Clinical Study Protocol

Primary Study Intervention(s)	*Shigella* 4-component generalized modules for membrane antigens vaccine (altSonflex1-2-3)
Other Study Intervention(s)	• Typhoid Vi-CRM_{197} conjugate vaccine (*TYPHIBEV*) • Diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis (inactivated) and *Haemophilus influenzae* type b vaccine (adsorbed) (*Infanrix hexa*) • Measles and rubella vaccine (live) (*MR-VAC*)
Study Identifier	219449
E*udra*CT Number	***2023-000945-18***
Approval Date	19 Dec 2022
Protocol Amendment Approval Date	19 Apr 2024
Title	A Phase 2 single-blind, randomized, controlled, single center study to assess the immunogenicity and safety of a 2-dose schedule with GVGH altSonflex1-2-3 vaccine in African infants (H06_02TP)
Brief Title	A study on the immunogenicity and safety of a multicomponent *Shigella* vaccine in preventing shigellosis in infants
Sponsor	GlaxoSmithKline Biologicals SA Rue De L'Institut 89 1330 Rixensart Belgium
Sponsor signatory	Ashwani Kumar Arora Head of Clinical Development & Regulatory Affairs

Medical monitor name and contact *information* can be found in *the* local study contact information document

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Protocol *Amendment 1* Investigator Agreement

I agree:

- To conduct the study in compliance with this protocol, any future protocol amendments, with the terms of the clinical trial agreement and with any other study conduct procedures and/or study conduct documents provided by GSK.
- To assume responsibility for the proper conduct of the study at this site.
- That I am aware of and will comply with GCP and all applicable regulatory requirements.
- That I will comply with the terms of the site agreement.
- To comply with local bio-safety legislation.
- 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 study-related duties and functions conducted at the study site.
- To ensure that any individual or party to whom I have delegated study-related duties and functions conducted at the study site are qualified to perform those study-related duties and functions.
- 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 on-site or elsewhere without the approval of GSK and the express physical informed consent of the participant and/or the participant's LAR.
- 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 and data management processes of the study with respect to data entry and resolution of queries about the data.
- To have control of all essential documents and records generated under my responsibility before, during, and after the study.
- 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 study intervention(s), and more generally about their 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.

Study identifier	219449
E*udra*CT number	***2023-000945-18***
Approval Date	19 Dec 2022
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Title	A Phase 2 single-blind, randomized, controlled, single center study to assess the immunogenicity and safety of a 2-dose schedule with GVGH altSonflex1-2-3 vaccine in African infants (H06_02TP)
Investigator name	
Signature	
Date of signature (DD Month YYYY)	

Protocol Amendment Summary Of Changes Table

DOCUMENT HISTORY	
Document	**Date of Issue**
Amendment 1	19 Apr 2024
Original Protocol	19 December 2022

Amendment 1: (19 Apr 2024)

Overall rationale for the current Amendment:

The amendment has been prepared to improve safety monitoring of participants by modifying the creatinine grading scale based on normal reference range that better represents the population being evaluated and by introducing blood urea, sodium, and potassium testing to ensure further monitoring of the renal function. Endpoints have been added to capture the potential impact of vaccination on the respective endpoints as a broader evaluation of the vaccine profile. Other administrative changes have been made as requested by ethics committee reviewer and updated internal company guidance.

LIST OF MAIN CHANGES IN THE PROTOCOL AND THEIR RATIONALE:

Section # and title	Description of change	Brief rationale
Global	Correction of grammar, formatting, or spelling, mistakes	To correct minor errors.
Title page	EudraCT Number added. Token for date added. Wording updated.	EudraCT number added because the trial is in scope of Article 46 of Pediatric Regulation (EC) No 1901/2006. Change due to template update from v02 to v03.
Sponsor Signatory Approval	EudraCT Number added.	EudraCT number added because the trial is in scope of Article 46 of Pediatric Regulation (EC) No 1901/2006.
List of abbreviations and definitions of terms	Terms added or removed. Definitions added or adapted.	To align with GSK internal changes and due to template update from v02 to v03.
Section 1.1 Synopsis	Extended wording added for Rationale, Objectives, Endpoints, and Estimands, Overall design, Number of participants and Data Monitoring/Other Committee.	Changes due to template update from v02 to v03.
Section 1.3 Schedule of Activities	Internal references updated. Table footnotes adapted. Marks used to indicate procedure that requires documentation in the individual eCRF. Footnote added to Table 2.	Changes made to ensure completeness of SoA, for alignment with GSK standard and due to template update from v02 to v03. Changes made to reflect information to be included in the eCRF. To reflect out of window visits.
Section 2.2 Background	Wording added. Study number added for Phase 1/2 clinical study. IM replaced with intramuscular.	Changes made to better reflect disease background and current studies. Change due to template update from v02 to v03.
Section 2.3 Benefit/risk assessment	Generic name and SmPCs added for comparator vaccines.	Change due to template update from v02 to v03 and GSK internal changes.
Section 3. Objectives, endpoints and estimands	Wording adapted for objectives to include “of age”. Endpoints adapted. Footnotes adapted.	To ensure objectives completeness. To reflect safety and immunogenicity assessments to be performed. To include additional serotypes testing.
Section 4.1 Overall design	Wording adapted. Safety monitoring reference added.	To reflect clinical study location. To align with GSK internal changes.
Section 4.2 Scientific rationale for the study	“~” replaced with “approximately”.	To align with GSK internal changes.
Section 4.2.1 Participant input into design	Wording removed.	Changes due to template update from v02 to v03.
Section 5.1 Inclusion criteria	“INC#” tag and numbering added to each criterion.	Change due to template update from v02 to v03.
Section 5.2 Exclusion criteria	“EXC#” tag and numbering added to each criterion. “IM” replaced with “intramuscular”.	Changes due to template update from v02 to v03.

Section # and title	Description of change	Brief rationale
Section 5.4 Screen failures	Wording adapted.	Change made to reflect rescreening.
Section 6.1 Study intervention(s) administered	Table 4 adapted. Comparators identified according to new classification. Footnote added.	Changes due to template update from v02 to v03. To clarify how dilution of altSonflex1-2-3 is performed.
Section 6.3 Assignment to study intervention	Randomization system updated to RTSM.	To align with GSK internal changes.
Section 6.8 Treatment of overdose	Wording added.	Changes due to template update from v02 to v03.
Section 6.9 Prior and concomitant therapy	Wording on antibiotic use added. "Dosage" replaced with "dose". Wording adapted.	To allow the collection of additional data on antibiotics use by participants during the study. Changes due to template update from v02 to v03.
Section 7.1 Discontinuation of study intervention Section 7.2 Participant discontinuation/withdrawal from the study	Lists of reasons adapted	Changes due to template update to v03, to align with eCRF.
Section 7.2 Participant discontinuation/withdrawal from the study	Wording adapted.	To reflect data and samples availability for the study analyses.
Section 8.2.1 Biological samples	"~" replaced with "approximately".	To align with GSK internal changes.
Section 8.2.2 Laboratory assays	Table 7 footnotes added.	To ensure abbreviation definitions completeness.
Section 8.2.3 Immunological read-outs	Table 8: number of participants and footnotes adapted.	To reflect participants subsets and to ensure abbreviation definitions completeness.
Section 8.3 Safety assessment	Wording adapted.	To reflect study interventions discontinuation.
Section 8.3.1 Physical examination/history directed physical examination	Wording adapted.	Changes made to reflect information to be included in the eCRF.
Section 8.3.4 Safety monitoring.	Wording adapted.	To reflect study interventions discontinuation.
Section 8.4 1 AEs, SAEs, and other safety reporting	Wording adapted.	To ensure SAE recording accuracy and sections references completeness.
Section 8.4.1 Time period and frequency for collecting AE, SAE, and other safety information	Wording adapted. Footnotes added.	To reflect collection and reporting of safety information.
Section 8.4.2 Method of detecting AEs and SAEs Section 8.4.3 Follow-up of AEs and SAEs	Internal references adapted.	Due to removal of section on TEAE definition (TEAE definition removed as is equivalent to AE following immunization and it is already captured in the section of solicited/unsolicited AEs).
Section 8.4.5 Regulatory reporting requirements for SAEs	Wording added.	Changes due to template update from v02 to v03.

Section # and title	Description of change	Brief rationale
Section 9.3.1.1 Definition of endpoints Section 9.3.2 Secondary endpoints analysis Section 9.3.3 Tertiary endpoint analysis	Wording adapted.	Change made to reflect statistics to be computed.
Section 9.3.1.2 Main analytical approach Section 9.2 Analysis sets	"FAS" replaced with "ES". Definition for FAS, Unsolicited Safety Set and Solicited Safety Set removed from Table 12.	Change made to reflect participants sets to be used.
Section 9.5 Pre-dose sample size determination	Wording adapted.	To reflect withdrawals from the study.
Section 10.1.3 Informed consent process Section 10.1.4 Data protection Section 10.1.7 Data quality assurance Section 10.1.10 Publication policy	Wording added and/or adapted.	Changes due to template update from v02 to v03.
Section 10.1.6 Dissemination of Clinical Study Data	Wording adapted.	To reflect period for summaries submission after primary/study completion date. Changes due to template update from v02 to v03.
Section 10.1.10 Publication policy	Wording replaced.	Change due to template update from v02 to v03.
Section 10.2 Appendix 2: Clinical laboratory tests	Wording adapted. Table 14: Sodium, Potassium, Blood urea added to Clinical chemistry safety laboratory assays.	Change to reflect Anti-*Shigella* serotype-specific antibody determination. Change made to ensure appropriate monitoring of the renal function.
Section 10.3.2 Definition of SAE	Possible Hy's Law case – wording adapted.	Change due to template update from v02 to v03.
Section 10.3.5.7 Reporting of SAEs	"NIMP" replaced with "product that is not part of the study design"	Change due to template update from v02 to v03.
Section 10.5 Appendix 5	Grading scales for creatinine updated. Footnote reference year adapted.	Change made to better reflect the population being evaluated (previous creatinine grading scale may not accurately reflect the potential severity of renal impairment in infant participants, as low creatinine baseline values may be observed in this population).
Section 11 References	References added.	To ensure information in the document is accurately referenced. Changes due to template update from v02 to v03 to include SmPCs of comparators used in the study.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADR	***Adverse drug reaction***
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AST	***Aspartate aminotransferase***
CFR	Code of federal regulations
CHIM	Controlled human infection model
CI	Confidence interval
CoP	Correlate of protection
COVID-19	Coronavirus disease 2019
CRF	Case report form
CSR	Clinical study report
DNA	Deoxyribonucleic acid
ES	***Exposed set***
eCRF	Electronic case report form
ELISA	Enzyme-linked immunoassay
EoS	End-of-study
EPI	Expanded Program on Immunization
FSFV	First subject first visit
FTiH	First-time in human
GCP	Good clinical practices
GMC	Geometric mean concentration
GMMA	Generalized modules for membrane antigens

Abbreviation	Definition
GMR	Geometric mean ratio
GMT	Geometric mean titer
GSK	GlaxoSmithKline Biologicals SA
GVGH	GlaxoSmithKline Vaccines Institute for Global Health
HLA-B27	Human leukocyte antigen B27
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Council on Harmonisation
IEC	Independent ethics committee
IgG	Immunoglobulin G
IHME	Institute for Health Metrics and Evaluation
IMP	Investigational medicinal product
INR	International normalized ratio
IRB	Institutional review board
iSRC	Internal safety review committee
LAR	***Legally acceptable representative***
LAZ	***Length-for-age z-score***
LMIC	Low- and middle-income countries
LPS	Lipopolysaccharide
LSLV	Last subject last visit
MedDRA	Medical Dictionary for Regulatory Activities
MR-VAC	***Measles and rubella vaccine***
OAg	O-Antigen
OD	Optical density

Abbreviation	**Definition**
pDiary	Paper diary
PI	Principal investigator
PP	Project physician
PPS	Per Protocol Set
QTL	Quality tolerance limit
RTMS	***Randomization and trial supply management system***
SAE	Serious adverse event
SBA	Serum bactericidal assay
SmPC	Summary of product characteristics
SoA	Schedule of activities
SRT	Safety review team
SUSAR	***Suspected unexpected serious adverse reaction***
TAU	Tel Aviv University
TCV	Typhoid conjugate vaccine
ULN	Upper limit ***of*** normal

Term	Definition
ADR	***An AE where a causal relationship between a medicinal product and the AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out.*** ***In the context of a clinical trial, an ADR can be serious or nonserious. Serious ADRs may be subject to expedited reporting if they are considered unexpected (see SUSAR definition).*** ***For marketed products, ADRs are subject to expedited reporting within the country where they are authorized.***
Blinding	A procedure in which 1 or more parties to the study 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 study, and only when the data are cleaned to an acceptable level of quality will appropriate personnel be unblinded or when required in case of a SAE. In a single-blind study, the investigator(s) and/or their staff are aware of the intervention assignment, but the participant is 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 their 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.
Child in care	A child who has been placed under the control or protection of an agency, organization, institution or entity by the courts, the government or a government body, acting in accordance with powers conferred on them by law or regulation. The definition of a child in care can

