



CLINICAL STUDY PROTOCOL H03_01E1TP

Version

1

A Phase 1, open label, non-randomized, single center study to evaluate the safety and immunogenicity of 1 booster vaccination with GVGH *Shigella sonnei* 1790GAHB vaccine administered intramuscularly in healthy adults previously primed with three doses of the same vaccine in study H03_01TP compared to 1 vaccination with 1790GAHB administered intramuscularly either to subjects who received placebo in the H03_01TP study or naïve subjects who were not part of H03_01TP study

Shigella sonnei GMMA vaccine in healthy French adult extension Phase I vaccine trial

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PROTOCOL SYNOPSIS [H03_01E1TP, Version 1]

Name of Sponsor: GlaxoSmithKline Biologicals SA (GSK Bio)	Protocol number: H03_01E1TP	Generic name of study vaccine(s): GVGH <i>Shigella sonnei</i> 1790GAHB vaccine
Title of Study: A Phase 1, open label, non-randomized, single center study to evaluate the safety and immunogenicity of 1 booster vaccination with GVGH <i>Shigella sonnei</i> 1790GAHB vaccine administered intramuscularly in healthy adults previously primed with three doses of the same vaccine in study H03_01TP compared to 1 vaccination with 1790GAHB administered intramuscularly either to subjects who received placebo in the H03_01TP study or naïve subjects who were not part of H03_01TP study.		
Study Period: Each subject will be followed-up for 84 days (approximately 3 months) after vaccination		Clinical Phase: Phase 1

Background and Rationale: The trial H03_01TP evaluated the safety and immunogenicity profile of 5 different doses of GVGH *Shigella sonnei* 1790GAHB vaccine (1 µg to 100 µg) compared to placebo, when administered in 3 injections to 50 healthy adults. The immunogenicity was evaluated at baseline, 28 days after each vaccination and at 168 days after third vaccination, by measuring the anti-LPS *S. sonnei* serum IgG. Overall, an antibody response was observed across all the vaccine groups. However, at most of the time points, the response was higher in subjects who received higher antigen doses (e.g., 25 µg, 50 µg, and 100 µg) than those who received lower doses (e.g., 1 µg and 5 µg). More specifically, a vaccine dose of 25 µg was very well tolerated and induced median antibody concentrations above 121 EU/mL at all post vaccination time points. Since 121 EU/mL is the median antibody titer in a panel of 87 convalescents previously exposed to *S. sonnei* infection and therefore protected against re-infection from the same serotype, a vaccine dose of 25 µg has the potential to be protective when included in a vaccine against *S. sonnei*.

After unblinding the immunogenicity database, it was observed that the trial subjects could be classified in 2 groups based on *S. sonnei* antibody concentration at baseline, with approximately 50% having undetectable and the other 50% having detectable antiLPS *S. sonnei* serum IgG antibody concentrations. Therefore, for a better understanding of the immunological response induced by the vaccine in naïve and primed subjects and for a better planning of new clinical studies, additional analyses were carried out. To mitigate the small size of study groups, subjects who received vaccines containing 1 µg and 5 µg antigen/dose were combined into a single group and then stratified by the presence or absence of detectable antibodies at baseline. Same was done for subjects who received vaccines containing 25 µg, 50 µg, and 100 µg antigen/dose. As shown in

Name of Sponsor:	Protocol number:	Generic name of study vaccine(s):
GlaxoSmithKline Biologicals SA (GSK Bio)	H03_01E1TP	GVGH <i>Shigella sonnei</i> 1790GAHB vaccine

Figure 1 below, subjects vaccinated with 25 µg, 50 µg and 100 µg vaccines, with detectable antibody concentrations at baseline, showed, at all-time points (1 month after the first, second and the third vaccinations and 6 months after the third vaccination), median antibody concentrations far higher than 121 EU/mL. Subjects vaccinated with 1 µg and 5 µg vaccines, with detectable antibody concentrations at baseline, showed median antibody concentrations slightly higher than 121 EU/mL only at 1 month after the third vaccination.

Figure 1: Median anti-LPS *S. sonnei* IgG ELISA concentrations and interquartile range in subjects with detectable antibodies at baseline (subjects with data at all visits)

