	blood urea nitrogen
CI:	confidence intervals
CoP:	Correlate of Protection)
CRM_{197}	Cross- Reacting Material 197
CSR	Clinical Study Report
eCRF:	electronic Case Report Form
EoS:	End of Study
FAS:	Full Analysis Set
FDA:	Food and Drug Administration, United States of America
FSFV:	First Subject First Visit
FTIH:	first-time-in-human
GCP:	Good Clinical Practice
GMC:	geometric mean concentration
GMR:	geometric mean ratio
CCI [redacted]	
GS:	Global Safety (GSK)
GSK:	GlaxoSmithKline
GVGH:	GSK Vaccines Institute for Global Health
HCP:	healthcare professional
IB:	Investigator Brochure
ICF:	Informed Consent Form
ICH:	International Council on Harmonisation
IEC:	Independent Ethics Committee
IND:	Investigational New Drug
IRB:	Institutional Review Board

iSRC: Internal Safety Review Committee

LSLV: Last Subject Last Visit

MedDRA: Medical Dictionary for Regulatory Activities

CCI [redacted]

PP: Project Physician

PPS: Per-Protocol Set

QTL: quality tolerance limit

RBC: red blood cell

SADE: serious adverse device effect

SAE: serious adverse event

CCI [redacted]

SmPC: Summary of Product Characteristics

SoA: Schedule of Activities

SPM: Study Procedures Manual

SRT: Safety Review Team

SUSAR Suspected Unexpected Serious Adverse Reaction

ULN: upper limit of normal

USADE: unanticipated serious adverse device effect

WBC: white blood cell

WHO: World Health Organization

WOCBP woman of childbearing potential

10.10.2. 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 AE can therefore be any unfavourable 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 (i.e., 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 an SAE.

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.

For this study, single-blind means the Sponsor will be aware of the study intervention assignment but the Investigator and/or his staff will not.

Caregiver: A ‘caregiver’ is someone who

- lives in the close surroundings of a participant and has a continuous caring role or
- has substantial periods of contact with a participant and is engaged in his/her daily health care (e.g., a relative of the participant, a nurse who helps with daily activities in case of residence in a nursing home).

In the context of a clinical study, a caregiver could include an individual appointed to oversee and support the participant’s compliance with protocol specified procedures.

Certified copy:	A copy (irrespective of the type of media used) of the original record that has been verified (i.e., 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 enrolment into the study based upon strict adherence to inclusion/exclusion criteria.
Enrolment:	The process of registering a participant into a clinical study by assigning participant identification number after signing the ICF.
Essential documents	Documents which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced.
eTrack:	GSK's tracking tool for clinical trials.
Evaluable:	Meeting all eligibility criteria, complying with the procedures defined in the protocol, and, therefore, included in the per-protocol analysis.
GSK Vaccines Institute for Global Health (GVGH):	A GSK-owned company, part of the GSK Global Health Programme, committed to develop vaccines for major neglected diseases of impoverished communities.
Immunological correlate of protection:	A correlate of risk that has been validated to predict a certain level of protection from the targeted endpoint.
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.
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 authorisation 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.
Legally acceptable representative:	An individual, judicial or other body authorised under applicable law to consent on behalf of a prospective participant to the participant's participation in the clinical trial. The terms legal representative or legally authorised representative are used in some settings.
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.
Pharmacogenomics:	The ICH E15 Guidance for Industry defines pharmacogenomics as the "Study of variation of DNA and RNA characteristics as related to drug or treatment response."

	Pharmacogenetics, a subset of pharmacogenomics, is "the study of variations in DNA sequence as related to drug response." Pharmacogenomic biomarkers include germline (host) DNA and RNA as well as somatic changes (e.g., mutations) that occur in cells or tissues. Pharmacogenomic biomarkers are not limited to human samples but include samples from viruses and infectious agents as well as animal samples. The term pharmacogenomic experiment includes both the generation of new genetic or genomic (DNA and/or RNA) data with subsequent analysis as well as the analysis of existing genetic or genomic data to understand drug or treatment response (pharmacokinetics, safety, efficacy or effectiveness, mode of action). Proteomic and metabolomic biomarker research is not pharmacogenomics.
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 pre-specified protocol or was terminated.
Protocol administrative change:	A protocol administrative change addresses changes to only logistical or administrative aspects of the study.
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.
Randomisation:	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 led by GSK global safety is comprised of core representatives from GSK safety, clinical, epidemiology, regulatory, and statistics departments, who are also part of the study team.
Self-contained study:	Study with objectives not linked to the data of another study.