Term	Definition
	include a child cared for by foster parents or living in a care home or institution, provided that the arrangement falls within the definition above. The definition of a child in care does not include a child who is adopted or has an appointed legal guardian.
Co-administered product	***A product given to clinical trial participants as required in the protocol as part of their standard care for a condition that is not the indication for which the IMP is being tested and is therefore not part of the objective of the study.***
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.
Comparator	***Any product used as a reference (including placebo, marketed product, GSK, or non-GSK) for an investigational product being tested in a clinical trial. This is any product that is being used to assess the safety, efficacy, or other measurable value against the test product (IMP).***
Eligible	Qualified for enrollment into the study based upon strict adherence to inclusion/exclusion criteria.
Essential documents	Documents ***that*** individually and collectively permit evaluation of the conduct of a study and the quality of the data produced.
Intercurrent event	***Event occurring after study intervention initiation that affects either the interpretation or the existence of the measurements associated with the clinical question of interest.***
Intervention number	A number identifying an intervention to a participant, according to intervention allocation.
IMP	A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorization but used or assembled (formulated or

Term	Definition
	packaged) in a way different from the authorized form, or when used for an unauthorized indication, or when used to gain further information about the authorized form.
Investigator	A person responsible for the conduct of the clinical study at a study site. If a study is conducted by a team of individuals at a study site, the investigator is the responsible leader of the team and may be called the principal investigator. The investigator can delegate study-related duties and functions conducted at the study site to qualified individual or party to perform those study-related duties and functions.
LAR	An individual, judicial or other body authorized under applicable law to consent on behalf of a prospective participant to the participant's participation in the clinical study. The terms legal representative or legally authorized representative are used in some settings.
LSLV	***The date on which the last participant in a clinical study was examined or received an intervention/treatment to collect final data for the primary outcome measures, secondary outcome measures, and AEs (that is, the last participant's last visit or LSLV).***
Participant ***identifier***	A unique identification number assigned to each participant who consents to participate in the study.
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.
Placebo	***An inactive substance or treatment that looks the same as, and is given in the same way as, an active drug or intervention/treatment being studied.***
Randomization	Process of random attribution of intervention to participants to reduce selection bias.

Term	Definition
Remote visit	***A visit conducted in the place other than the study site.***
Source data	All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. Source data are contained in source documents (original records or certified copies).
Study intervention	***Term used throughout the clinical study to cover all types of investigational and non-investigational products including medical devices and vaccines intended to be administered to the study participants during the study conduct. Procedures conducted to manage participants or to collect data are excluded from the usage of this term.***
SUSAR	***In a clinical trial, a serious adverse reaction that is considered unexpected, i.e., the nature or severity of which is not consistent with the reference safety information (e.g., IB for an unapproved IMP). All ADRs that are both serious and unexpected are subject to expedited reporting.***

1. PROTOCOL SUMMARY

1.1. Synopsis

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

Brief Title: A study on the immunogenicity and safety of a multicomponent *Shigella* vaccine in preventing shigellosis in infants.

Rationale: ***An important objective for GSK is to develop a multicomponent Shigella vaccine to prevent the burden of shigellosis in infants and children in developing countries where shigellosis is endemic. Currently, there are no widely used vaccines against Shigella sonnei (S. sonnei) and Shigella flexneri (S. flexneri) serotypes despite several attempts in the last decades. The candidate vaccine, altSonflex1-2-3, is currently evaluated in a Phase 2 age de-escalation clinical study in Kenya, with the aim of identifying a preferred dose, using a 3-dose vaccinations schedule in infants from 9 months of age (NCT05073003). The current Phase 2 clinical study will evaluate the immunogenicity and safety of an alternative 2-dose vaccination schedule.***

For further details refer to Section 2.1.

Objectives, Endpoints, and Estimands: ***The primary objectives of this study are to evaluate the immunogenicity profile of the altSonflex1-2-3 vaccine administered at 9 and 15 months of age in terms of GMCs/GMTs of antibodies against Shigella LPS/OAg before each study intervention administration (Day 1 and Day 169), and 28 days after each study intervention administration (Day 29 and Day 197), and in terms of seroresponse rate at 28 days after each study intervention administration (Day 29 and Day 197), compared to baseline (Day 1), and compared to pre-administration (Day 1 and Day 169, respectively).***

The key secondary objective of this study is to evaluate the safety and reactogenicity of the altSonflex1-2-3 vaccine administered at 9 and 15 months of age and to evaluate the immunogenicity of co-administered MR-VAC administered at 9 and 15 months of age in terms of anti-measles and anti-rubella IgG concentrations.

For further details, see Section 3.

Overall Design: ***This is a Phase 2, single (participants' parent[s]/LAR[s]) blind, randomized, controlled, single center, 2-dose study. Participants will be randomized to receive dose A or dose B or dose C of an investigational Shigella vaccine or a comparator licensed vaccine (Typhibev and Infanrix Hexa).***

Participants will also be co-administered with MR-VAC.

For further details, see Section 4.1.

Number of Participants: ***The study will include 200 infants at 9 months of age randomly assigned in a 1:1:1:1 ratio to the different study groups: Dose_A, Dose_B, Dose_C and Control (approximately 50 participants in each study group) to whom either the study vaccine or control vaccines will be administered.***

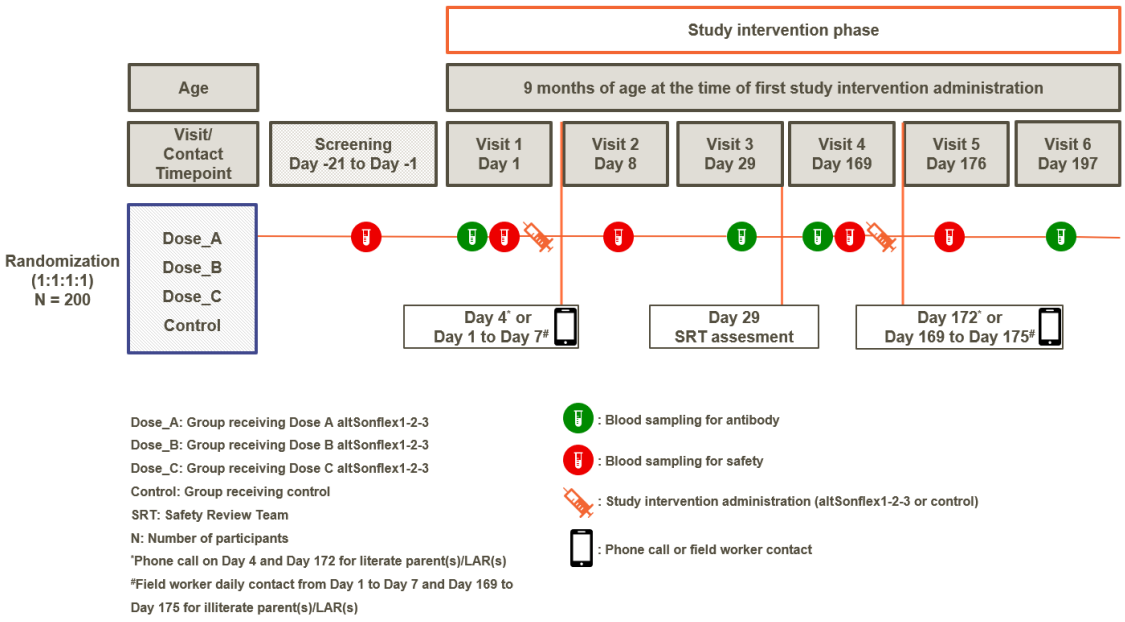
For further details see Section 9.5.

Data Monitoring/Other Committee: ***An internal GSK SRT will evaluate the benefit-risk profile of the investigational product.***

For further details, see Section 10.1.5.

1.2. Schema

Figure 1 Study design overview



1.3. Schedule of activities (SoA)

Table 1 Schedule of Activities

Age		9 months				10 months	15 months				16 months	Notes
Type of contact	Screening period	Visit 1	Reminder phone contact [a]	Field worker daily home visit [b]	Visit 2	Visit 3	Visit 4	Reminder phone contact [a]	Field worker daily home visit [b]	Visit 5	Visit 6	
Timepoints	Day -21 to Day-1	Day 1	Day 4	Day 1 to Day 7	Day 8	Day 29	Day 169	Day 172	Day 169 to Day 175	Day 176	Day 197	
Informed consent by parent(s)/LAR(s)	●											See Section 10.1.3 for details.
Check inclusion/exclusion criteria	●	●					●					See Section 5.1 and ***Section*** 5.2 for Inclusion and Exclusion criteria.
Collect demographic data	●											See Section 8.1.1 for more information.
Medical and vaccination history	●											See Section 8.1.2 for more information.
Physical examination (including vital sign assessment and body temperature measurement)	●	●					●					See Section 8.3.1 for more information.
Symptom-directed physical examination					○	○				○	○	See Section 8.3.1 for more information.
Weight and length measurements	●	●			●	●	●			●	●	See Section 8.3.1 for more information.
Check contraindications, warnings and precautions to vaccination	○	○					○					See Section 8.3.3 for more information.
Check criteria for temporary delay for enrollment and/or study intervention administration	○	○					○					See Section 5.5 for more information.

Age		9 months				10 months	15 months				16 months	Notes
Type of contact	**Screening period**	**Visit 1**	**Reminder phone contact [a]**	**Field worker daily home visit [b]**	**Visit 2**	**Visit 3**	**Visit 4**	**Reminder phone contact [a]**	**Field worker daily home visit [b]**	**Visit 5**	**Visit 6**	
Timepoints	**Day -21 to Day-1**	**Day 1**	**Day 4**	**Day 1 to Day 7**	**Day 8**	**Day 29**	**Day 169**	**Day 172**	**Day 169 to Day 175**	**Day 176**	**Day 197**	
Body temperature measurement					○	○				○	○	The preferred location for measuring temperature will be: • axilla. ***Fever is defined as temperature ≥38.0°C.***
Study group and study intervention number allocation		○										See Section 6.3 for more information.
Study intervention number retrieval for subsequent dose							○					See Section 6.4 for more information.
Recording of administered study intervention number		●					●					See Section 6.4 for more information.
AltSonflex1-2-3 or Control vaccine administration		●[c]					●[d]					See Section 6.1 for more information.
MR-VAC co-administration		●					●					See Section 6.1 for more information.
Laboratory assessments												
Blood sampling for antibody determination (***approximately*** 5 mL)		●				●	●				●	See Section ***8.2.1*** for more information.
Blood sampling for safety screening laboratory assays (hematology panel, clinical chemistry, viral serologic analyses, and HLA-B27) (***approximately*** 9 mL)	●											See Section ***8.2.1*** for more information.

Age		9 months				10 months	15 months				16 months	Notes
Type of contact	**Screening period**	**Visit 1**	**Reminder phone contact [a]**	**Field worker daily home visit [b]**	**Visit 2**	**Visit 3**	**Visit 4**	**Reminder phone contact [a]**	**Field worker daily home visit [b]**	**Visit 5**	**Visit 6**	
Timepoints	**Day -21 to Day-1**	**Day 1**	**Day 4**	**Day 1 to Day 7**	**Day 8**	**Day 29**	**Day 169**	**Day 172**	**Day 169 to Day 175**	**Day 176**	**Day 197**	
Blood sampling for safety laboratory assays (hematology panel and clinical chemistry analyses) (***approximately*** 2 mL)		●			●		●			●		See Section ***8.2.1*** for more information.
Safety assessments												
Record any concomitant medications/vaccinations	●	●			●	●	●			●	●	See Section 6.9 for more information.
Record any intercurrent ***events***/medical conditions		●			●	●	●			●	●	See Section ***7.1.1***, ***Section 8.1.2 and Section 8.4.1*** for more information.
Recording of solicited events in paper Diary (Days 1 to Day 7 post-administration)		○		○ [e]			○		○ [e]			See Section 10.3.5 for more information.
Recording of unsolicited AEs in the source document (Days 1-28 post-administration)		○			○		○			○		See Section 10.3.5 for more information.
Transcription of unsolicited AEs in the eCRF by the investigator or delegate		●			●	●	●			●	●	See Section 10.3.5 for more information.
Safety surveillance (including vital sign assessment and body temperature measurement) (60 minutes post-administration)		●					●					See Section 10.3.5 for more information.
Reporting of SAEs related to study participation or concurrent GSK medication/vaccine	●	●			●	●	●			●	●	See Section 10.3.5 for more information.