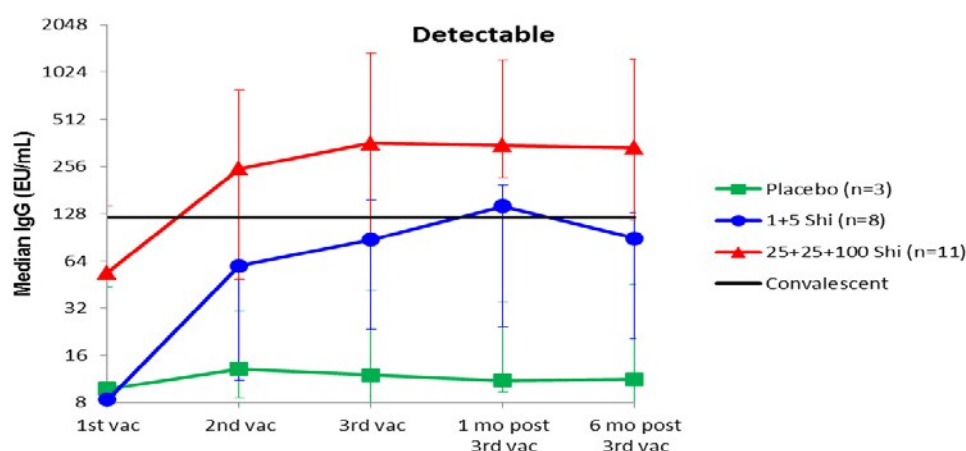
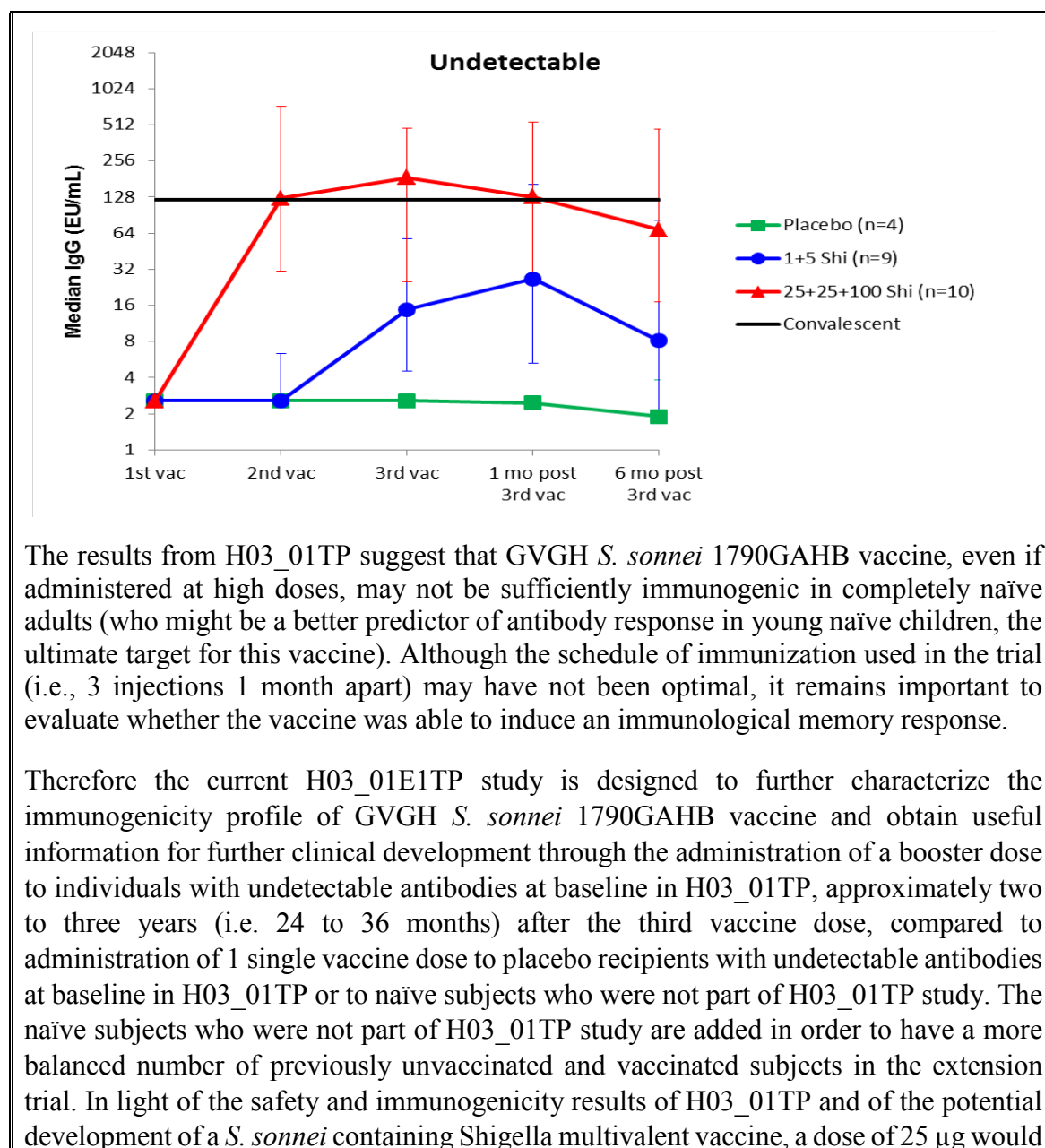


Figure 2 below, with subjects vaccinated with 25 µg, 50 µg and 100 µg vaccines, with undetectable antibody concentrations at baseline, showed median antibody concentrations higher than 121 EU/mL at 1 month after the first, second and the third vaccination, while at 6 months after the third vaccination the median antibody concentration was less than 121 EU/mL. Subjects vaccinated with 1 µg and 5 µg vaccines, with undetectable antibody concentrations at baseline, did not reach the 121 EU/mL threshold at any time point.

Figure 2: Median anti-LPS *S. sonnei* IgG ELISA concentrations and interquartile range in subjects with undetectable antibodies at baseline (subjects with data at all visits)

Name of Sponsor:	Protocol number:	Generic name of study vaccine(s):
GlaxoSmithKline Biologicals SA (GSK Bio)	H03_01E1TP	GVGH <i>Shigella sonnei</i> 1790GAHB vaccine



be preferable for further development. Therefore, the use of this antigen dose is proposed for immunization of all subjects to provide further useful information for a more complete characterization of this vaccine strength.

Study Objectives:

Name of Sponsor:	Protocol number:	Generic name of study vaccine(s):
GlaxoSmithKline Biologicals SA (GSK Bio)	H03_01E1TP	GVGH <i>Shigella</i> <i>sonnei</i> 1790GAHB vaccine

Primary Objective(s):

To evaluate the memory response, as measured by anti-LPS *S. sonnei* serum IgG, 7 days after vaccination with a booster dose of GVGH *S. sonnei* 1790GAHB vaccine in individuals who had undetectable antibody titers at baseline in H03_01TP, approximately two to three years after the third vaccine dose, compared to administration of 1 single vaccine dose to placebo recipients with undetectable antibody titers at baseline in H03_01TP or naïve subjects who were not part of H03_01TP study.

Secondary Objective(s):

1) Safety:

- a. To evaluate the safety profile of one dose of GVGH *S. sonnei* 1790GAHB vaccine in subjects who previously received three vaccinations with 1790GAHB and in subjects receiving one dose 1790GAHB for the first time (either placebo recipients in H03_01TP or naïve subjects who were not part of H03_01TP study).
- b. To evaluate the safety profile of one dose of GVGH *S. sonnei* 1790GAHB vaccine in subjects receiving one dose 1790GAHB for the first time and having detectable antibodies at baseline of the extension trial.

2) Immunogenicity:

- a. To evaluate the immunogenicity profile 7, 14, 28 and 84 days after vaccination with one dose of GVGH *S. sonnei* 1790GAHB vaccine in subjects with undetectable antibody titers at baseline who previously received three vaccinations of GVGH *S. sonnei* 1790GAHB vaccine in H03_01TP and in placebo recipients with undetectable antibody titers at baseline in H03_01TP or naïve subjects who were not part of H03_01TP study.
- b. To evaluate the immunogenicity profile of one dose of GVGH *S. sonnei* 1790GAHB vaccine in subjects receiving one dose 1790GAHB for the first time and having detectable antibodies at baseline of the extension trial.
- c. To evaluate the persistence of anti-LPS *S. sonnei* serum IgG antibody titers approximately two to three years after the third vaccination with 1790GAHB. 3)

Exploratory:

Other immunological assays might be performed to further characterize the immune response to the study vaccine including serum secretory IgA.