Site Monitor:	An individual assigned by the Sponsor and responsible for assuring proper conduct of clinical studies at 1 or more investigational sites.
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 (e.g. 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.
Telemedicine:	Telemedicine refers to the use of information technologies and electronic communications to provide clinical services to patients virtually. The digital transmission of medical imaging, virtual medical diagnosis and evaluations, and video consultations with specialists are all examples of telemedicine.
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.

Virtual visit: This term refers to study visits conducted using multimedia or technological platforms.

10.11. Appendix 11: Protocol amendment history

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

DOCUMENT HISTORY	
Document	**Date of Issue**
Protocol Final	23 August 2022
Protocol amendment 1 Final	25 May 2023
Protocol amendment 2 Final	21 August 2023

Amendments summary of changes table:

Document	Date of issue	Section # and title	Description of change	Brief rationale
Protocol amendment 1	25 May 2023	Section 1.1 (Synopsis); Section 1.3 (Schedule of activities), Table 1 (Schedule of Activities); Section 2.1 (Study rationale); Section 2.2 (Background); Section 4.1 (Overall design)	The first vaccination with the Typhoid and Paratyphoid A conjugate vaccine will be called a priming, whereas the second vaccination after 6 months will be called a booster.	The target vaccine profile has been updated to a single dose (priming dose). The second dose is being studied as a booster in case the single dose is not sufficient.
		Section 1.2 (Schema); Section 4.1 (Overall design), Figure 1 (Study design overview); Section 8.2.2.1 (Staggered vaccination)	It is clarified that only at Visit 1 should sentinel participants receive vaccination 1 day apart.	This is a clarification consistent with the initial safety strategy.
		Section 1.3 (Schedule of Activities), Table 2 (Intervals between study visits)	An allowed interval range between Visit 4 (2nd vaccination visit) and reminder phone call 2 has been added.	This is to provide flexibility to the study site so an earlier reminder can be provided to the participant.
		Section 4.1 (Overall design), Table 4 (Study groups, intervention, and blinding); Section 6.3.4 (Blinding and	After the first interim analysis (planned after Visit 3), the study will be considered single-blind, with both Investigator and participants	This is implemented because of the risk that members of the study team may become unblinded to the intervention of some participants during the interim analysis. Although

Document	Date of issue	Section # and title	Description of change	Brief rationale
		unblinding); Section 9.5.1 (Sequence of analyses); Section 10.10.2 (Glossary of terms)	remaining blinded, until the last Contact (Safety phone call).	individual/randomisation listings are not foreseen for interim analysis, indirect unblinding could occur by a combination of information from unblinded safety group results and participant information accessible via other clinical trial documents/systems. For this Phase 1, non-pivotal, study, single-blinding is deemed sufficient to not compromise the quality of the data.
		Section 5.2.4 (Other exclusions)	A clarification to the exclusion criterion on travel to endemic areas has been added to mention that it covers also travel during the study duration.	This clarification is a more specific instruction to the Investigator.
		Section 8.2.1.3 (Physical examination); Section 8.2.1.5 (Pre-vaccination body temperature)	The maximum amount of time before vaccination to obtain body temperature and vital signs has been set to 60 minutes.	This clarification is a more specific instruction to the Investigator.
		Section 8.2.2.1 (Staggered vaccination), Table 10 (Safety evaluation schedule)	The possibility of combining safety evaluations #3 and #4 has been added in case these may occur close together.	The rationale is to improve efficiency for the study conduct.
		Section 9.3.1 (Criteria for elimination from analysis)	Criteria for elimination for analyses will be listed also in the Protocol Deviation Management Plan.	This is consistent with the latest GSK Standard Operating Procedures and allows easy documentation and update of criteria for elimination for analyses.
		Section 9.5.1 (Sequence of analyses)	It has been specified that an interim clinical study report will be produced after the first interim.	This is in alignment with the new project strategy to consider the asset as a 1-dose vaccine and allow regulatory submissions for the subsequent study.