Age		9 months				10 months	15 months				16 months	Notes
Type of contact	**Screening period**	**Visit 1**	**Reminder phone contact [a]**	**Field worker daily home visit [b]**	**Visit 2**	**Visit 3**	**Visit 4**	**Reminder phone contact [a]**	**Field worker daily home visit [b]**	**Visit 5**	**Visit 6**	
Timepoints	**Day -21 to Day-1**	**Day 1**	**Day 4**	**Day 1 to Day 7**	**Day 8**	**Day 29**	**Day 169**	**Day 172**	**Day 169 to Day 175**	**Day 176**	**Day 197**	
Reporting of SAEs		●			●	●	●			●	●	See Section ***10.3.5.7 and Section 8.4.5*** for more information.
Recording of AEs leading to withdrawal ***or discontinuation from further vaccinations***		●			●	●	●			●	●	See Section ***10.3.5*** for more information.
Diary cards												
Distribution of diary cards		○					○					See Section ***10.3.5.1*** for more information.
Phone call for diary card completion reminder to literate parent(s)/LAR(s)			●					●				See Section 10.3.5 for more information.
Field worker visit for diary card completion for illiterate parent(s)/LAR(s)				●					●			See Section ***10.3.5.1*** for more information.
Diary card transcription in the eCRF by investigator or delegate					●					●		See Section 10.3.5 for more information.
Return of diary cards					●[f]					●[f]		See Section ***10.3.5.1*** for more information.
Participant study conclusion											●	See Section 4.4 for more information.

● 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.
AE = Adverse event; eCRF = electronic case report form; HLA-B27 = Human leukocyte antigen B27; LAR(s) =Legally acceptable representative(s); ***MR-VAC = Measles and rubella vaccine;*** SAE = Serious adverse event.
a. For literate parent(s)/LAR(s) only.
b. For illiterate parent(s)/LAR(s) only.
c. The first control vaccination will consist of *TYPHIBEV*.

d. The second control vaccination will consist of *Infanrix hexa*.
e. For illiterate parent(s)/LAR(s), diary cards will be completed by the site field worker.
f. For illiterate parent(s)/LAR(s), diary cards can be returned by the field worker at the end of the 7-days after study intervention administration.

Note: *TYPHIBEV* vaccination will be offered at the end of the study to infants in the intervention groups who received the altSonflex1-2-3 vaccines.

Table 2 Intervals between study visits

Interval	Planned visit interval	Allowed interval range*
Visit 1→Reminder phone contact	3 days	1 day to 4 days
Visit 1→Visit 2	7 days	7 days to 10 days
Visit 1→Visit 3	28 days	28 days to 33 days
Visit 1→Visit 4	168 days	158 days to 178 days
Visit 4→Reminder phone contact	3 days	1 days to 4 days
Visit 4→Visit 5	7 days	7 days to 10 days
Visit 4→Visit 6	28 days	28 days to 33 days

In case a participant is out of window for a particular visit, the next visit should be scheduled based on the originally planned protocol visit intervals and allowed interval ranges

2. INTRODUCTION

2.1. Study rationale

An important objective for GSK is to develop a multicomponent *Shigella* vaccine to prevent the burden of shigellosis in infants and children in developing countries where shigellosis is endemic. Currently, there are no widely used vaccines against *Shigella sonnei* (*S. sonnei*) and *Shigella flexneri* (*S. flexneri*) serotypes despite several attempts in the last decades. GVGH has developed a new candidate *Shigell*a 4-component GMMA vaccine (altSonflex1-2-3) against *S. sonnei* and *S. flexneri* serotypes 1b, 2a, and 3a, which is based on the previously developed GVGH monovalent *S. sonnei* vaccine (1790GAHB vaccine) using the GMMA-platform technology. The candidate vaccine, altSonflex1-2-3, has been evaluated for the FTiH in adults in Belgium, and is currently evaluated in a Phase 2 age de-escalation clinical study in Kenya, with the aim of identifying a preferred dose, using a 3-dose vaccinations schedule in infants from 9 months of age (NCT05073003). The current Phase 2 clinical study will evaluate the immunogenicity and safety of an alternative 2-dose vaccination schedule.

2.2. Background

Shigellosis remains a major public health problem around the world; it is one of the leading causes of diarrheal disease in LMIC, particularly in young children. The Global Burden of Disease study estimated that in 2017 *Shigella* caused approximately 238 000 deaths globally and it ranked second with regard to pathogen contributions in global diarrheal deaths (15.2%) [IHME, 2017]. In infants, in LMIC, particularly when healthcare resources are limited, shigellosis can often lead to death. In 2016, *Shigella* was responsible for 63 713 deaths among children less than 5 years of age and 212 438 deaths among all ages [GBD, 2018].

Water and sanitation risk factors as well as exposure risks from animals contribute to enteric infections in children [Berendes, 2023] with presently no widely available vaccine against *Shigella*. Treatment for shigellosis is mainly supportive to keep patients stable and restore lost electrolytes due to diarrhea. ***Cases of moderate to severe diarrhea can become persistent (≥14 days duration) in infants (11.3%), children 12 to 23 months of age (9.9%) or 24 to 59 months of age (7.3%) [Buchwald, 2023].*** If available, specific antibiotics are sometimes used for severe cases of shigellosis. Current drug therapies are

under threat from the increasing rates of antibiotic resistance in *Shigella* serotypes around the world ***[Bengtsson, 2022]. In a study examining children 0-59 months of age with moderate to severe diarrhea antimicrobial resistant Shigella cases showed AMR data as follows: trimethoprim-sulfamethoxazole (94.9%), ampicillin (48.4%), nalidixic acid (1.7%), ceftriaxone (0.3%), azithromycin (0.3%), and ciprofloxacin (0.0%) [Kasumba, 2023].***

The immune response against the OAg of LPS of *Shigella* bacteria is known to confer serotype-specific immunity and protection against infection in participants that have recovered from primary infections, as well as those that have been challenged with an infectious dose of the bacteria in human challenge vaccine studies [Cohen, 1991; Ferreccio, 1991]. ***The IgG against S. Sonnei LPS has been suggested to predict the vaccine efficacy in adults [Cohen, 2023].*** GVGH has developed and characterized a monovalent vaccine against *S. sonnei* (1790GAHB vaccine) using the GMMA technology. The 1790GAHB vaccine is composed of purified GMMA adsorbed on *Alhydrogel*. The GMMA are designed to present the OAg portion of *S. sonnei* LPS molecule as an active moiety.

The 1790GAHB vaccine was tested in 2 Phase 1 dose-escalation studies (NCT02017899 and NCT02034500) in Europe (3 vaccinations, 1 month apart via 3 routes of administration: ***intramuscular***, intranasal, and intradermal) and in 1 Phase 1 booster study in France (NCT3089879) for the evaluation of the immunological memory response after a 1-dose booster vaccination with the 1790GAHB vaccine. Results have shown that by the ***intramuscular*** route up to the 6/100 µg GMMA OAg/proteins dose has an acceptable safety profile and induces antibody responses of at least the same magnitude as the one previously observed following natural exposure to the pathogen [Cohen, 1988, Launay, 2017;]. A booster injection elicited a strong immune response, regardless of the priming dose [Launay, 2019].

A Phase 2a study (NCT02676895) evaluated the safety and immunogenicity of 2 doses (1.5/25 µg and 6/100 µg OAg/protein) of the *S. sonnei* 1790GAHB vaccine, delivered by ***intramuscular*** route to healthy adults from a shigellosis-endemic country, Kenya, with a schedule of 2 vaccinations, 1 month apart. This study confirmed the acceptable safety profile and the immunogenicity induced by the vaccine 28 days after first and second vaccination despite a high baseline antibody concentration [Obiero, 2017]. A Phase 2b *S. sonnei* CHIM study (NCT03527173) was conducted in the United States at the Cincinnati Children's Hospital Medical Center to evaluate the efficacy, immunogenicity, and safety of the candidate *S. sonnei* 1790GAHB vaccine at a dose of 1.5/25 µg OAg/GMMA proteins. The vaccine confirmed the safety and immunogenicity profiles shown in previous studies but did not show efficacy against *Shigella* infection for the primary objective or any of the clinical endpoints for moderate to severe shigellosis. Analysis of the results of the CHIM trial identified suboptimal immunogenicity as the most likely root cause for the lack of clinical efficacy and has been taken into consideration for the study design of the current study.

The monovalent *S. sonnei* 1790GAHB vaccine was the predecessor to the development of a multicomponent broadly protective *Shigella* 4-component GMMA vaccine (altSonflex1-2-3) for vaccination of infants 9 months of age in LMIC where shigellosis is

endemic. Both the *S. sonnei* 1790GAHB vaccine and the altSonflex 1-2-3 vaccines consist of purified GMMA adsorbed on *Alhydrogel*, which present the OAg portion of LPS molecules, and act as the vaccine's active moiety for the principal immune response. The amount of OAg in the altSonflex1-2-3 formulation has been guided by the results of the CHIM study (NCT03527173) and by the dose-response relationship observed in the Phase 1 dose-escalation study in France [Micoli, 2021]. Additionally, the strong booster immune response seen in the extension study has suggested the need to evaluate longer intervals between primary vaccinations with altSonflex1-2-3 in the Phase 1 stage of the study. For the *S. sonnei* component, 1790GMMA used in previous GVGH 1790GAHB trials, is replaced by the newly developed 2929GMMA. This alternate construct expresses an increased OAg density and, having a higher OAg to protein and Lipid A ratio than 1790GMMA, it allows an increase in the amount of OAg without affecting the safety profile of the vaccine. The altSonflex1-2-3 GMMA vaccine is formulated at a full dose containing 15µg OAg of each serotype.

The Phase 1/2 clinical study ***(212149 NCT [NCT05073003])*** evaluated the safety and immunogenicity of the altSonflex1-2-3 GMMA candidate vaccine against *S. sonnei* and *S. flexneri* serotypes 1b, 2a, and 3a. The candidate altSonflex1-2-3 vaccine was administered intramuscularly first to adults 18 to 50 years of age in Europe and, subsequently, administered to adults 18 to 50 years of age in Africa, children 24 to 59 months of age, and infants 9 months of age in Africa, using 3 different dose-levels of the vaccine (A [low], B [medium], and C [high]). The current Phase 2 clinical study will evaluate the safety and immunogenicity of a different clinical schedule of the altSonflex1-2-3 GMMA candidate vaccine in infants 9 months of age, in a shigellosis-endemic population in Africa, which is the main target age group for this vaccine. The highest vaccine dose (Dose C), that has been tested without any safety concerns in toxicological studies and in European adults, contains 15 µg of each *S. sonnei* and *S. flexneri* 1b, 2a, 3a GMMA. Since the main burden of shigellosis is in children below 5 years of age in developing countries (with a peak in the second and third year of life), it is expected that a broadly protective *Shigella* vaccine will be used in young children in shigellosis-endemic countries at the age of 9 months, concomitantly with other EPI vaccines, such as measles, mumps, rubella or yellow fever depending on a country's EPI schedule.

Please refer to the current IB for information regarding preclinical studies and the latest safety data regarding altSonflex1-2-3.

2.3. Benefit/risk assessment

More detailed information about the known and expected benefits and risks, and expected AEs of altSonflex1-2-3 can be found in the IB.

More detailed information about the known and expected benefits and risks, and expected AEs of *TYPHIBEV (**Typhoid Vi-CRM$_{197}$ conjugate vaccine, [WHO, 2022])**, MR-VAC **(Measles and rubella vaccine, [WHO, 2021a])**,* and *Infanrix hexa (**DTPa-HBV-IPV/Hib vaccine, [EMA, 2023])*** can be found in the relevant Prescribing Information/SmPC.

2.3.1. Risk assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention altSonflex1-2-3		
Important potential risk: Anaphylaxis	Anaphylaxis is considered a potential risk since vaccines are a mixture of compounds and allergic sensitization can occur to any component. Participants may be sensitized to the vaccine antigens, adjuvants, excipients used in the manufacturing process, or a latex stopper on the vial [Erlewyn-Lajeunesse , 2007]. However, the incidence of anaphylaxis is generally very low, and estimates are in the range of 1–10 per 1 million doses distributed depending on the vaccine studied [Rüggeberg, 2007].	Participants will be closely monitored for any symptoms of anaphylaxis. Medical treatment will be readily available in case of anaphylactic reactions following vaccine/control/placebo administration. For example, epinephrine 1:1000, diphenhydramine, and/or other medications for treating anaphylaxis will be available.
Study Procedures		
Risks related to blood sample collection	When blood samples are taken from a vein, there is a risk of bruising at the site. There is a rare possibility of bleeding, fainting and infection or of nerve injury soreness.	Safe sampling procedures will be applied by appropriately trained and qualified staff to minimize distress and sampling errors. The potential risk of feeling faint, or experiencing mild local pain, bruising, irritation, or redness at the site where blood was taken, is mentioned in the ICF. The amount of blood to be taken for sampling is within the locally accepted range for the age groups and is not expected to be harmful to the participant's health.