Study Design:

Name of Sponsor: GlaxoSmithKline Biologicals SA (GSK Bio)	Protocol number: H03_01E1TP	Generic name of study vaccine(s): GVGH <i>Shigella sonnei</i> 1790GAHB vaccine
This is an open label, non-randomized, single center, Phase 1 clinical trial. The study includes a screening visit (performed at study Days -21to -1), one clinical visit with vaccination (performed at study Day 1), 4 clinical visits (performed 7, 14, 28 and 84 days after vaccination), and 2 phone calls (performed 2 and 6 days after the vaccination).		
Table 1 H03_01TP Study Design		
H03_01TP		H03_01E1TP
Vaccine group	No. subjects*	New enrolled subjects No. subjects Vaccine group
1790GAHB – 1 µg**	5	5 1790GAHB – 25 µg
1790GAHB – 5 µg	4	4 1790GAHB – 25 µg
1790GAHB – 25 µg	2	2 1790GAHB – 25 µg
1790GAHB – 50 µg	4	4 1790GAHB – 25 µg
1790GAHB – 100 µg	5	5 1790GAHB – 25 µg
Placebo	4	4 1790GAHB – 25 µg
Total H03_01TP	24	Naïve subjects 26 1790GAHB – 25 µg
Grand total		50
*only subjects with undetectable antibodies at baseline. ** µg of total protein		

Number of Subjects planned:

Up to 50 subjects will be enrolled into this trial. Up to 24 subjects are eligible from the parent H03_01TP trial. With respect to naïve subjects who were not part of H03_01TP study, considering that in the original H03_01TP population 50% of subjects did not have detectable antibodies at baseline, with 26 subjects, approximately 13 subjects should not have detectable antibodies. This number combined with that of placebo recipients in H03_01TP should be sufficient to allow a balanced contribution of previously unvaccinated and vaccinated subjects in the extension trial. Subjects withdrawn or lost to follow up will not be replaced. The sample size is not driven by any statistical hypothesis, but by availability of subjects from H03_01TP study and fulfilling inclusion criteria.

Study Population and Subject Characteristics:

The study population will consist of adult healthy volunteer subjects meeting all inclusion and no exclusion criteria.

The list of inclusion and exclusion criteria is included in protocol [section 4, Selection of](#)

Name of Sponsor:	Protocol number:	Generic name of study vaccine(s):
GlaxoSmithKline Biologicals SA (GSK Bio)	H03_01E1TP	GVGH <i>Shigella</i> <i>sonnei</i> 1790GAHB vaccine
Study Population.		

Study Procedures:

Before any study procedure is performed, informed consent will be obtained; subjects will be enrolled only after their eligibility for participation is confirmed by the investigator. Safety procedures:

All subjects providing informed consent will undergo review of medical history, a general physical examination including vital signs measurement (temperature, respiratory rate, heart rate, blood systolic and diastolic pressure) at the screening visit (study Days -21 to -1) and at Visit 1 (Day 1) for evaluation of the general health status by clinical assessment and verification of inclusion and exclusion criteria. At clinic Visit 2 and at subsequent visits, a brief symptom-directed physical examination (if necessary according to symptoms the subject has reported) will be performed. Throughout the study it will be checked whether continued participation in the study is in the subject best interest in terms of safety. For all women of childbearing potential before vaccination at visit 1, a urine pregnancy test will be conducted and will also be repeated at visit 5 (Day 85). Women with positive test or refusing to perform the test will be immediately excluded from the study. Female subjects must use acceptable (defined as oral, injected or implantable contraceptives) birth control measures during study participation.

Blood Draw Procedure:

Approximately 15 mL blood draw will be obtained for hematological and serological (HIV, hepatitis B and C) for subjects who were part of the parent trial (H03_01TP). For naïve subjects however 25 mL of blood draw will be obtained for the same hematological and serological test mentioned above and in addition HLA-B27 testing as part of the initial screening. One additional blood draw of 6 mL for hematological tests will be obtained at 7 days (Visit 2) and 84 days (Visit 5) after vaccination (see [Table 2](#)). Each subject will have 20 mL of blood drawn for immunological studies before and 7, 14, 28 and 84 days after vaccination. For the purpose of creating a standard reference serum for the serological assay, volunteers will be asked to provide an additional blood sample of 20 mL at 28 days after vaccination (Visit 4).

Clinically significant modifications in hematology will be assessed by medical judgment based on interpretation of deviations from institution's normal values and recommendations from [CBER FDA GUIDANCE FOR INDUSTRY](#): Toxicity Grading

Name of Sponsor:	Protocol number:	Generic name of study vaccine(s):
GlaxoSmithKline Biologicals SA (GSK Bio)	H03_01E1TP	GVGH <i>Shigella sonnei</i> 1790GAHB vaccine

Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials.

Vaccination Procedure:

All eligible subjects will receive one intramuscular vaccination (into the deltoid area of the non-dominant arm) with GVGH *S. sonnei* 1790GAHB vaccine containing 25µg/dose. Subjects will be observed at the clinic site for 4 hours after vaccination.

Procedure for Collection of Solicited AEs:

Beginning in the evening following study vaccine administration (approximately 6 hours), and daily during the following 6 days following vaccination, diary cards will be used to collect solicited local and systemic adverse events including other reactions (i.e. body temperature measurements and use of analgesics/antipyretics). A reminder phone call will be performed or an email will be sent by the site staff to the subject 2 and 6 days following vaccination to remind subjects that the diary card should be completed (no update on the status of the subject's health will be solicited during these contacts that are not intended for safety data collection).

Seven days following vaccination, a clinical visit (Visit 2) will be performed at the study site and all information recorded in the diary card will be reported on e-CRF in order to document all safety data occurred during the one week follow-up post vaccination.

In addition to the solicited adverse events data, any unsolicited AE, solicited local and systemic AE that continue at 7 days after study vaccination (Visit 2), will be collected and recorded at V2, V3 and V4 by clinical study staff in the in the subject's source document. All Serious Adverse Events (SAEs), all AEs leading to vaccine/study withdrawal, all Adverse Events of Special Interest (AESI, see below) and all concomitant medications associated with those events, will be collected and recorded in the subject's source document and on an Adverse Events CRF(s) from the time of vaccination (visit 1) to study termination (visit 5). These data will be captured through interview of the subject and by review of available medical records.

Reactive arthritis and neutropenia will be collected and analyzed as AESIs for this study.

A summary of the main medical and safety data to be collected into the e-CRF during the study is provided in [Table 2](#).

Name of Sponsor: GlaxoSmithKline Biologicals SA (GSK Bio)	Protocol number: H03_01E1TP	Generic name of study vaccine(s): GVGH <i>Shigella sonnei</i> 1790GAHB vaccine
<p>Study Vaccines: GVGH <i>S. sonnei</i> (1790GAHB) vaccine</p> <p>The investigational agent is the GVGH <i>S. sonnei</i> 1790GAHB vaccine. The vaccine consists of <i>S. sonnei</i> OAg containing 1790-GMMA (approximately 200 µg/mL measured by protein content) adsorbed to Alhydrogel, (0.7 mg Al³⁺/mL) in Trisbuffered saline. The vaccine does not contain any preservative and is available in a liquid formulation as a single dose vials with 0.7 mL of injectable solution containing approximately 140 µg of GMMA (as protein content), adsorbed onto 0.49 mg Al³⁺.</p> <p>The vaccine will be used at a dose of 25 µg and will be obtained by bed-side mixing. Following dilution, the volume administered by intramuscular route will be 0.5 mL.</p> <p>Therefore, each 0.5 mL dose of GVGH <i>S. sonnei</i> 1790GAHB vaccine will contain 3+. approximately 25 µg of GMMA total protein and 0.35 mg of Al</p>		

Primary Endpoint(s):

This study has no primary efficacy or safety endpoints.