Detailed description of the current Protocol amendment 2:

<u>Section 1 (Synopsis) and Section 3 (Objectives and Endpoints), Table 3 (Study objectives and endpoints)</u>

In the primary objective sections, clarification regarding the baseline for each post-vaccination laboratory estimation has been added. CCI [redacted]

Objectives	Endpoints
Primary	
Evaluate the safety profile of the Vi-CRM_{197}+O:2-CRM_{197} vaccine, with and without adjuvant.	• Percentage of participants with solicited administration-site events during 7 days after each vaccination, on the days of vaccination and the 6 subsequent days (study intervention administered on Day 1 and Day 169), per study group. • Percentage of participants with solicited systemic events during 7 days after each vaccination, on the days of vaccination and the 6 subsequent days (study intervention administered on Day 1 and Day 169), per study group. • Percentage of participants with unsolicited adverse events (AE) during 28 days after each vaccination, on the days of vaccination and 27 subsequent days (study intervention administered on Day 1 and Day 169), per study group. • Percentage of participants with any serious adverse event (SAE) from first vaccination until 28 days after second study intervention administration (Day 1 to Day 197), per study group. • Percentage of participants with AEs/SAEs leading to withdrawal from the study or withholding further study intervention administration, from first study intervention administration until 28 days after second study intervention administration (Day 1 to Day 197), per study group. • Percentage of participants with deviations from normal or baseline† values of haematological, renal, and hepatic panel test results at 7 days after each vaccination (Day 8 and Day 176), per study group.
Secondary	
Evaluate the long-term safety profile of the Vi-CRM_{197}+O:2-CRM_{197} vaccine, with and without adjuvant.	• Percentage of participants with any SAE from 28 days after second vaccination (Day 197) up to Day 337, per study group. • Percentage of participants with AEs/SAEs leading to withdrawal from the study from 28 days after second vaccination (Day 197) up to Day 337, per study group.
Evaluate the immunogenicity profile of the typhoid and paratyphoid A components of the Vi-CRM_{197}+O:2-CRM_{197} vaccine, with and without adjuvant, using enzyme-linked immunoassay (ELISA).	• Geometric mean concentration (GMC) of anti-Vi antigen Immunoglobulin G (IgG) antibody concentrations as measured by ELISA, before first vaccination (Day 1), 28 days after first vaccination (Day 29), before second vaccination (Day 169), 7 days after second vaccination (Day 176), and 28 days after second vaccination (Day 197), per study group. • GMC of Anti-O:2 IgG antibody concentrations, as measured by ELISA, before first vaccination (Day 1), 28 days after first vaccination (Day 29), before second vaccination (Day 169), 7 days after second vaccination (Day 176), and 28 days after second vaccination (Day 197), per study group.
Evaluate different seroresponse rates to the typhoid and paratyphoid A component of the Vi-CRM_{197}+O:2-CRM_{197} vaccine, with and without adjuvant.	• Percentage of participants achieving anti-Vi antigen IgG antibody concentrations ≥4.3 µg/mL*, as measured by ELISA, before first vaccination (Day 1), 28 days after first

Objectives	Endpoints
	vaccination (Day 29), before second vaccination (Day 169), 7 days after second vaccination (Day 176), and 28 days after second vaccination (Day 197), per study group. • Percentage of participants achieving anti-Vi antigen IgG antibody concentrations ≥2.0 µg/mL**, as measured by ELISA, before first vaccination (Day 1), 28 days after first vaccination (Day 29), before second vaccination (Day 169), 7 days after second vaccination (Day 176), and 28 days after second vaccination (Day 197), per study group. • Percentage of participants achieving at least 4-fold*** increase in Anti-O:2 IgG antibody concentrations, as measured by ELISA, at 28 days after first vaccination (Day 29), before second vaccination (Day 169), 7 days after second vaccination (Day 176), and 28 days after second vaccination (Day 197) compared to first vaccination baseline (Day 1), per study group. *This threshold, estimated to be protective against typhoid fever, was established in previous studies [Szu, 2013; WHO, 2020] and then used in the registration of Vi conjugated vaccine in India. **This threshold, estimated to be protective against typhoid fever, was defined as a short-term threshold in a previous study [Szu, 2014]. ***This threshold is chosen as a clinically meaningful threshold that, in the absence of an established correlate of protection, could allow quantitative decisions to be made for further development of this component of the vaccine.
CCI [redacted]	

†***Baseline for post-first vaccination at Day 8 is Day 1 (Can also be screening blood draw, if performed within 3 days of first vaccination) and baseline for post-second vaccination at Day 176 is Day 169.***

Section 9.4 (Statistical analyses), Section 9.4.1 (Primary endpoint)

In Section 9.4.1, clarification regarding the baseline for each post-vaccination laboratory estimation has been added.