ICF = Informed consent form.

2.3.2. Benefit assessment

Participants' parents or caregivers can gain medical advice about their children's health status through the medical evaluations and laboratory assessments associated with the study. They will also receive ancillary care for minor ailments at the clinical site throughout their participation in the study.

Vaccination with the investigational vaccine may provide protection against *S. sonnei* and *S. flexneri* bacteria. Co-administered vaccines or vaccines administered as control and not routinely given may provide protection against additional diseases (measles, rubella, typhoid, diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis and *Haemophilus influenzae* type b). Additionally, TCV vaccination will also be offered at the end of the study to infants in the intervention groups who did not receive TCV (*TYPHIBEV*) as a control vaccine, so they may be protected against typhoid fever.

The participants, by participating in the study, will contribute to the process of developing therapies in an area of unmet need. They may also help provide valuable data, about the immune response and tolerability of the investigational vaccine, and about its potential ability to provide clinical protection against shigellosis.

2.3.3. Overall benefit-risk conclusion

Shigellosis remains a major public health problem around the world; it is one of the leading causes of diarrheal disease in LMIC, particularly in children under 5 years old [Kotloff, 2017].

Treatment for shigellosis is mainly supportive to keep patients stable and restore lost electrolytes due to diarrhea. Antibiotic therapy is recommended for cases of dysentery, severe disease and immunocompromised individuals. However antibiotic resistance is on the rise, highlighting the need for an effective vaccine to prevent moderate to severe shigellosis [Puzari, 2018]. No licensed vaccine is currently widely available and therefore, a *Shigella* vaccine is a significant unmet medical need [Mani, 2016].

The mitigation strategy that will be applied in this study for the risks linked to the study vaccines are collection, monitoring and reporting of AEs following vaccination. The vaccines will be administered by trained health care professionals who will follow the specific instructions for vaccine preparation and administration. In accordance with GCP, a physical examination will be performed prior to vaccination and participants will be observed for at least 60 minutes following vaccination, and medical treatment will be readily available after vaccination in case of severe or serious adverse reactions.

Taking into account the measures taken to minimize risk to participants participating in this study, the potential risks with use of the altSonflex1-2-3 candidate vaccine are justified by the anticipated benefits that may be provided to study participants for the prevention of shigellosis in 9 months of age infants.

The control vaccines administered to participants in this study as active comparators and the co-administered vaccines are already licensed and widely used. They have demonstrated medical benefit in the prevention of diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis and *Haemophilus influenzae* type b (*Infanrix hexa*), typhoid fever caused by *Salmonella* typhi (*TYPHIBEV*) and measles and rubella (*MR-VAC*).

3. OBJECTIVES, ENDPOINTS AND ESTIMANDS

Table 3 Objectives and endpoints

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

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

CCI [redacted]

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

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

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

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

4. STUDY DESIGN

4.1. Overall design

This is a Phase 2, single (participants' parent[s]/LAR[s]) blind, randomized, controlled, single center, 2-dose study. An eCRF and a pDiary will be used for data collection, which will include biological sampling (blood) and safety follow-ups.

The clinical study will be performed in the same center (Kenya Medical Research Institute ["KEMRI"]/ United States Army Medical Research Directorate-Africa/Kenya [MRD-A/K]) ***located in Kericho***, where the altSonflex1-2-3 vaccine ***D***ose A, ***Dose*** B and ***Dose*** C ***are being tested*** in infants 9 months of age with a 3-dose vaccination schedule, in a FTiH Phase 1/2 study (NCT05073003). The Phase 1/2 clinical study included a Phase 1 (FTiH) part, conducted in healthy adults in Belgium; the Phase 2 part is ongoing in Kenya, using an age de-escalation approach, including adults, children and infants, with the primary objectives of identifying the preferred dose of the candidate vaccine among infants and evaluating the safety and reactogenicity of the candidate vaccine among adults, children and infants.

The present study will only commence enrollment after all the planned safety reviews by the GSK iSRC and SRT in the Phase 1/2 trial have been completed as per protocol (i.e., after evaluation of data collected up to 7 days after the first study intervention administration in the dose-finding cohort of all infants who were vaccinated in the first 7 weeks of enrollment), and after enrollment has been completed.

The same dose-levels as in the Phase 1/2 clinical study will be tested, to ensure that the preferred dose and the preferred schedule can be evaluated in parallel. Participants will also receive an EPI vaccination with *MR-VAC* concomitantly to study interventions.

The study will include 200 infants at 9 months of age randomly assigned in a 1:1:1:1 ratio to the different study groups: Dose_A, Dose_B, Dose_C and Control (approximately 50 participants in each study group) to whom either the study vaccine or control vaccines will be administered. The completion date will be at Visit 6 (Day 197).

A GSK product specific SRT will review all safety data collected up to 28 days after the first vaccination in infants to evaluate any trends in safety and potential safety signals after the first vaccination ***(refer to Section 8.3.4).*** Figure 1 shows a visual representation of the study design.

4.2. Scientific rationale for study design

In children, 75% of deaths from shigellosis occur in Africa and South-East Asia. Both *S. sonnei* and *S. flexneri* are present in LMIC with ***approximately*** 24% of the deaths being attributable to *S. sonnei*, ***approximately*** 20% to *S. flexneri* 2a, and ***approximately*** 10% each to *S. flexneri* 1b, 2b, 3a, and 6 [Livio, 2014]. Thus, altSonflex1-2-3 would be able to target an important part of the responsible serotypes that affect LMIC.

The number of doses required for achieving an adequate immune response varies from one vaccine to another. For example, measles and rubella vaccines are administered as a 2-dose series starting at 9 months of age, with the second dose in the second year of life, whereas meningococcal vaccine against group B (*Bexsero*) may require 2 primary doses and a third (booster) dose in the second year of life.

4.2.1. Participant input into design

Participants' parent(s)/LAR(s) were interviewed by the PI and the site Community Advisory Board to obtain their feedback regarding the study design and the study procedures.

The participants' parent(s)/LAR(s) raised comments regarding the burden of the study procedures and the duration of the overall study, while acknowledging the importance of the study objectives.

4.3. Justification for dose

CCI



CCI

[redacted]

4.4. End-of-study definition

A participant is considered to have completed the study if the participant has completed all periods of the study including the last visit or the last scheduled procedure shown in the SoA (Section 1.3).

EoS or Date of the last testing released of the Human Biological Samples, related to primary and secondary endpoints, whichever occurs later. EoS must be achieved no later than 8 months after LSLV. EoS cannot be before LSLV.

5. STUDY POPULATION

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

5.1. Inclusion criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

- Participants' parent(s)/LAR(s), 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). ***INC#1***
- Written or witnessed/thumb printed informed consent obtained from the parent(s)/LAR(s) of the participant prior to performance of any study specific procedure. ***INC#2***
- Healthy participants as established by medical history**,** clinical examination, and laboratory assessment. ***INC#3***
- Participants satisfying all screening requirements. ***INC#4***
- Participants seronegative for hepatitis B, and hepatitis C. ***INC#5***
- A male or female 9 months of age at the time of the first study intervention administration. ***INC#6***

- Normal nutritional (weight-for-length) ***z*-**score (-2 standard deviations or greater). ***INC#7***
- Previously completed routine childhood vaccinations to the best knowledge of the participant's parent(s)/LAR(s). ***INC#8***
- Born at a gestation period of ≥37 weeks to the best knowledge of the participant's parent(s)/LAR(s). ***INC#9***
- Participants negative for human immunodeficiency virus as confirmed by DNA polymerase chain reaction testing. ***INC#10***
- Participants negative for HLA-B27. ***INC#11***

5.2. Exclusion criteria

Participants are excluded from the study if any of the following criteria apply:

5.2.1. Medical conditions

- Known exposure to *Shigella* during lifetime of the participant as confirmed during interview with the participant's parent(s)/LAR(s) or documented by participant's records (e.g., history of microbiologically-confirmed *Shigella* infection). ***EXC#1***
- Progressive, unstable, or uncontrolled clinical conditions. ***EXC#2***
- History (known or suspected) of any reaction or hypersensitivity likely to be exacerbated by any component of the study intervention. ***EXC#3***
- Major congenital defects, as assessed by the investigator. ***EXC#4***
- Recurrent history or uncontrolled neurological disorders or seizures. ***EXC#5***
- Any confirmed or suspected immunosuppressive or immunodeficient condition, based on medical history and physical examination (no laboratory testing required). ***EXC#6***
- Hypersensitivity (known or suspected), including allergy, to medicinal products, vaccines, or medical equipment whose use is foreseen in this study. ***EXC#7***
- Clinical conditions representing a contraindication to ***intramuscular*** vaccination and blood draws. ***EXC#8***
- Any behavioral or cognitive impairment or psychiatric disease that, in the opinion of the investigator, may interfere with the participant's ability to participate in the study. ***EXC#9***
- Acute disease and/or fever (defined as temperature ≥38.0°C) at the time of enrollment*. ***EXC#10***

*The participant can still be enrolled into the study at a time when the acute disease and/or fever has resolved.

- Any clinically significant* hematological and/or biochemical laboratory abnormality. ***EXC#11***

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

- Confirmed positive COVID-19 test during the period starting 30 days before the first administration of study interventions (Day -30 to Day 1). ***EXC#12***
- Any other clinical condition that, in the opinion of the investigator, might pose additional risk to the participant due to participation in the study. ***EXC#13***
- Acute or chronic clinically significant pulmonary, cardiovascular, hepatic, or renal functional abnormality, as determined by physical examination or laboratory screening tests. ***EXC#14***

5.2.2. Prior/Concomitant therapy

- Use of any investigational or non-registered product (drug, vaccine or invasive medical device)* other than the study intervention(s) during the period beginning 30 days before the first dose of study intervention(s) (Day - 30 to Day 1), or their planned use during the study period. ***EXC#15***

*Use of herbs and traditional treatments is not considered an exclusion criterion.

- Planned administration/administration of a vaccine/product ***not foreseen by the Protocol*** in the period starting 21 days before the first dose and ending after the last dose of study intervention(s) administration* with the exception of COVID-19 vaccines and EPI vaccines. The recommended time intervals for administration of these vaccines are at least 7 days before or 7 days after (at least 14 days before or 14 days after in case of live vaccines) each dose of study intervention administration. ***EXC#16***
- Administration of long-acting immune-modifying drugs at any time during the study period (e.g., infliximab). ***EXC#17***
- Prior receipt of an experimental *Shigella* vaccine or live *Shigella* challenge. ***EXC#18***
- Prior receipt of a TCV. ***EXC#19***
- Administration of immunoglobulins and/or any blood products or plasma derivatives, or bone marrow transplantation, from birth or planned administration during the study period. ***EXC#20***
- Chronic administration of immune-modifying drugs (defined as more than 14 days consecutive days in total) and/or planned use of long-acting immune-modifying treatments at any time up to the end of the study.
  - Up to 3 months prior to the study intervention administration:

For corticosteroids, this will mean prednisone equivalent ≥0.5 mg/kg/day with maximum of 20 mg/day for pediatric participants. Inhaled and topical steroids are allowed.

– Up to 3 months prior to study intervention administration: long-acting immune-modifying drugs including among others immunotherapy (e.g., TNF-inhibitors), monoclonal antibodies, antitumoral medication. ***EXC#21***

*If emergency mass vaccination for an unforeseen public health threat (e.g., a pandemic) is recommended and/or organized by public health authorities outside the routine immunization program, the time period described above can be reduced provided it is used according to the local governmental recommendations and that sponsor is notified. 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.

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 intervention drug or invasive medical device. ***EXC#22***

5.2.4. Other exclusion criteria

- Any study personnel or immediate dependents, family, or household member. ***EXC#23***
- Child in care. Please refer to the Definitions of terms for the definition of child in care. ***EXC#24***
- Participants who do not meet eligibility criteria for administration of control vaccines. ***EXC#25***

5.3. Lifestyle considerations

No restrictions are required.

5.4. Screen failures

A screen failure is an individual for whom a consent to participate in this study was obtained but is not entered in the study (was not randomized, did not receive study intervention, and did not undergo a post-screening study procedure).

The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Individuals who do not meet the criteria for participation in this study ***within the allowed window*** (screen failure) may be rescreened. Rescreened participants should be assigned a new participant number for every rescreening event ***performed outside of the permitted screening window.***

5.5. Criteria for temporarily delaying enrollment/randomization/administration of study intervention

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

- Participants with hematological/biochemical values out of laboratory reference range which are expected to be temporary may be rescreened/dosed at a later date within the allowed time interval.
- Acute disease and/or fever at the time of enrollment 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 diarrhea, mild upper respiratory infection) without fever may be enrolled and/or dosed at the discretion of the investigator.
- Use of antipyretics and/or analgesics and/or antibiotics within 3 days prior to study intervention administration.
- Participants with a positive COVID-19 test 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 COVID-19 vaccines, administered 7 days before each planned dose (14 days before in case of live vaccines).
- There is a clinical circumstance that warrants delay of blood collection for immunogenicity assessments in this study: participant has received a dose of systemic antibiotics less than 3 days before the intended blood collection. In the event that a participant meets this criterion for delay of blood collection, blood collection may proceed once the window for delay has passed.