Primary Immunogenicity Endpoint(s)

Memory response, against the OAg of *S. sonnei* will be evaluated by measuring IgG Geometric mean concentrations (GMCs) after vaccination as determined by ELISA with O-antigen containing LPS as coating antigen.

Secondary safety endpoint(s):

The measures of safety will include:

- a. Numbers of subjects with deviations from normal values of hematological tests after vaccination.
- b. Numbers of subjects with solicited local and systemic reactions during 7 days following vaccination. Solicited local reactions include injection site erythema, injection site induration and injection site pain; solicited systemic reactions include headache, arthralgia, chills, fatigue, malaise, myalgia, and fever (as measured orally).
- c. Numbers of subjects with reported unsolicited adverse events (of any nature and severity) during 84 days following vaccination.
- d. Number of subjects with reported SAEs throughout the study duration.

Name of Sponsor:	Protocol number:	Generic name of study vaccine(s):
GlaxoSmithKline Biologicals SA (GSK Bio)	H03_01E1TP	GVGH <i>Shigella sonnei</i> 1790GAHB vaccine

Secondary Immunogenicity Endpoint(s)

- a. IgG Geometric mean concentrations (GMCs) at 7, 14, 28 and 84 days after vaccination as determined by ELISA and applicable geometric mean ratios between post vaccination and baseline samples.
- b. Number and percentage of subjects with seroresponse for anti- LPS *S. sonnei* at 7, 14, 28 and 84 days after vaccination. Seroresponse is aimed to define a significant increase in post vaccination samples based on the biological performance of this specific serology assay and it is defined as follows:
 - If the baseline value is greater than 50 ELISA Units (EU) then an increase of at least 50% in the post-vaccination sample as compared to baseline [i.e. $((\text{Post-vac minus baseline})/\text{baseline})100\% \geq 50\%$].
 - If the baseline value is less or equal to 50 EU then an increase of at least 25 EU in the post-vaccination sample as compared to baseline [i.e. $(\text{Postvac minus baseline}) \geq 25 \text{ EU}$].
- c. Number and percentage of subjects with titers post vaccination concentration ≥ 121 EU/ml for anti-LPS *S. sonnei* at 7, 14, 28 and 84 days after vaccination.

A post-vaccination concentration ≥ 121 anti-LPS serum IgG units in the GVGH ELISA with O-antigen containing LPS as coating antigen corresponds to a titer of 1:800 in the ELISA method used by Cohen et al. (1989 *J. Clin. Microbiol.* 27:162). This antibody level is the median antibody concentration of a set of 87 convalescent subjects previously infected by *S. sonnei*. The value of 121 anti-LPS serum IgG units in the GVGH ELISA was determined by calibration against the Cohen ELISA (i.e., the GVGH standard serum was tested in Cohen's lab using the Cohen's methodology).

The serologic assays on clinical samples will be performed at GSK, Clinical Laboratory Science (CLS), Marburg, Germany, or a delegated laboratory.

Exploratory Immunogenicity Endpoint(s):

Other assays, including serum secretory IgA, might be done to further characterize the immune response to the study vaccine. The analysis will be described in the statistical analysis plan.

Statistical Analyses:

Name of Sponsor:	Protocol number:	Generic name of study vaccine(s):
GlaxoSmithKline Biologicals SA (GSK Bio)	H03_01E1TP	GVGH <i>Shigella sonnei</i> 1790GAHB vaccine

This Phase 1 safety and immunogenicity extension trial is aimed to descriptively evaluate the safety and immunogenicity profiles of the study vaccine, used either a booster (4th dose) or as a first dose. No specific hypotheses are tested in this trial. Descriptive analyses will be performed to describe and summarize the data (e.g. mean, median, min and max).

Interim Analysis: No interim analysis is planned for this trial.

Data Monitoring Committee:

No ad hoc DSMB will be established for this trial as no interim assessment of safety data is anticipated.

Table 2 Time and Event Table- Treatment Period

Visit Type		Clinic Visit	Clinic Visit	Phone Call	Clinic Visit	Clinic Visit	Clinic Visit	Clinic Visit
			1	3, 7 V1+2 days; V1+6 days	8 V1+7 days	15 V1+14 days	29 V1+28 days	85 V1+84 days
		Study Day						
		Visit Window (Days)	-21 to -1	n/a	n/a	0 to -1	0 to +4	-3 to +4
Visit Number		Screening	1		2	3	4	5
Study Event	References							
Study Treatment								
Vaccination	Section 5.2		X					
Screening and Safety								
Informed Consent ^a	Section 5.1.1	X						
Medical History	Sections 5.1.2	X						
Physical Exam ^b	Sections 5.1.2 and 5.1.3	X	X					
Symptom-directed physical Exam ^b	Section 5.3.1				X	X	X	X

Vital signs (temperature, respiratory rate, heart rate, blood systolic and diastolic pressure)	Sections 5.1.2 Screening and 5.2.1 Post-vaccination Procedures	X	X					
Safety blood draw (Hematology) ^e	Sections 3.5 and 7.1.7	X			X			X

	Visit Type	Clinic Visit	Clinic Visit	Phone Call	Clinic Visit	Clinic Visit	Clinic Visit	Clinic Visit
	Study Day		1	3, 7 V1+2 days; V1+6 days	8 V1+7 days	15 V1+14 days	29 V1+28 days	85 V1+84 days
	Visit Window (Days)	-21 to -1	n/a	n/a	0 to -1	0 to +4	-3 to +4	-3 to +7
	Visit Number	Screening	1		2	3	4	5
Study Event	References							
Serology (HIV, hepatitis B and C, and HLA-B27 testing only for naïve subjects) ^d	Section 3.5 and 5.1.2	X						
Pregnancy Test	Sections 3.5 and 5.1.2		X					X
Exclusion/Inclusion Criteria	Section 4	X						
Post Injection Assessment ^e	Section 5.2.1		X					
Subject Diary Dispensed with Training	Section 5.2.1		X					

Subject Diary Reminder Call	Section 5.2.2			X				
Subject Diary Reviewed and Collected	Section 5.3.1				X			
Assess all AEs	Section 7.1	X	X		X	X	X	
Assess SAEs	Section 7.1.4	X	X		X	X	X	X
Assess for NOCDs, medically attended AEs, AEs leading to withdrawal, and AESIs	Sections 7.1.4.1 and 7.1.3		X		X	X	X	X