Endpoint description	Analysis set	Statistical analysis methods
• Percentage of participants with solicited administration-site events during 7 days after each vaccination, on the days of vaccination and the 6 subsequent days (study intervention administered on Day 1 and Day 169), per study group	Solicited Safety Set	• Number and percentages of participants with at least one, any, and Grade 3 administration-site solicited AEs
• Percentage of participants with solicited systemic events during 7 days after each vaccination, on the days of vaccination and the 6 subsequent days (study intervention administered on Day 1 and Day 169), per study group	Solicited Safety Set	• Number and percentages of participants with at least one, any, and Grade 3 systemic solicited AEs
• Percentage of participants with unsolicited AEs during 28 days after each vaccination, on the days of vaccination and 27 subsequent days (study intervention administered on Day 1 and Day 169), per study group	Unsolicited Safety Set	• Number and percentages of participants with unsolicited AEs
• Percentage of participants with any SAEs from first vaccination until 28 days after second study intervention administration (Day 1 to Day 197), per study group	Exposed Set	• Number and percentages of participants with SAEs
• Percentage of participants with AEs leading to withdrawal from the study or withholding further study intervention administration, from first study intervention administration until 28 days after second study intervention administration (Day 1 to Day 197), per study group	Exposed Set	• Number and Percentage of participants with AEs/SAEs leading to withdrawal from the study or withholding further study intervention administration
• Percentage of participants with deviations from normal or baseline [†] values of haematological, renal, and hepatic panel test results at 7 days after each vaccination Day 8 and Day 176 per study group	Exposed Set	• ***Number*** and percentages of participants having haematological, renal, and hepatic abnormalities

[†]***Baseline for post-first vaccination at Day 8 is Day 1 (can also be screening blood draw, if performed within 3 days of first vaccination), and baseline for post-second vaccination at Day 176 is Day 169***.

Section 9.4 (Statistical analyses), Section 9.4.2 (Secondary endpoint)

In Section 9.4.2, "Number" has been added in the statistical analysis methods column for completeness, for the last endpoint to calculate within-subject increase of at least 4-fold in Anti-O:2 IgG antibody concentrations, as measured by ELISA, per study group.

Endpoint description	Analysis set	Statistical analysis methods
• Percentage of participants with any SAE from 28 days after second vaccination (Day 197) up to Day 337, per study group	Exposed Set	• Number and percentages of participants with SAEs
• Percentage of participants with AEs/SAEs leading to withdrawal from the study from 28 days after second vaccination (Day 197) up to Day 337, per study group	Exposed Set	• Number and percentage of participants with AEs/SAEs leading to withdrawal from the study
• Anti-Vi antigen IgG antibody concentrations as measured by ELISA, at selected timepoints, per study group • Anti-O:2 IgG antibody concentrations, as measured by ELISA, at selected timepoints, per study group	PPS, FAS (only if number of participants differs more than 10%)	• Geometric Mean Concentrations (with 95% CI) at Day 1, Day 29, Day 169, Day 176, and Day 197 • Within-subject geometric mean ratios (with 95% CI) at Day 29, Day 169, Day 176, and Day 197 versus Day 1 baseline, and at Day 176 and Day 197 versus Day 169 baseline
• Anti-Vi antigen IgG antibody concentrations ≥ 4.3 µg/mL, as measured by ELISA, per study group • Anti-Vi antigen IgG antibody concentrations ≥ 2.0 µg/mL, as measured by ELISA, per study group • Within-subject increase of at least 4-fold in Anti-O:2 IgG antibody concentrations, as measured by ELISA, per study group	PPS, FAS (only if number of participants differs more than 10%)	• Number and percentage (with 95% CI) of participants with Anti-Vi antigen IgG antibody concentrations ≥ 4.3 µg/mL at Day 1, Day 29, Day 169, Day 176, and Day 197 • Number and percentage (with 95% CI) of participants with Anti-Vi antigen IgG antibody concentrations ≥ 2.0 µg/mL at Day 1, Day 29, Day 169, Day 176, and Day 197 • ***Number and*** percentage (with 95% CI) of participants with at least 4-fold in Anti-O:2 IgG antibody concentrations at, Day 29, Day 169, Day 176, and Day 197 compared to Day 1 baseline

Section 9.4 (Statistical analyses), CCI [redacted]

CCI [redacted]

Section 10.2 (Appendix 2: Clinical laboratory tests)

In Section 10.2, information regarding VaccZyme Human anti-Vi IgG kit was deleted and replaced with a general description of an IgG ELISA assay

Anti-Vi antigen IgG determination from serum

Anti-Vi specific IgG antibodies will be measured by a ***qualified, fit for purpose,*** anti-Vi IgG ELISA ~~kit~~ ***assay,*** ~~developed by BioE based on the commercially available VaccZyme Human anti-Vi IgG kit (BindingSite, UK)~~. The assay ***setup, qualifications, and serology testing*** will be performed in a laboratory designated by GVGH.