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

The definition of study intervention is provided in the table of definitions.

6.1. Study intervention(s) administered

Table 4 shows the study interventions that will be administered during the study.

The candidate vaccine, altSonflex1-2-3, will be administered intramuscularly by study site staff and contains 15 µg (Dose C), 7.5 µg (Dose B), or 3.75 µg (Dose A) of OAg for each antigen component (refer to the Pharmacy Manual for additional details). CCI [redacted]. Table 4 shows formulation details of all study interventions to be administered in the study.

Table 4 Study Intervention(s) administered

Study intervention name	AltSonflex1-2-3 Dose A (diluted from Dose C*)	AltSonflex1-2-3 Dose B (diluted from Dose C*)	AltSonflex1-2-3 Dose C	*TYPHIBEV* (TCV)	*Infanrix hexa* (DTPa-HBV-IPV/Hib vaccine)	*MR-VAC*
Study intervention formulation	CCI [redacted]					

Study intervention name	AltSonflex1-2-3 Dose A (diluted from Dose C*)	AltSonflex1-2-3 Dose B (diluted from Dose C*)	AltSonflex1-2-3 Dose C	*TYPHIBEV* (TCV)	*Infanrix hexa* (DTPa-HBV-IPV/Hib vaccine)	*MR-VAC*
Presentation	CCI [redacted]					
Use	***IMP***	***IMP***	***IMP***	***Comparator***	***Comparator***	***Co-administered product***
Type	Biologic	Biologic	Biologic	Biologic	Combination product	Biologic
Route of administration	Intramuscular i***njection***					Subcutaneous
Administration-site:						
• **Location**	Thigh			Thigh	Thigh	Deltoid
• **Directionality**	Anterolateral					Upper
• **Laterality**	***Left or right***					
Number of doses to be administered:	2	2	2	1	1	2
Volume to be administered	0.5 mL	0.5 mL	0.5 mL	0.5 mL	0.5 mL	0.5 mL
Sourcing	***Provided centrally by the sponsor***					***Provided locally by the clinical site***
Packaging and labeling	Refer to the Pharmacy Manual for further details					
Responsible for manufacture	Dilution at clinical site (Refer to the Pharmacy Manual/Laboratory Manual for further details)		GSK	Biological E. Limited	GSK	Serum Institute of India

CCI [redacted] $CCID_{50}$ = Cell culture infectious dose 50%; CRM_{197} = Cross-reactive material 197; DAgU = D-antigen units; DT = Diphtheria toxoid; CCI [redacted]; CCI [redacted] GSK = GlaxoSmithKline Biologicals SA; Hib = Haemophilus influenzae type b; IPV = Inactivated polio virus; *MR-VAC* = Measles-rubella vaccine; CCI [redacted]; PRN = Pertactin; CCI [redacted]; TCV = Typhoid conjugate vaccine; TT = Tetanus toxoid; Vi = Salmonella enterica serovar Typhi.

**** Dilution is performed using Al(OH)$_3$ suspended in buffered saline (altSonflex-Placebo vial).***

Table 5. Study arms

Arm Title	Dose_A	Dose_B	Dose_C	Control
Arm Type	Experimental	Experimental	Experimental	Control
Arm Description	Participants will receive 0.5 mL of altSonflex1-2-3 Dose A and 0.5 mL of *MR-VAC* twice, on Day 1 and Day 169.	Participants will receive 0.5 mL altSonflex1-2-3 Dose B and 0.5 mL of *MR-VAC* twice, on Day 1 and Day 169.	Participants will receive 0.5 mL altSonflex1-2-3 Dose C and 0.5 mL of *MR-VAC* twice, on Day 1 and Day 169.	Participants will receive 0.5 mL of *TYPHIBEV* on Day 1, 0.5 mL of *Infanrix hexa* on Day 169 ***and 0.5 mL of MR-VAC twice, on Day 1 and Day 169.***
Associated Intervention Labels	AltSonflex1-2-3 Dose A *MR-VAC*	AltSonflex1-2-3 Dose B *MR-VAC*	AltSonflex1-2-3 Dose C *MR-VAC*	*TYPHIBEV* *Infanrix hexa* ***MR-VAC***

MR-VAC = Measles and rubella vaccine.

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, syncope. For example, epinephrine 1:1000, diphenhydramine, and/or other medications for treating anaphylaxis should be available.

6.2. Preparation, handling, storage, and accountability

- The investigator or designee must confirm appropriate conditions (e.g., temperature) have been maintained during transit for all study intervention received, and any discrepancies are reported and resolved before use of the study intervention.
- Only participants enrolled in the study may receive study intervention, and only authorized site staff may supply, prepare, or administer study intervention.
- All study intervention must be stored in a secure, environmentally controlled and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
- The investigator is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
- Further guidance and information for the final disposition of unused study interventions are provided in the Pharmacy Manual.

6.3. Assignment to study intervention

Participant identification numbers will be assigned sequentially to the participants who have a consent to participate in the clinical study, according to the range of participant identification numbers allowed for the study.

The target will be to enroll approximately 200 eligible participants who will be randomly assigned in a 1:1:1:1 ratio to the different study groups: Dose_A, Dose_B, Dose_C and Control (approximately 50 participants in each study group).

The allocation of the participant to a study group at the investigator site will be performed using a Randomization and Trial Supply Management System (herein referred to as RTSM).

After obtaining the signed and dated ICF from the participant's parent(s)/LAR(s) and having checked the eligibility of the participant, the study staff in charge of the study intervention administration will access ***RTMS.*** Upon providing information about participant identification number, the randomization system will determine the study group and will provide the study intervention number to be used for the first dose. The number of each administered study intervention must be recorded in the eCRF on the Vaccine Administration Form.

The study intervention number(s) to be used for subsequent dosing will be provided by the same automated Internet-based system RTSM.

When the RTSM is not available, please refer to the RTSM user guide for specific instructions. Refer to study Pharmacy Manual for additional information about the study intervention number allocation.

6.4. Blinding, masking

Data will be collected in a single (participant)-blind manner. To do so, study interventions will be prepared and administered by qualified staff who may participate in data collection, evaluation, review, or the entry of any study endpoint (i.e., reactogenicity, safety).

Investigators and the study team will remain unblinded to each participant's assigned study intervention throughout the course of the study. Vaccine dilution and all possibly necessary additional activities involving vaccines (e.g., re-labeling of clinical study materials at the study site) will be performed by site staff according to instructions and training provided by GSK. The site staff responsible for these activities will be personnel who are respectively qualified according to applicable local laws and regulations. To maintain the blinding during the administration of the vaccine(s), the participant or participant's parent(s) or LAR(s) will be instructed not to look at the injection syringe while the study intervention is administered. The site staff will be responsible for completing the Vaccine Administration Log and Vaccine Accountability Log to ensure final accountability. Refer to the Pharmacy Manual for further details on blinding procedures and management.

The laboratory in charge of sample testing will be unblinded to the study intervention assignment.

Type of study	
Single (participant) blinded	Only the participants' parent(s)/caregiver/LAR(s) are blinded to the study intervention, but the Investigator and sponsor's study team are unblinded to the study intervention assigned.
Emergency unblinding (PI will provide)	A physician other than the investigator (e.g., an emergency room physician) or participant/participant's caregiver or family member may also request emergency access to the participant's study intervention information as per participant card.

PI = Principal investigator.

6.5. Study intervention compliance

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

6.6. Dose modification

Not applicable.

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

During the study conclusion (Visit 6), the investigator will ask each parent(s)/LAR(s) if they are interested in allowing the participant to join a long-term evaluation study. If a parent(s)/LAR(s) is/are not interested in joining the booster study/long-term evaluation study the reason for refusal will be documented, when available, in the participant's eCRF.

The investigator is encouraged to share the immunological assay results of non-responders with the study participants' parent(s)/LAR(s).

It is the responsibility of the investigator to determine the medical care of the non-responder as per local/regional practices, such as re-vaccination.

At study conclusion, the investigator will be supported to offer TCV participants who did not receive TCV as a study intervention.

6.8. Treatment of overdose

GSK does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator should:

- ***Evaluate the participant to determine, in consultation with the medical monitor, if possible, whether study intervention should be interrupted.***
- ***Closely monitor the participant for any AE/SAE and laboratory abnormalities until EoS as planned (at least 28 days post last dose), or as medically appropriate.***

6.9. Prior and concomitant therapy

Any medication or vaccine (including over-the-counter or prescription medicines) or other specific categories of interest that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use.
- Dates of administration including start and end dates.
- Dose and frequency.

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-administration.
- 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 vaccine/***control vaccine*** and ending at the participant's last study visit/contact.

- Any concomitant vaccination administered in the period starting 30 days before the first dose of study vaccine and ending at the participant's last study visit/contact (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 AEs, 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 Section 5.2.2 for further details).
- All concomitant medication which may explain/cause/be used to treat an SAE including vaccines/products, as defined in Sections 8.4.1 and Section 8.4.3. These must also be recorded in the Expedited Adverse Event report.
- ***All antibiotics administered after the first dose of study intervention (Day 1 to Day 197).***

The GVGH PP 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 in the eCRF based on the list below:

Reasons
AE (AE requiring expedited reporting to GSK, Solicited AE, Unsolicited nonserious AE)
Withdrawal by participant's parent(s)/LAR(s), not due to an AE (Burden of procedure, Participant relocated, COVID 19 Pandemic, Other)
Lost to follow-up (Participant relocated, Other) ***Study terminated by sponsor*** ***Sponsor terminated study intervention***
Physician decision
Protocol deviation
Other

AE =Adverse event; LAR = Legally acceptable representative.

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 Section 5.2.1 and Section 5.2.2 should not receive additional doses of study intervention. Such participants should be encouraged to continue other study procedures, at the investigator's discretion. All relevant criteria for discontinuation of study intervention administration must be recorded in the eCRF.

- Participants who experience any SAE judged to be possibly or probably related to study intervention or non-study concomitant vaccine/product, including hypersensitivity reactions.
- Participants who develop any new condition which, in the opinion of the investigator, may pose additional risk to the participants if they continue to participate in the study.
- Anaphylaxis following the administration of study intervention(s).
- Condition that in the judgment of the investigator would make injection unsafe.

7.2. Participant discontinuation/withdrawal from the study

A participant may withdraw from the study at any time at the participant's parent(s)/LAR(s) request for any reason (or without providing any reason).

A participant may be withdrawn at any time at the discretion of the investigator for safety, behavioral, or compliance reasons.

Investigators will attempt to contact participants' parent(s)/LAR(s) who do not return for scheduled visits or follow-up.

The participant will be permanently discontinued from the study intervention and the study at that time.

All data and samples collected up to and including the date of withdrawal of/last contact with the participant will be ***available for*** the study analyses. If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the study, the participant's parent(s)/LAR(s) may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

The primary reason for participant discontinuation/withdrawal from the study will be documented in the eCRF based on the list below:

Reasons
AE (AE requiring expedited reporting to GSK, Unsolicited nonserious AE, Solicited AE)
Death
Lost to follow-up (Participant relocated, Other)
Study terminated by sponsor
Withdrawal by participant's parent(s)/LAR(s), not due to an AE (Burden of Procedure, Participant relocated, COVID 19 Pandemic, or Other)
Protocol deviations
Physician decision
Other

AE = Adverse event; LAR = Legally acceptable representative.

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 8.4.3).

7.3. Lost to follow-up

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

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

- The site must attempt to contact the participant's parent(s)/LAR(s) and reschedule the missed visit as soon as possible, counsel the participant's parent(s)/LAR(s) on the importance of maintaining the assigned visit schedule and ascertain whether the participant's parent(s)/LAR(s) wishes for their child to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant 's parent(s)/LAR(s). These contact attempts should be documented in the participant's medical record.
- Should the participant's parent(s)/LAR(s) continue to be unreachable, the participant will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed.
- Adherence to the study design requirements, including those specified in the SoA is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. Participants for whom parent(s)/LAR(s) have signed informed consent, but are not eligible to proceed, should be recorded in the eCRF with a status of 'screen failure'.
- Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of the ICF may be utilized for screening ***or baseline*** purposes provided the procedures met the protocol-specified criteria and were performed (at one of the accredited study laboratories) within the timeframe defined in the SoA.
- In the event of a significant study-continuity issue (e.g., caused by a pandemic), alternate strategies for participant visits, assessments, study intervention distribution and monitoring may be implemented by the sponsor or the investigator, as per local health authority/ethics requirements.

The amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will be about 37 mL.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1. Administrative and general/baseline procedures

8.1.1. Collection of demographic data

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

Collection of sex and race data is necessary to assess and monitor the diversity of the trial participants, and to determine if the trial participants are truly representative of the impacted population.

Full date of birth is collected to verify that the participant is of the right age to be enrolled in the study.

8.1.2. Medical/vaccination history

Obtain the participant's medical history and vaccination history by interviewing the parent(s)/LAR(s) and/or review of the participant's medical records. Record any pre-existing conditions, signs and/or symptoms present prior to the first dose of study intervention in the eCRF.

As part of the participant's parent(s)/LAR(s) interview during screening and to evaluate whether the participant meets exclusion criterion of known exposure to *Shigella*, the investigator or delegate should assess whether there are any medical records showing confirmed microbiological diagnosis of *Shigella* diarrhea in the lifetime of the participant. Additionally, any medical history suggestive of *Shigella* diarrhea should be obtained based on the following features and the medical judgment of the investigator:

- History of watery diarrhea with or without blood associated with excessive crying.
- History of fever, toxicity and anorexia.
- Features suggestive of hemorrhagic uremic syndrome.
- Features of acute abdomen following diarrheal illness.
- History of similar illness in other household members.

8.2. Immunogenicity assessments

Planned timepoints for all immunogenicity assessments are provided in the SoA (Section 1.3).

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's parent(s)/LAR(s).

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.

8.2.1. Biological samples

An overall volume of about 37 mL will be collected during the entire study period. Refer to Table 6 and SoA (Section 1.3) for information on volumes collected for different assessments.

In case of abnormal safety laboratory results, repeat or unscheduled samples may be taken.

Table 6 Biological samples

Sample type	Quantity	Unit	Timepoint
Blood sampling for antibody determination*	***Approximately*** 5	mL	As scheduled; refer to Table 1 and Figure 1
Blood sampling for safety screening laboratory assays* (hematology panel, clinical chemistry, viral serologic analyses, and HLA-B27)	***Approximately*** 9	mL	As scheduled; refer to Table 1 and Figure 1
Blood sampling for safety laboratory assays* (hematology panel and clinical chemistry analyses)	***Approximately*** 2	mL	As scheduled; refer to Table 1 and Figure 1

HLA-B27 = Human leukocyte antigen B27.
*The addresses of the clinical laboratories used for sample analysis are provided in a separate document accompanying this Study Protocol.

8.2.2. Laboratory assays

Table 7 Laboratory assays

Test classification	System	Component	Method	Laboratory*
Humoral Immunity (Antibody determination)	Serum	Anti-*S. sonnei* LPS total IgG	ELISA	GVGH or GVGH designated laboratory
		Anti-*S. flexneri* 1b OAg total IgG		
		Anti-*S. flexneri* 2a OAg total IgG		
		Anti-*S. flexneri* 3a OAg total IgG		
		Bactericidal antibodies against *S. sonnei*	SBA	
		Bactericidal antibodies against *S. flexneri* 1b		
		Bactericidal antibodies against *S. flexneri* 2a		
		Bactericidal antibodies against *S. flexneri* 3a		
		Measles	ELISA	
		Rubella		

ELISA = Enzyme-linked immunosorbent assay; GVGH = GSK Vaccines Institute for Global Health; IgG = Immunoglobulin G; LPS = Lipopolysaccharide; OAg = O-antigen; ***S. flexneri = Shigella flexneri; S. sonnei = Shigella sonnei***; SBA = Serum bactericidal assay.
*The addresses of the clinical laboratories used for sample analysis are provided in a separate document accompanying this Study Protocol.

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

GSK clinical laboratories 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.

8.2.3. Immunological read-outs

Table 8 Immunological read-outs

Blood sampling timepoint		Subset name	No. participants	Component
Type of contact and timepoint	Sampling timepoint			
Visit 1 (Day 1), Visit 4 (Day 169)	Pre- administration	N/A	200	Anti-*S. sonnei* LPS total IgG
				Anti-*S. flexneri* 1b OAg total IgG
				Anti-*S. flexneri* 2a OAg total IgG
				Anti-*S. flexneri* 3a OAg total IgG
Visit 3 (Day 29) Visit 6 (Day 197)	Post-administration	N/A	200	Anti-*S. sonnei* LPS total IgG
				Anti-*S. flexneri* 1b OAg total IgG
				Anti-*S. flexneri* 2a OAg total IgG
				Anti-*S. flexneri* 3a OAg total IgG
Visit 1 (Day 1) Visit 4 (Day 169)	Pre-administration	N/A	***70***	Bactericidal antibodies against *S. sonnei*
				Bactericidal antibodies against *S. flexneri* 1b
				Bactericidal antibodies against *S. flexneri* 2a
				Bactericidal antibodies against *S. flexneri* 3a
Visit 3 (Day 29) Visit 6 (Day 197)	Post-administration	N/A	***70***	Bactericidal antibodies against *S. sonnei*
				Bactericidal antibodies against *S. flexneri* 1b
				Bactericidal antibodies against *S. flexneri* 2a
				Bactericidal antibodies against *S. flexneri* 3a
Visit 1 (Day 1)	Pre-administration	N/A	200	Measles IgG
				Rubella IgG
Visit 6 (Day 197)	Post-administration	N/A	200	Measles IgG
				Rubella IgG

IgG = Immunoglobulin G; LPS = Lipopolysaccharide; N/A = Not applicable; ***No. = Number***; OAg = O-Antigen; ***S. flexneri = Shigella flexneri; S. sonnei = Shigella sonnei***.

8.2.4. Immunological CoP

No generally accepted immunological CoP has been demonstrated so far for the antigens used in the study intervention.

For the measles antigen, the conventional CoP is measles IgG antibody titer seroprotection threshold of ≥200 mIU/mL as measured by ELISA at 28 days after the second *MR-VAC* vaccination. For the rubella antigen, the conventional CoP is rubella IgG antibody titer seroprotection threshold of ≥4 IU/mL as measured by ELISA at 28 days after the second *MR-VAC* vaccination.

The immunological assay results will be communicated to the investigator not later than 12 months after the Visit 6 date at which sampling allows the assessment of whether the threshold for protection has been reached.

No other antigen measurements that can assess an immunological CoP are planned in this study.

Refer to Section 6.7 for details regarding treatment for non-responders.

8.2.5. Warnings and precautions to administration of study intervention

Warnings and precautions to administration of study intervention must be checked at each visit with planned administration of study intervention as specified in SoA (Section 1.3).

Refer to the IB for the altSonflex1-2-3 vaccine. Refer to the approved product label/package for all other vaccines.

8.3. Safety assessments

AEs, SAEs and other safety reporting will be captured as per SoA (Section 1.3).

Safety evaluation as a secondary endpoint will assess the occurrence of solicited administration-site and systemic events which occur within 7 days after each study intervention administration, unsolicited AEs which occur within 28 days after each study intervention administration, laboratory abnormal values at 7 days after each study intervention administration (including deviations from reference values or baseline values) and SAEs throughout the study duration. The occurrence of withdrawals, or ***study intervention discontinuation,*** due to AEs will also be assessed throughout the study duration. Currently, there are no AESIs foreseen in this study. SAEs related to study participation or concurrent GSK medication/vaccine will also be recorded and analyzed.

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, 2020]. 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 interventions or the study.

Planned timepoints for all safety assessments are provided in the SoA (Section 1.3).

8.3.1. Physical examination/history directed physical examination

A complete physical examination will be performed at screening and on each study intervention administration visit before the study intervention administration (refer to Section 1.3). The physical examination will be performed by the investigator and clinically relevant findings should be recorded in the participant source documents and in the eCRF (only for enrolled participants).

A symptom-directed physical examination of the participant will be performed on visits where no study intervention is administered (refer to Section 1.3). The nature of the physical examination will be driven by any specific symptoms reported by the participant. The symptom-directed physical examination will not be recorded in the eCRF. However, any abnormalities detected that meet the definition of AE will be recorded as such in the eCRF.

Length and weight will be recorded at all study visits and entered in the source documents ***and transcribed to 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.

8.3.2. Vital signs

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

8.3.3. Clinical safety laboratory tests

- See Section 10.2 for the list of clinical laboratory tests to be performed in accordance with Laboratory Manual and the SoA (Section 1.3).
- The investigator must review the laboratory results, document this review and record any clinically significant changes occurring during the study as an AE. The laboratory results must be retained with source documents.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 28 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or GVGH PP.
  - In the absence of a diagnosis, abnormal laboratory findings assessments 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 Section 10.3.1 and Section 10.3.2).
  - If abnormal values do not return to reference range/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
  - If laboratory values from non-protocol-specified laboratory tests performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification), then the results must be recorded.
  - In case abnormal values are not considered clinically significant by the investigator, additional evaluations could be requested by the GVGH PP.

8.3.4. Safety monitoring

- Participant safety will be continuously monitored by the GVGH PP, throughout the study. Pertinent findings and conclusions are shared with the product's SRT for review of the overall benefit-risk profile of the product.

- In addition, an unblinded early aggregated safety data review will be performed by SRT as defined in the protocol. The goal of this is to allow for a cautious approach to the second study intervention administration and to guarantee early potential safety signal detection during the study. The safety review for this study is planned for the first 200 participants who are dosed and have provided all safety data within 28 days after administration of ***the first study intervention administration*** (on the day of study intervention administration and the 27 subsequent days).
- Data will be reviewed by the sponsor for identification of events that would potentially contribute to a requirement to pause/stop the study.
- If a safety concern is identified in the Phase 1/2 trial (NCT05073003) that may change the benefit-risk profile of 1 or more dose-levels, appropriate actions will be taken also in the current study (e.g., termination of administration of ***1*** or more dose-levels and enrollment will be performed with approximately 50 participants per group only for the dose-levels that continue).
- The GVGH PP will be accountable for notifying all investigators of any decision whether to suspend, modify or continue the conduct of the study on all groups or on selected groups.

8.4. AEs, SAEs, and other safety reporting

For definitions relating to safety information see Section 10.3.

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and other safety information and remain responsible for following up all AEs (see Section 7 ***and sections below)***. This includes events reported by the participant's parent(s)/LAR(s) or caregiver.

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.3.

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

SAEs will be collected from the signing of the ICF until Visit 6 at the time points specified in the SoA (Section 1.3).

SAEs assessed as related to study participation (e.g., study intervention, 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 ***until the first study intervention administration***.

All AEs will be collected from the start of study intervention until Visit 6 at the timepoints specified in the SoA (Section 1.3).

Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded as medical history/current medical conditions, not as

AEs, unless events are defined as SAE related to study procedures ***or to GSK medications/vaccines. Details of timelines for safety reporting are presented in Table 9.***

Table 9 Collection and reporting of safety information

Event	SCR* D-21 to D1	Dose 1 D1	D7	D29	Dose2 D169	D175	Study Conclusion D197
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 ***or discontinuation from further vaccinations***		D1 to D197					
SAEs		D1 to D197					
SAEs related to the study intervention		D1 to D197					
SAEs related to study participation or concurrent GSK medication/vaccine**	D-21 to D197						
Any other event of interest for the study		D1 to D197					

AEs = Adverse events; D = Day; ***GSK = GlaxoSmithKline Biologicals SA;*** SAE = Serious adverse events; SCR = Screening.
* Consent obtained.
**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.
The shaded regions in the ***t***able indicate time period of data collection.

All SAEs will be recorded and reported to the sponsor or designee immediately, and under no circumstance should this exceed 24 hours, as indicated in Section 8.4.5 ***and Section*** 10.3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

A poststudy AE/SAE is defined as any event that occurs outside of the AE/SAE reporting period defined in Section 8.4.1/Table 9.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, after a participant has been discharged from the study, the investigator must record it in the medical records ***per the local country requirements***. If the

investigator considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

See Section 8.4.7 for contact information.

8.4.2. Method of detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and SAEs. Open-ended and non-leading verbal questioning of the participants' parent(s)/LAR(s) is the preferred method to inquire about AE occurrences.

Detection and recording of AE/SAE are detailed in Section ***10.3.5***.

Assessment of AE/SAE intensity, causality and outcome are described in Section ***10.3.5***.

8.4.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Section 10.3.5.5**.**

8.4.4. AESIs

Not applicable.

8.4.5. Regulatory reporting requirements for SAEs

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study intervention under clinical investigation are met. See Section 8.4.1 for reporting timeframes.
- For SAEs, the investigator must always provide an assessment of causality at the time of the initial report, as defined in the Section ***10.3.5***.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the IB/package insert or SmPC and will notify the IRB/IEC, if appropriate according to local requirements.
- ***Investigators have to report to the sponsor any medication errors, abuse and misuse even in the absence of an AE/SAE as these may be subjected to local regulatory reporting requirements for the sponsor.***
- ***Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.***

Table 10 Timeframes for submitting SAE and other events reports to GSK

Type of event	Initial reports		Follow-up of relevant information on a previous report	
	Timeframe	Documents	Timeframe	Documents
SAEs	24 hours*‡	electronic Adverse Events Report	24 hours*	electronic Adverse Events Report

SAEs = Serious adverse events.
*Timeframe allowed after receipt or awareness of the information by the investigator/site staff.
‡Paper Adverse Events Report will be dated and signed by the investigator (or designee). 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.