Number	Visit Type	Clinic Visit	Clinic Visit	Phone Call	Clinic Visit	Clinic Visit	Clinic Visit	Clinic Visit
	Study Day		1	3, 7 V1+2 days; V1+6 days	8 V1+7 days	15 V1+14 days	29 V1+28 days	85 V1+84 days
	Visit (Days)							
	Window	-21 to -1	n/a	n/a	0 to -1	0 to +4	-3 to +4	-3 to +7
Number	Visit	Screening	1		2	3	4	5
	Study Event	References						
Assess relevant medications	Sections 5.1.2 and 6.5	X	X		X	X	X	X
Immunogenicity								
Serology blood draw	Section 3.5		X		X	X	X	X

Additional blood draw for preparation of standard serum	Section 3.5						X	
Study Completion Procedures								
Study Termination ^f	Section 5.5							X
<p>Notes:</p> <p>^a Informed Consent to be confirmed (oral confirmation) on Visit 1 prior to vaccination</p> <p>^b Physical examination must be performed by a qualified health professional in accordance with local regulations and licensing requirements designated within the Site Responsibility Delegation Log.</p> <p>^c In case of neutropenia, Complete Blood Count to be repeated on a weekly basis until resolution. If neutropenia occurs at the last study visit, Complete Blood Count to be repeated on a regular basis until resolution.</p> <p>^d The serology tests that are performed at screening are HIV, hepatitis B and hepatitis C and they are conducted for subjects in the parent trial and for the naïve subjects. HLA-B27 testing is performed at screening only for the naïve subjects.</p> <p>^e A post-injection local and systemic adverse event and body temperature and vital signs measurement will be performed approximately 30 minutes and 4 hours after vaccination. ^f Subjects who terminate the study early are recommended to complete certain study-related procedures. See protocol section 5.5 for further details.</p>								

Table 3 Safety Tests Table

HEMATOLOGY
White Blood Cells (WBC)
Red Blood Cells (RBC)
Haemoglobin
Haematocrit
Platelets
Eosinophils
Basophils

Neutrophils
Monocytes
Lymphocytes
Prothrombin time*
SEROLOGY
HIV antibodies*
HbsAg*
Hepatitis C antibodies*
HLA-B27 testing**
PREGNANCY TEST
Human chorionic gonadotropin (hCG) in urine

* Performed at screening only ** Performed at screening only for naïve subjects.

LIST OF ABBREVIATIONS

AE	Adverse Event
AESI	Adverse Events of Special Interest
AP	(Statistical) Analysis Plan
ANC	Absolute Neutrophil Count
BMI	Body mass index
CBC	Complete Blood Count
CI	Confidence Interval
CLS	Clinical Laboratory Science
CRF	Case Report Form
CRO	Contract Research Organization
DM	Data Management
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ELISA	Enzyme-linked Immunosorbent Assay
EMA	European Medicines Agency
EU	ELISA Unit
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practices
GMC	Geometric Mean Concentration
GMMA	Generalized Modules for Membrane Antigens
GMR	Geometric Mean Ratio
GMT	Geometric Mean Titer
GVGH	GSK Vaccines Institute for Global Health
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IRB	Institutional Review Board
ITT	Intention-To-Treat
MSD	Moderate to Severe Diarrhea
LPS	Lipopolysaccharide
LSLV	Last Subject Last Visit
MedDRA	Medical Dictionary for Regulatory Activities
NOCD	New onsets of chronic diseases
OAg	O antigen (of <i>Shigella sonnei</i>)
pIMD	Potential Immuno-Mediated Diseases
PP	Per Protocol

ReA	Reactive arthritis
SAE	Serious Adverse Event
SDA	Source Data Agreement
SDAF	Source Documentation Agreement Form
SOC	System Organ Class
SOP	Standard Operating Procedure
SPC	Summary of Product Characteristics
WHO	World Health Organization

1. BACKGROUND AND RATIONALE

1.1 Background

Shigellosis remains a major health problem in developing countries with approximately 100 million cases per year mostly in children ≤ 5 years (Kotloff et al., 1999). Antibiotic resistance of *Shigella* is increasing and no vaccine is currently available against shigellosis. Livio et al showed that a quadrivalent vaccine containing *S. sonnei* and 3 serotype/subserotypes of *S. flexneri* (*S. flexneri* 2a, *S. flexneri* 3a, and *S. flexneri* 6) can provide broad coverage against *Shigella* serotypes (up to 65%) (Livio et al., 2014), which cause shigellosis in the developing world, and can also provide broad coverage for travelers.

In this view, GSK Vaccines Institute for Global Health (GVGH) developed the *S. sonnei* 1790GAHB vaccine that has been tested in two Phase 1 trials in European adult population: one trial of the trials (protocol H03_01TP), looking at the intramuscular (IM) administration was conducted in France. In that study different antigen doses were evaluated and showed to be safe and well tolerated. More specifically, the trial evaluated the safety and immunogenicity profile of 5 different doses of GVGH *Shigella sonnei* 1790GAHB vaccine (1 μ g to 100 μ g) compared to placebo, when administered in 3 injections 1 month apart to 50 healthy adults. The immunogenicity was evaluated at baseline, 28 days after each vaccination and at 168 days after third vaccination, by measuring the anti-LPS *S. sonnei* serum IgG. Overall, an antibody response was observed across all the vaccine groups. However, at most of the time points, the response was higher in subjects who received higher antigen doses (i.e., 25 μ g, 50 μ g, and 100 μ g) than those who received lower doses (i.e., 1 μ g and 5 μ g).

More specifically, a vaccine dose of 25 μ g was very well tolerated and induced median antibody concentrations above 121 EU/mL at all post vaccination time points. Since 121 EU/mL is the median antibody titer in a panel of 87 convalescents previously exposed to *S. sonnei* infection and therefore protected against re-infection from the same serotype (Cohen et al, 1989), a vaccine dose of 25 μ g has the potential to be protective when included in a vaccine against *S. sonnei*. After unblinding the immunogenicity database, it was observed that the trial subjects could be grouped in 2 groups based on *S. sonnei* antibody concentration at baseline, with 50% having undetectable and 50% having detectable anti-LPS *S. sonnei* serum IgG antibody concentrations. Therefore, for a better understanding of the immunological response induced by the vaccine in naïve and primed subjects and for a better planning of new clinical studies, additional analyses were carried out. To mitigate the small size of study groups, subjects who received vaccines containing 1 μ g and 5 μ g antigen/dose were combined into a single group in which those with detectable antibody concentrations at baseline, showed median antibody concentrations slightly higher than 121 EU/mL only at 1 month after the third vaccination. Same was done for subjects who received vaccines containing 25 μ g, 50 μ g, and 100 μ g antigen/dose, among whom those with detectable antibody concentrations at baseline, showed, at all-time points (1 month

after the first, second and the third vaccinations and 6 months after the third vaccination), median antibody concentrations far higher than 121 EU/mL.