11. REFERENCES

Barkume C, Date K, Saha SK, et al. Phase I of the surveillance for enteric fever in Asia Project (SEAP): an overview and lessons learned. *JID*. 2018;218:S188-94.

Bhutta ZA, Capeding MR, Bavdekar A, et al. Immunogenicity and safety of the Vi-CRM197 conjugate vaccine against typhoid fever in adults, children, and infants in south and southeast Asia: results from two randomized, observer-blind, age de-escalation, phase 2 trials. *Lancet Infect Dis*. 2014;14(2) 119-29.

Chung AW, Kumar MP, Arnold KB, et al. Dissecting polyclonal vaccine-induced humoral immunity against HIM using Systems Serology. *Cell*. 2015;163: 988-98.

GBD 2017 Typhoid and Paratyphoid Collaborators. The global burden of typhoid and paratyphoid fevers: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet Infect Dis*. 2019;19:369-81.

John J, Van Aart CJC, Grassly NC, et al. The burden of typhoid and paratyphoid in India: systematic review and meta-analysis. *PLOS Negl Trop Dis*. 2016;10:e0004616.

Kasi SG, Shivananda S, Marathe S, et al. Indian Academy of Pediatrics (IAP) Advisory Committee on Vaccines and Immunization Practices (ACVIP): Recommended Immunization Schedule (2020-21) and Update on Immunization for Children Aged 0 Through 18 Years. *Indian Pediatr*. 2021;58:44-53.

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.

Micoli F, Rondini S, Gavini M, et al. O:2-CRM(197) conjugates against *Salmonella* Paratyphi A. *PloS One*. 2012;7(11):e47039.

Micoli F, Bjarnarson SP, Arcuri M, et al. Short Vi-polysaccharide abrogates T-independent immune response and hyporesponsiveness elicited by long Vi-CRM197 conjugate vaccine. *PNAS*. 2020;117(39):24443-9.

CCI [redacted]

Owais A, Sultana S, Zaman U, et al. Incidence of typhoid bacteremia in infants and young children in southern coastal Pakistan. *Pediatr Infect Dis J*. 2010;29(11):1035-9.

CCI [redacted]

Saha S, Saha S, Das RC, et al. Enteric fever and related contextual factors in Bangladesh. *Am J Trop Med Hyg*. 2018;99:20-5.

Szu S, Hunt S, Xie G, et al. A human IgG anti-Vi reference for Salmonella typhi with weight-based antibody units assigned. *Vaccine*. 2013;31(15):1970-4.

Szu SC, Klugman KP, Hunt S. Re-examination of immune response and estimation of anti-Vi IgG protective threshold against typhoid fever-based on the efficacy trial of Vi conjugate in young children. *Vaccine*. 2014;32(20):2359-63.

U.S. Department of Health and Human Services. Guidance for Industry-Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials 2007. Accessed 1 August 2022. https://www.fda.gov/media/73679/download

van Damme P, Kafeja F, Anemona A, et al. Safety, immunogenicity and dose ranging of a new Vi-CRM_{197} conjugate vaccine against typhoid fever: randomized clinical testing in healthy adults. *PLoS One*. 2011;6:e25398.

World Health Organization (WHO). Recommendations to assure the quality, safety and efficacy of typhoid conjugate vaccines, Annex 2, TRS No 1030. 5 November 2020. Meeting Report. Accessed 1 August 2022. https://www.who.int/publications/m/item/tcv71-recommendations

World Health Organization (WHO). WHO COVID-19: Case Definitions. Updated in Public health surveillance for COVID-19. Updated 22 July 2022. Accessed 1 August 2022. https://www.who.int/publications/i/item/WHO-2019-nCoV-Surveillance_Case_Definition-2022.1

CCI [redacted]

Signature Page for 205480 TMF-16430589 v1.0

Reason for signing: Approved	Name: PPD Role: Approver Date of signature: 25-Aug-2023 15:53:39 GMT+0000

Signature Page for TMF-16430589 v1.0