8.4.6. Pregnancy

Not applicable.

8.4.7. Contact information for reporting SAEs

Table 11 Contact information for reporting SAEs

Study contact for questions regarding SAEs Contact GSK's local and/or medical contacts
Contacts for reporting SAEs Available 24/24 hours and 7/7 days ogm28723@gsk.com

GSK = GlaxoSmithKline Biologicals SA; SAEs = Serious adverse events.

8.4.8. Participant card

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

8.5. Pharmacokinetics

Not applicable.

8.6. Pharmacodynamics

Not applicable.

8.7. Genetics

To minimize any risk of autoimmune reactions, blood samples collected for safety during screening will undergo sampling for the HLA-B27 genetic marker. Participants with a positive test result will not be included in the study. In case of participant rescreening, this test should not be repeated.

8.8. Biomarkers

Not applicable.

8.9. Immunogenicity assessments

Not applicable.

8.10. Health economics or medical resource utilization and health economics

Not applicable.

9. STATISTICAL CONSIDERATIONS

The statistical analysis plan will be finalized prior to first participant first visit and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary, secondary, and tertiary endpoints.

9.1. Statistical hypothesis

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

9.2. Analysis sets

Table 12 Analysis sets

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

AEs = Adverse events.

9.3. Statistical analyses

9.3.1. Primary endpoints analysis

9.3.1.1. Definition of endpoints

- For each study group, for each sampling timepoint, and for each serotype, the following statistics will be computed:
  - Unadjusted GMTs/GMCs with 95% CI of anti-serotype-specific *Shigella* LPS/OAg* total IgG as measured by ELISA.
  - ***Geometric mean with 95% CI of within-participant ratio of each post-dose 1 titer versus pre-dose 1 titer (Day1) of anti-serotype-specific Shigella LPS/OAg* total IgG as measured by ELISA.***
  - ***Geometric mean with 95% CI of within-participant ratio of post-dose 2 titer versus pre-dose titer (Day 169) of anti-serotype-specific Shigella LPS/OAg* total IgG as measured by ELISA.***
  - Number and percentage of participants with at least 4-fold increase compared to baseline (Day 1) and pre-administration (Day 169), with exact 95% CI as measured by ELISA.

- For each study group, for each sampling timepoint, and for *S. sonnei* serotype only, the following statistics will be computed:
  - Number and percentage of participants achieving an ELISA level ≥1:800 TAU titers equivalent against *S. sonnei* LPS with exact 95% CI.
  - Number and percentage of participants achieving an ELISA level ≥1:1600 TAU titers equivalent against *S. sonnei* LPS with exact 95% CI.

The distribution of antibody concentrations for each serotype will be displayed using reverse cumulative distribution curves and box plots.

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

9.3.1.2. Main analytical approach

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

9.3.2. Secondary endpoints analyses

- For each study group during 7-day follow-up period after each study intervention administration for solicited events the following statistics will be computed:
  - The number and percentage of doses associated with at least 1 administration-site solicited event, with at least 1 systemic event, and with any solicited event will be tabulated for the overall study intervention administration course. The same calculations will be performed for events rated as Grade 3.
  - ***The number and percentage of participants with at least 1 administration-site solicited event, with at least 1 systemic event, and with any solicited event will be tabulated. The same tabulations will be performed for events rated as Grade 3.***
  - The ***number and*** percentages of participants reporting each individual solicited administration-site event by maximum intensity during the 7 days follow-up period will be tabulated. The ***number and*** percentage of doses associated with each individual solicited administration-site event will be tabulated for the overall study intervention administration course. The same tabulation will be performed for events rated as Grade 3. The ***number and*** percentages of participants reporting the solicited systemic event (fever) by maximum intensity during the 7 days follow-up period will be tabulated. The ***number and*** percentage of doses associated with the solicited systemic event (fever) will be tabulated for the overall study intervention administration course. The same tabulation will be performed for events rated as Grade 3 and according to relationship to study intervention administration.
  - The ***number and*** percentages of participants reporting temperature ≥38°C in 0.5°C cumulative increments ***classes*** during the 7 days follow-up period will be

reported, including grading. This will be tabulated for each group after each dose. The same tabulation will be performed according to relationship to study intervention administration.

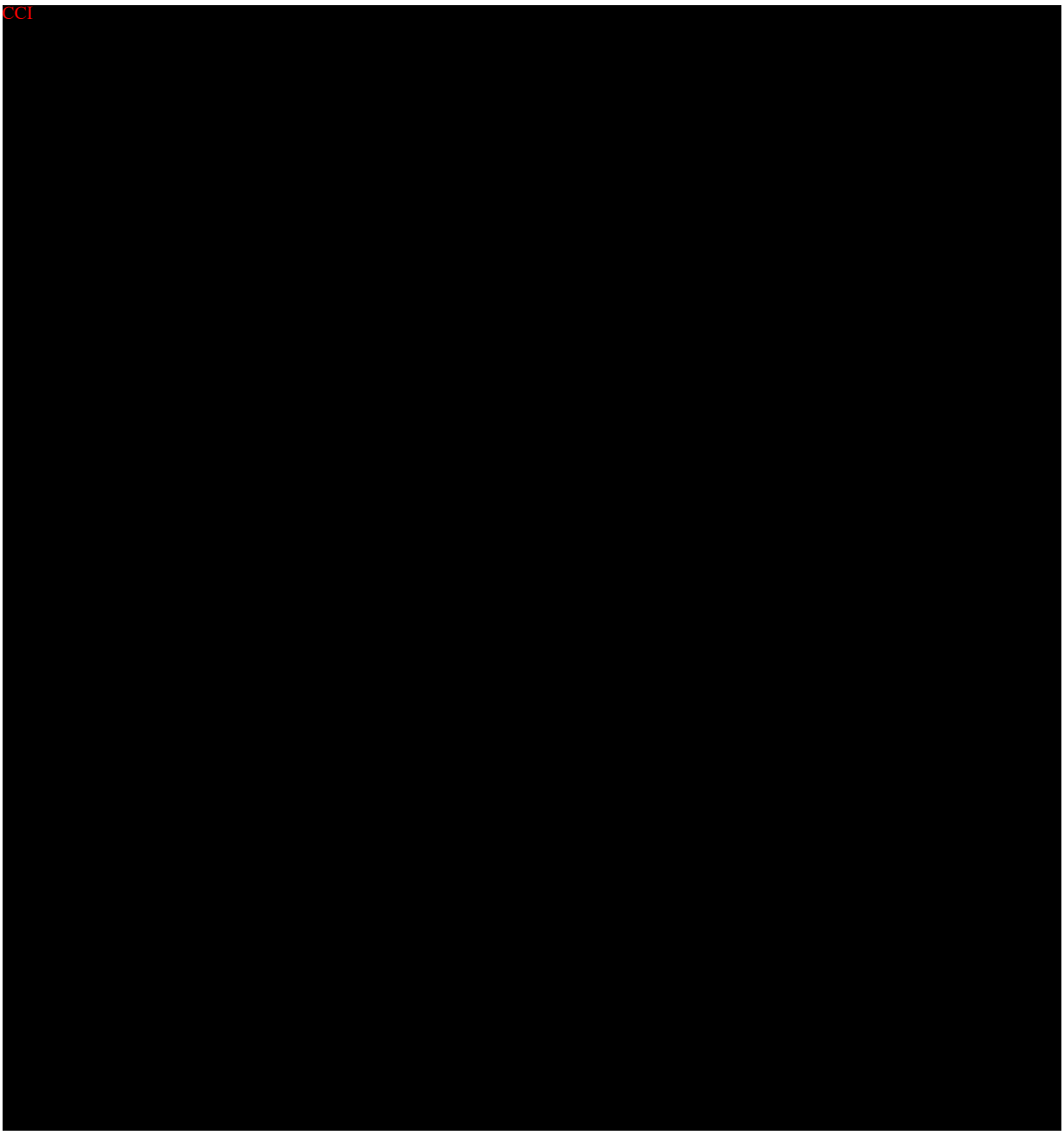
- For each study group for unsolicited AEs the following statistics will be computed:
  - The ***number and*** percentage of participants with at least 1 reported unsolicited AE within 28 days after each study intervention administration as classified by the MedDRA preferred term will be tabulated. The same tabulation will be performed for Grade 3 unsolicited AEs and for unsolicited AEs according to relationship to study intervention administration.
  - ***The number and percentage of doses associated with at least 1 reported unsolicited AE within 28 days after each study intervention administration as classified by the MedDRA preferred term will be tabulated for the overall study intervention administration course. The same tabulation will be performed for Grade 3 unsolicited AEs.***
  - The ***number and*** percentage of participants reporting SAEs and AEs/SAEs leading to withdrawal and/or ***study intervention discontinuation*** from the clinical study during the participant period participation as classified by the MedDRA preferred term will be tabulated. The detailed listings will also be produced.
- For each study group and for each hematological, renal and hepatic panel test results at 7 days after each study intervention administration:
  - The ***number and*** percentage of participants having results below or above the laboratory reference ranges versus baseline (Day 1 and Day 169) values will be tabulated.
  - The ***number and*** percentage of participants with abnormal results by Grade values ***versus baseline (Day 1 and Day 169) Grade values*** will be tabulated.

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

- For each study group, for the sampling timepoint before the first vaccination and 28 days after the second *MR-VAC* vaccination, the following statistics will be computed for the anti-measles and anti-rubella antigens, as measured by ELISA:
  - Unadjusted GMCs with 95% CI of anti-measles and anti-rubella antibodies.
  - Percentage of participants with measles seroresponse of ≥150 mIU/mL and ≥200 mIU/mL, with exact 95% CI.
  - Percentage of participants with rubella seroresponse of ≥4 mIU/mL and ≥10 mIU/mL, with exact 95% CI.

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

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9.4. Interim analyses

There is only 1 planned analysis at the EoS covering all study objectives.

9.5. Pre-dose sample size determination

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

Statistical considerations for the immunogenicity are based on the percentage of participants with ***at least*** 4-fold increase in anti-serotype-specific *Shigella* LPS/OAg serum IgG among the 4 serotypes. Table 13 shows the associated precision in terms of 95% CI for different scenarios of number/percentage of participants with ***at least*** 4-fold increase assuming 44 evaluable participants in each group.

Table 13 95% confidence intervals in participants with *at least* 4-fold increase receiving the altSonflex1-2-3 vaccine

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

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

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

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 the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences international ethical guidelines.
  - Applicable ICH GCP guidelines.
  - Applicable laws and regulations.
- The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.

- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following, as applicable:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
  - Providing oversight of the conduct of the study at the 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 will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed consent process

- The investigator or the investigator's representative will explain the nature of the study, including the risks and benefits, to the participants' parent(s)/LAR(s) and answer all questions regarding the study.
- Potential participants' parent(s)/LAR(s) must be informed that their participation is voluntary. Their parents(s)/LAR(s) will be required to physically sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/IEC or study center.
- ***Sample testing will be done in accordance with the recorded consent of the individual participant's parent(s)/LAR(s).***
- ***By default, collected samples for the study will be stored for a maximum of 20 years. This storage period begins when the last participant completes 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.***

- The medical record must include a statement that physical informed consent was obtained before the participant was enrolled in the study and the date the physical consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants' parent(s)/LAR(s) must be reconsented to the most current version of the ICF(s) during their child's participation in the study.
- A physical copy of the ICF(s) must be provided to the participants' parent(s)/LAR(s).
- ***Parent(s)/LAR(s) of*** participant who is rescreened ***are*** not required to sign another ICF.

For participants who are rescreened, participants' parent(s)/LAR(s) 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' parent(s)/LAR(s) 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 investigator. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- GSK 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.
- The participants' parent(s)/LAR(s) must be informed that their child's study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participants' parent(s)/LAR(s), that their child's data will be used as described in the informed consent.
- The participants' parent(s)/LAR(s) must be informed that their child's medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- ***The contract between sponsor and study sites specifies responsibilities of the parties related data protection, including handling of data security breaches and respective communication and cooperation of the parties.***
- Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.
- ***GSK has a global, internal policy that requires all GSK staff and complementary workers to report data incidents or breaches immediately, using dedicated tools. Clear procedures are defined for assessing and investigating data breaches to***

identify and to take appropriate remediation steps, to contain and to mitigate any risks for individuals resulting from a breach, in compliance with applicable laws.