Based on the results from this trial, it has been decided to proceed with further development using only the IM route of immunization and a dose of 25 µg was selected as the lowest dose that in phase 1 induced antibody titers comparable to antibodies in a population of convalescent subjects after natural infection already after the first vaccination.

The results from H03_01TP suggest that 1790GAHB, even if administered at high doses, may not be sufficiently immunogenic in completely naïve adults (who might be a better predictor of antibody response in young naïve children, the ultimate target for this vaccine). Although the schedule of immunization used in the trial (i.e., 3 injections 1 month apart) may have not been optimal, it remains important to evaluate whether the vaccine was able to induce an immunological memory response.

1.2 Rationale

The current H03_01E1TP study is designed to further characterize the immunogenicity profile of GVGH *S. sonnei* 1790GAHB vaccine and obtain useful information for further clinical development through the administration of a booster dose to individuals with undetectable antibodies at baseline in H03_01TP, approximately two to three years (i.e., 24 to 36 months) after the third vaccine dose, compared to administration of 1 single vaccine dose to placebo recipients with undetectable antibodies at baseline in H03_01TP or to naïve subjects who were not part of H03_01TP study. The naïve subjects who were not part of H03_01TP study are added in order to have a more balanced number of previously unvaccinated and vaccinated subjects in the extension trial. In light of the safety and immunogenicity results of H03_01TP and of the potential development of a *S. sonnei* containing Shigella multivalent vaccine, a dose of 25 µg would be preferable for further development. Therefore, the use of this antigen dose is proposed for immunization of all subjects to provide further useful information for a more complete characterization of this vaccine strength.

2. OBJECTIVES

2.1 Primary Objective(s)

Primary Safety Objective(s)

This study has no primary safety objective

Primary Efficacy Objective(s)

This study has no primary efficacy objective

Primary Immunogenicity Objective(s)

To evaluate the memory response, as measured by anti-LPS *S. sonnei* serum IgG, 7 days after vaccination with a booster dose of GVGH *S. sonnei* 1790GAHB vaccine in individuals who had undetectable antibody titers at baseline in H03_01TP, approximately two to three years after the third vaccine dose, compared to administration of 1 single vaccine dose to placebo recipients with undetectable antibody titers at baseline in H03_01TP or naïve subjects who were not part of H03_01TP study.

2.2 Secondary Objective(s)

Secondary Safety Objective(s)

- a. To evaluate the safety profile of one dose of GVGH *S. sonnei* 1790GAHB vaccine in subjects who previously received three vaccinations with 1790GAHB and in subjects receiving one dose 1790GAHB for the first time (either placebo recipients in H03_01TP or naïve subjects who were not part of H03_01TP study).
- b. To evaluate the safety profile of one dose of GVGH *S. sonnei* 1790GAHB vaccine in subjects receiving one dose 1790GAHB for the first time and having detectable antibodies at baseline of the extension trial. **Secondary Efficacy Objective(s)**

This study has no secondary efficacy objectives.

Secondary Immunogenicity Objective(s)

- a. To evaluate the immunogenicity profile 7, 14, 28 and 84 days after vaccination with one dose of GVGH *S. sonnei* 1790GAHB in subjects with undetectable antibody titers at baseline who previously received three vaccinations of 1790GAHB in H03_01TP and in placebo recipients with undetectable antibody titers at baseline in H03_01TP or naïve subjects who were not part of H03_01TP study.
- b. To evaluate the immunogenicity profile of one dose of GVGH *S. sonnei* 1790GAHB vaccine in subjects receiving one dose 1790GAHB for the first time and having detectable antibodies at baseline of the extension trial.
- c. To evaluate the persistence of anti-LPS *S. sonnei* serum IgG antibody titers approximately two to three years after the third vaccination with 1790GAHB.

2.3 Exploratory Objective(s)

Other immunological assays might be performed to further characterize the immune response to the study vaccine including serum secretory IgA.

3. STUDY DESIGN

3.1 Overview of Study Design

This is an open label, non-randomized, single center, Phase 1 clinical trial designed to further characterize the immunogenicity profile of GVGH *S. sonnei* 1790GAHB vaccine through the administration of a booster dose to individuals with undetectable antibodies at baseline in H03_01TP parent study, approximately two to three years (i.e., 24 to 36 months) after the third vaccine dose, compared to administration of 1 single vaccine dose to placebo recipients with undetectable antibodies at baseline in H03_01TP parent study or to naïve subjects who were not part of H03_01TP study. The study includes a screening visit (performed at study Days -21 to -1), one clinical visit with vaccination (performed at study Day 1), 4 clinical visits (performed 7, 14, 28 and 84 days after vaccination), and 2 phone calls or email contacts (performed 2 and 6 days after the vaccination). No subject or study staff will be blinded for any study procedure.

During the screening period, subjects giving informed consent will be screened for general health status. No pharmacokinetic tests will be performed as evaluation of pharmacokinetic properties is not required for vaccines unless new delivery systems are employed or when the vaccine contains novel adjuvants or excipients ([Berlanda Scorza et al., 2012](#)). Subjects who meet all inclusion criteria and none of the exclusion criteria, with screening tests within normal values and women of child bearing potential with negative urine pregnancy test at V1 will be eligible for enrollment. Female subjects of child bearing potential must use birth control measures during study participation.

Up to 50 subjects will be enrolled into this trial. 24 subjects are eligible from the parent H03_01TP trial. With respect to naïve subjects who were not part of H03_01TP study, considering that in the original H03_01TP population 50% of subjects did not have detectable antibodies at baseline, with 26 subjects, it is anticipated that at least 13 subjects should not have detectable antibodies. This number combined with that of placebo recipients in H03_01TP should be sufficient to allow a balanced contribution of previously unvaccinated and vaccinated subjects in the extension trial. Subjects withdrawn or lost to follow up will not be replaced. The sample size is not driven by any statistical hypothesis, but by availability of subjects from H03_01TP study and fulfilling inclusion criteria. Subjects will be recruited as detailed in [table 1](#).

No randomization will be required since all subjects will receive the same dose of the same vaccine.

Screening/baseline clinical safety labs will take place before Visit 1 (from -21 up to -1 day). All subjects providing informed consent will undergo review of medical history, a complete physical examination including vital signs measurement (temperature, respiratory rate, heart rate, blood systolic and diastolic pressure) at the screening visit (study Day -21 to -1) and at visit 1 (Day 1) for evaluation of the general health status by clinical assessment and verification of inclusion and exclusion criteria. At clinic visit 2 and at subsequent visits, a

brief symptom-directed physical examination (if necessary according to symptoms the subject has reported) will be performed.