10.1.5. Committees structure

A SRT is in place for each GSK product. It comprises of a global cross-functional team responsible for the ongoing assessment of benefit-risk for a product. The SRT contribute to the continual assessment of incoming new efficacy and safety information.

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 ***6 months of primary/study completion date*****.** Where external regulations require earlier disclosure, GSK will follow those timelines.
- Where required by regulation, summaries will also be posted on applicable national or regional clinical study registers.
- Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the study report, and provided reasonable access to statistical tables, figures, and relevant reports. GSK will also provide the investigator with the full summary of the study results, including a summary of trial results understandable to laypersons. The investigator is encouraged to share the plain language summary with the study participants, as appropriate. The full study report will be made available upon request, after decision on marketing authorization by regulatory authorities.
- ***Where required by regulation, the names of the sponsor signatory and investigator signatory will be made public.***
- GSK intends to make anonymized participant-level data from this study available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient care. This helps ensure the data provided by study participants are used to maximum effect in the creation of knowledge and understanding. ***Data will be shared with researchers in a non-identifying way, and appropriate measures will be taken to protect PI; these measures will comply with data protection and privacy laws that apply.***

10.1.7. Data quality assurance

- All participant data relating to the study will be recorded on printed or eCRFs unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- Guidance on completion of eCRFs will be provided in eCRF completion guidelines.

- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections, and provide direct access to source documents.
- QTLs will be predefined in the Study Risk Register (GVGH Study Risk-Based Quality Assessment Template) to identify systematic issues that can impact participant right, safety and/or reliability of study results. These predefined parameters will be monitored during the study, and important deviations from the QTLs, and remedial actions taken will be summarized in the CSR.
- Monitoring details describing strategy, including definition of study critical data items and processes (e.g., risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring, involvement of central reading mechanism) methods, responsibilities, and requirements, including handling of non-compliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan.
- The sponsor or designee is responsible for the data management of this study, including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., contract research organizations).
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years from the issue of the final CSR/ equivalent summary, ***or in accordance with Applicable Law, whichever is longer,*** unless local regulations or institutional policies require a different 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. ***In the event of a conflict between this Protocol and the fully executed clinical study agreement, the protocol shall prevail with respect to records retention.***

10.1.8. Source documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the eCRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the 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.
- Definition of what constitutes source data and its origin can be found Definition of terms.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.

- The sponsor or designee will perform monitoring to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents, that the safety and rights of participants are being protected, and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.9. Study and site start and closure

Start of study and first act of recruitment

The start of study is defined as FSFV.

Study/Site termination

GSK or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of GSK. Study sites will be closed upon study completion. A study site is considered closed when all required 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 sufficient notice is given 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:

For study termination:

- Discontinuation of further study intervention development.

For site termination:

- 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 or no recruitment (evaluated after a reasonable amount of time) of participants by the investigator.
- Total number of participants included earlier than expected.

If the study is prematurely terminated or temporarily suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or temporary 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.

10.1.10. Publication policy

GSK seeks to publish medically or scientifically significant results in searchable peer-reviewed scientific literature within 18 months from LSLV. We follow International Committee of Medical Journal Editors standards for authorship and use Good Publications practices to guide our publications.

10.2. Appendix 2: Clinical laboratory tests

Anti-*Shigella* serotype-specific antibody determination from serum using 1 or both of the following:

Anti-Shigella serotype-specific IgG antibodies in serum will be measured by an ELISA assay developed by the GVGH laboratories (Siena, Italy), based on a method previously reported [Launay, 2017; Launay, 2019]. The assay will be performed in a laboratory designated by GVGH. The ELISA is performed using S. sonnei or S. flexneri 1b, 2a or 3a polysaccharides 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 OD of 1.

Anti-*Shigella* serotype-specific IgG antibodies in serum ***could also*** be measured by ELISA in the WRAIR laboratories, based on a method previously reported [Riddle, 2016]. The ELISA is performed using *S. sonnei* or *S. flexneri* 1b, 2a or 3a LPS as coating antigen. Sera are serially diluted, and results are reported as endpoint titers, defined as the reciprocal of the last dilution of serum giving an OD value above the predefined assay cut-off.

Serum bactericidal activity in serum:

Serum bactericidal activity against *S. sonnei*, *S. flexneri 1b, S. flexneri 2a, S. flexneri 3a* will be measured by luminescence-based SBA, based on a method previously reported [Necchi, 2017; Rossi, 2020]. Results are expressed in serum titers, defined as serum dilutions giving 50% inhibition of bacterial growth (IC_{50}).

Measles and rubella ELISA:

Anti-measles and anti-rubella IgG antibodies will be determined by ELISA using commercial kits.

Table 14 Protocol-required safety laboratory tests

Laboratory tests	Parameters
Safety screening laboratory assays	
Hematology	• Leukocytes (WBC) • Erythrocytes (RBC) • Hemoglobin • Hematocrit • Platelets • Eosinophils • Basophils • Neutrophils • Monocytes • Lymphocytes
Clinical chemistry	• Total bilirubin • AST • ALT • γ-GT • LDH • AP • Total proteins • Glucose (random glucose) • Blood Urea • Creatinine • Sodium • Potassium
Other screening tests	• Hepatitis B surface antigen • Hepatitis C virus antibodies • HIV DNA by PCR • HLA-B27 • Prothrombin time

Laboratory tests	Parameters
Pre- and post-administration visit (non-screening) safety laboratory assays	
Hematology	• Leukocytes (WBC) • Erythrocytes (RBC) • Hemoglobin • Hematocrit • Platelets • Eosinophils • Basophils • Neutrophils • Monocytes • Lymphocytes
Clinical chemistry	• Creatinine • ***Sodium*** • ***Potassium*** • ***Blood urea*** • AST/SGOT • ALT/SGPT

ALT = Alanine aminotransferase; AP = Alkaline phosphatase; AST = Aspartate aminotransferase; DNA = Deoxyribonucleic acid; HLA-B27 = Human leukocyte antigen B27; HIV = human immunodeficiency virus; LDH = Lactic Dehydrogenase; PCR = Polymerase chain reaction; RBC = Red blood cells; SGOT = Serum glutamic-oxaloacetic transaminase; SGPT = Serum glutamic-pyruvic transaminase; WBC = White blood cells; γ-GT = γ-Glutamyl transferase.

The tests detailed in Table 14 will be performed by the local site laboratories.

10.3. Appendix 3: AEs and SAEs: Definitions and procedures for recording, evaluating, follow-up, and reporting

10.3.1. Definition of AE

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

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., electrocardiogram, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected intervention-intervention interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • Events that occur as a result of protocol-mandated procedures (i.e., invasive procedures, modification of participant's previous therapeutic regimen). • Significant failure of an expected pharmacologic or biological action.
Events <u>NOT</u> Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (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 diseases will be recorded in the medical history section of the eCRF. • Hospitalization for elective treatment of a pre-existing condition (known or diagnosed before signing the informed consent) that did not worsen from baseline.

10.3.2. Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets 1 or more of the criteria listed:

a. Results in death.

b. Is life-threatening

The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AE. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent or significant disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Other situations:

- Possible Hy's Law case: ALT ≥3x ULN AND total bilirubin ≥2x ULN ***(for participants with known Gilbert's syndrome these criteria only apply if total bilirubin ≥2xULN, and direct bilirubin ≥2xULN and at least doubled from baseline value)*** or INR >1.5 must be reported as SAE.
- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
  - Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions, or development of intervention dependency or intervention abuse.

10.3.3. Solicited events

• Definition of solicited event
• Solicited events are predefined events administration-site events and systemic events for which the participant's parent(s)/LAR(s) is specifically questioned, and which are noted by the participant's parent(s)/LAR(s) in their pDiary.

10.3.3.1. Solicited administration-site events.

The following administration-site events will be solicited:

Table 15 Solicited administration-site events

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

10.3.3.2. Solicited systemic events

The following systemic events will be solicited:

Table 16 Solicited systemic events

All participants
Fever

Note: Participants' parent(s)/LAR(s) 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' parent(s)/LAR(s) will be instructed to record the highest temperature in the diary card.

10.3.4. Unsolicited AE

• Definition of unsolicited AE
• An unsolicited AE is an AE 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 communicated by participant's parent(s)/LAR(s) who has signed the informed consent. Unsolicited AEs include both serious and nonserious AEs. • Potential unsolicited AEs may be medically attended (i.e., symptoms or illnesses requiring a hospitalization, emergency room visit, or visit to/by a healthcare provider). The participant's parent(s)/LAR(s) will be instructed to contact the site as soon as possible to report medically attended event(s), as well as any events that, though not medically attended, are of participant's parent(s) /LAR(s) concern. Detailed information about reported unsolicited AEs will be collected by qualified site personnel and documented in the participant's records. • Unsolicited AEs that are not medically attended nor perceived as a concern by the participant's parent(s)/LAR(s) will be collected during an interview with the participant's parent(s)/LAR(s) and by review of available medical records at the next visit.

10.3.5. Recording, assessment and follow-up of AEs and SAEs

10.3.5.1. AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information.
- It is not acceptable for the investigator to send photocopies of the participant's medical records to the sponsor in lieu of completion of the required form.
- There may be instances when copies of medical records for certain cases are requested by GVGH/GSK. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to GVGH/GSK.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
- A pDiary will be used in this study to capture solicited administration-site or systemic events. The participant's parent(s)/LAR(s) and field workers in case of illiterate participant's parent(s)/LAR(s) should be trained on how and when to complete the pDiary.

- Anyone who measures administration-site or systemic events and who will record the event in the pDiary should be trained on using the pDiary. This training must be documented in the participant's source record.
- For each solicited and unsolicited AE the participant experiences, the participant's parent(s)/LAR(s) will be asked if their child received medical attention (defined as unscheduled visit to or from medical personnel for any reason, including emergency room visits). This information will be recorded in the participant's diary. Medical attention received for SAEs will have to be reported using the normal AE reporting process in the eCRF.
- If any individual other than the participant's parent(s)/LAR(s) is making entries in the pDiary, their identity must be documented in the participant's source record.
- Any unreturned pDiary will be sought from the participant's parent(s)/LAR(s) through telephone call(s) or any other convenient procedure.
- The investigator or delegate will transcribe the required information into the eCRF in English.

10.3.5.2. Assessment of intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to one of the following categories:

- Mild:
  A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- Moderate:
  A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
- Severe:
  A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

The intensity of the following solicited AEs will be assessed as described in Table 17:

Table 17 Intensity scales for solicited events (participants less than 6 years of age)

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

*Refer to the SoA (Section 1.3) for the definition of fever and the preferred location for temperature measurement. Fever is defined as temperature ≥38.0°C.

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

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

The maximum intensity of fever will be scored as follows:

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

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.
Grading of laboratory parameters will be based on toxicity grading scale in Section 10.5 (Appendix 5).

10.3.5.3. Assessment of causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each fever (solicited systemic event), unsolicited AE/SAE. The investigator will use clinical judgment to determine the relationship.
- A *reasonable possibility* of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.
- For causality assessment, the investigator will also consult the IB and/or product information, for marketed products.

- The investigator must review and provide an assessment of causality for each fever (solicited systemic event), unsolicited AE/SAE and document this in the medical notes. There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to GSK. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to GSK.
- The investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

10.3.5.4. Assessment of outcomes

The investigator will assess the outcome of all serious and nonserious unsolicited AEs recorded during the study as:

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

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

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by GVGH/GSK to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- New or updated information will be recorded in the originally submitted documents.
- The investigator will submit any updated SAE data to GSK within 24 hours of receipt of the information.

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

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

Follow-up during the study

AEs documented at a previous visit/contact and defined as not recovered/not resolved or recovering/resolving will be reviewed at subsequent visits/contacts until 28 days after the last study intervention.

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

10.3.5.6. Updating of SAE information after removal of write access to the participant's eCRF

When additional SAE 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 sent to the Study contact for reporting SAEs (refer to Section 8.4.3).

10.3.5.7. Reporting of SAEs

SAE Reporting to GSK via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to GSK will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken offline to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken offline, then the site can report this information on a paper SAE form (see next section).
- If the site during the course of the study or post study becomes aware of any serious, nonserious AEs, related to any GSK ***product that is not part of the study design*****,** they will report these events to GSK or to the concerned competent authority-via the national spontaneous reporting system. These will be classified as spontaneous individual case safety reports.
- Contacts for SAE reporting can be found in Section 8.4.7.

SAE Reporting to GSK via Paper Data Collection Tool

- Email transmission of the SAE paper data collection tool is the preferred method to transmit this information to GSK.

- In rare circumstances and in the absence of email equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE data collection tool within the designated reporting timeframes.
- Contacts for SAE reporting can be found in Section 8.4.7.

10.4. Appendix 4: Country-specific requirements

Not applicable.

10.5. Appendix 5: Grading scales for hematology and biochemistry safety laboratory assessments

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

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

10.6. Appendix 6: Protocol amendment history

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

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