A blood sample will be obtained as part of the initial screening for hematology and serology (HIV, hepatitis B and C, and for HLA-B27 testing only for naïve subjects). Blood will be collected for hematology also on day 8 and 85 (visit 2 and 5 respectively). Each consented subject will have blood collected before vaccination on day 1 for baseline immunological testing and on day 8, 15, 29 and 85 (visit 2, 3, 4, and 5 respectively) post vaccination for immunological. Additional blood draw for preparation of standard serum will be done on day 29 post vaccination (visit 4). Urine pregnancy test will be done at visit 1 prior to vaccination and at visit 5. All individuals with neutropenia occurring at any time during the study will have additional blood draws to repeat complete blood count on a weekly basis until the neutropenia resolves. If neutropenia occurs at the last study visit, Complete Blood Count to be repeated on a regular basis until resolution (for classification of neutropenia during the trial, refer to [Section 3.8, Procedures Related to Neutropenia](#)).

Subjects will be observed at the clinic for 4 hour after vaccination on visit 1. Vital signs will be collected before vaccination and at 30 minutes and 4 hours post vaccination. Before leaving the clinic, they will be given a paper dairy card and trained to record in any adverse events occurring before visit 2 and will be reminded by phone call or email on day 3 and 7 post vaccination. These dairy cards will be collected and reviewed on day 8 post vaccination (visit 2).

Any unsolicited AE until visit 4, SAEs until study termination, all AEs leading to study withdrawal, reactive arthritis and severe neutropenia (AESI) and all concomitant medications associated with those events, will be collected and recorded in the subject's source document and in the eCRF. Further details on study procedure are found in [sections 5, Study Procedures and 7, Assessments](#).

3.2 Study Period

Each subject should expect to participate in the study for 85 days, from the time of enrolment through the last study visit.

3.3 Blinding Procedures

No blinding procedures will be applied for this study.

3.4 Data Collection

3.4.1 Data Collected from Subjects

The following data will be collected from each subject over the duration of their study participation:

- Demographic Information

- Medical History
- Post-vaccination immediate reactions
- Vital signs including but not limited to body temperature
- Adverse Events
- Concomitant Medications

All data collected must only be identified using the GSK Subject ID and Subject code, as described in [section 5.1.4, Randomization](#).

3.4.2 Tools Used for Data Collection

Subject Diary

Paper Diaries, hereafter referred to as Subject Diaries will be the only source document allowed for solicited local and systemic adverse events (including body temperature measurements), starting approximately 6 hours post-vaccination and collected by the subject. The following additional rules apply to documentation of safety information collected in the Subject Diary.

The Investigator or delegated staff should monitor the Subject's Diary status throughout the study for compliance and any solicited local and systemic adverse events that were of concern to the subject.

1. No corrections or additions to the information recorded by the subject within the Subject Diary will be allowed after it is delivered to the site.
2. Any blank or illegible fields on the Subject Diary must be described as missing in the CRF.

Case Report Forms

An electronic data capture (EDC) system (e.g., Inform™) will be used to expedite the entry of data. A qualified site staff member(s) will enter data in English into the web enable EDC system in a timely manner; the data will be stored in GSK clinical database management system. eCRF data will be reviewed routinely by GSK Data Management (DM) Group and GSK clinical monitors or representatives.

The information from the diary will be entered in the eCRF at visit 2. All data not recorded directly on the eCRFs must be verified by checking eCRF entries against source documents in order to ensure that the data have been completely and accurately reported as required by the study protocol.

Source data verification will be performed and recorded following GSK internal SOP. The subject must also allow access to his/her medical records. Each subject will be informed of this prior to the start of the study.

The following additional rules apply to documentation of Subject Diary information collected in the CRFs:

1. The site must enter all readable entries from the Subject Diary into the eCRF, including those values that may be biologically implausible (e.g. body temperature: 400°C).
2. Any illegible or implausible data should be reviewed with the subject. If an underlying solicited or unsolicited adverse event is described on review with the subject, this should be described in the source document and reported as an unsolicited adverse event in the Adverse Event CRF (e.g., if the subject above confirms body temperature of 40°C on the day in which body temperature: 400°C was written into his/her Subject Diary, this fever of 40°C should be recorded in the Adverse Event CRF).
3. Any newly described safety information (including a solicited adverse event) must not be written into the Subject Diary and must be described in the study file (studyspecific workbook) as a verbally reported adverse event. Any adverse event reported in this fashion must be described as an unsolicited adverse event and therefore entered on the Adverse Event CRF.

3.5 Collection of Clinical Specimens

Collected samples will be used for protocol mandated research and purposes related to the improvement, development and quality assurance of the laboratory tests described in this protocol. This may include the management of the quality of these tests, the maintenance or improvement of these tests, the development of new test methods, as well as making sure that new tests are comparable to previous methods and work reliably.

It is also possible that future findings may make it desirable to use the samples acquired in this study for future research, not described in this protocol. Therefore, all subjects in countries where this is allowed/all subjects will be asked to give a specific consent to allow the Sponsor or a contracted partner to use the samples for future research. Future research will be subject to the laws and regulations in France and will only be performed once an independent Ethics Committee or Review Board has approved this research. Information on further investigations and their rationale can be obtained from GSK.

Any sample testing will be done in line with the consent of the individual subject. If additional testing is performed, the marker priority ranking given in the table below may be changed.

Table 4 Blood For Immunological purposes

Blood sampling timepoint		Subset	No. subjects	Component	Components priority rank
Type of contact and timepoint	Sampling timepoint	/Subcohort Name			
Screening (Day -21 to 1)	Pre-Vacc	All subjects	50	HIV*	NA
		All subjects	50	anti-HBsAg*	
		All subjects	50	Hepatitis C*	

		Naïve subjects	26	HLA-B27	
Visit 1 (Day 1)	Pre-Vacc		50	Anti LPS IgG ELISA	NA
Visit 2 (Day 8)	Post-Vacc 1		50	Anti LPS IgG ELISA	NA
Visit 3 (Day 15)	Post-Vacc 2		50	Anti LPS IgG	NA
Visit 4 (Day 29)	Post-Vacc 3		50	Anti LPS IgG	1
	Standard Serum	TBD	TBD	Standard pool for ELISA	2
Visit 5 (Day 85)	Post-Vacc 4		50	Anti LPS IgG	NA

* The results of this testing might potentially impact the subject medical care

Processing of each specimen should be completed by a qualified site member and in accordance with the study-specific laboratory manual. Testing of clinical specimens will be performed by GSK Clinical Laboratory Science (CLS), Marburg, (Germany) or a delegated laboratory. Refer to the study-specific laboratory manual for additional details.

Blood Specimens

Approximately 15 mL blood draw will be obtained for hematological and serological (HIV, hepatitis B and C for subjects who were in the parent study. Naïve subjects will however have 25mL of blood drawn for HLA-B27 testing in addition of the hematological and serological (HIV, hepatitis B and C) tests as part of the initial screening. One additional blood draw of 6 mL for hematological tests will be obtained at 8 days (Visit 2) and 85 days (Visit 5) after vaccination (see [Table 2](#)). Each subject will have 20 mL of blood drawn for immunological studies before vaccination at Day 1 and 8, 15, 29 and 85 days after vaccination. For the purpose of creating a standard reference serum for the serological assay, study subjects will provide an additional blood sample of 20 ml at 29 days after vaccination.

All individuals with neutropenia occurring at any time during the study will have additional 6mL blood draws to repeat complete blood count on a weekly basis until the neutropenia resolves.

Clinically significant modifications in hematology will be assessed by medical judgment based on interpretation of deviations from institution's normal values and recommendations from [CBER FDA GUIDANCE FOR INDUSTRY: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials](#).

The total amount of blood collected over the study period per subject will be approximately 157 mL including screening for HLA for a subject who was not part of the parent study and the additional blood sample at day 29 for the standard pool serum for immunogenicity and excluding possible repeats of hematological tests in case of neutropenia.

Serum samples will be stored frozen below -20°C. The sera aliquots will be shipped according to guidelines provided by GSK to the laboratories for analysis. The serologic assays will be conducted at the GSK Clinical Laboratory Science, Marburg, (Germany) or a delegated laboratory.

Aliquots of sera will be archived for 20 years at the GSK laboratory in Marburg (Germany) for future research on immunogenicity of the *Shigella* vaccines. Study-related future research may include additional evaluation of immunogenicity on *Shigella sonnei* (i.e. IgM, IgA against the O antigen or IgG against other antigens of *Shigella sonnei*). It may not be possible to contact individual participants in the future in order to disseminate results obtained from research conducted on archived samples. However, these results, if relevant, will be published in peer-reviewed journals and disseminated to the scientific community. An archival time of 20 years should cover the entire vaccine development time, including the possibility to address potential questions from regulators during the registration time.

Complete instructions for processing, labeling, storage and shipping of samples are included in the Clinical Specimen Laboratory Manual provided to the investigators and available in the Investigator Site File.

Blood samples must be collected in the appropriate manner, using exclusively materials and guidelines supplied by GSK. The investigator must ensure that his/her personnel and the laboratory(ies) under his/her supervision comply with this requirement. The results of safety testing will be recorded in the source document and eCRF.

Urine Specimens

In this study urine samples will be collected from women of childbearing potential only for pregnancy testing before vaccination at Day 1 (visit1) and at study termination (visit 5).

3.6 Stopping/Pausing Guidelines

There are no predetermined stopping rules in this study. Subjects may be withdrawn from the study according to investigator discretion as described in [section 3.8, Premature Withdrawal from Study](#).

There are no predetermined stopping rules other than circumstances for which subjects may be withdrawn from the study according to the best interests of the subject as described in [section 3.8, Premature Withdrawal from Study](#).

3.7 Data Monitoring Committee

No Data Monitoring Committee will be established for this study.

3.8 Premature Withdrawal from Study

Subjects may withdraw at any time, or be dropped from the study at the discretion of the investigator should any untoward effects occur and/or for safety reasons. In addition, a subject may be withdrawn by the investigator or Sponsor if he/she violates the study plan or for administrative reasons. The investigator or study coordinator must notify the Sponsor immediately when a subject has been withdrawn due to an adverse event.

The circumstances above are referred to as premature withdrawal from the study, and the reason for premature withdrawal should be clearly documented and detailed in the source documentation. The investigator should make every attempt to evaluate the subject's safety, including resolution of ongoing AEs, at the time of premature withdrawal. If a subject wants to withdraw from the study prior to the last planned study visit, the subject will be asked to be followed for safety for the duration of the study. When a subject withdraws, or is withdrawn, from the study, the procedures described in [section 5.5.1, Early Termination Visit](#) should be completed if possible.

The reasons for premature withdrawal from the study include: Adverse event, death, withdrawal of consent, lost to follow-up, administrative reason, and protocol deviation. These reasons are described in greater detail below.

Adverse Event

For any subject withdrawn from study participation prior to the planned Study Termination Visit, it is important to determine if an AE was associated with the reason for discontinuing the study. This AE must be identified on the AE CRF page by indicating "Withdrawn from study due to AE". Any ongoing AEs at the time of study withdrawal must be followed until resolution or stabilization.

Death

For any subject withdrawn from study participation due to death, this should be noted on the Study Termination CRF page and the associated SAE that led to the death must be reported.

Withdrawal of consent

The subject can withdraw consent for participation in the study at any time without penalty or loss of benefit to which the subject is otherwise entitled. Reason for early termination should be deemed as "withdrawal of consent" if the subject withdraws from participation due to a non-medical reason (i.e., reason other than AE). If the subject intends to withdraw consent from the study, the investigator should clarify if the subject will withdraw completely from the study or if the subject will continue study participation for safety, or a subset of other study procedures. If the subject requests complete withdrawal from the study, no further study interventions will be performed with the subject.

Lost to Follow-Up

For subjects who fail to show up for final visits (clinic or telephone contacts), or for three consecutive visits, study staff are encouraged to make at least three documented attempts to contact the subject by telephone and at least one documented written attempt to contact the subject to encourage the completion of study termination procedures. These efforts to contact the subject should be recorded in the source document. The termination date for the subject to be captured on the Study Termination CRF page is the date of the last successful contact (clinic visit or telephone) with the subject.

Administrative Reason

Examples for subjects withdrawn from the study due to administrative reason can include: Sponsor decision to terminate the study, subject meeting a pre-specified withdrawal criterion, subject discontinuation for insurance issues, moving, no time, etc. This reason should be noted in the Study Termination CRF page and any ongoing AEs at the time of study withdrawal must be followed until resolution/stabilization.

If the clinical study is prematurely terminated by the Sponsor, the investigator is to promptly inform the study subjects and local EC/IRB and should assure appropriate therapy and follow up for the subjects. All procedures and requirements pertaining to the archiving of study documents should be followed. All other study materials (study medication/vaccines, etc.) must be returned to the Sponsor.

For subjects who are withdrawn from the study due to receipt of an excluded medication/vaccination or due to significant protocol non-compliance, this reason should be noted in the Study Termination CRF page.

Subjects should submit the diary card data at day 8 (visit 2). Subject must be contacted by phone if they fail to submit the diary card on visit 2 and proper arrangement be made for collection of diary.

Protocol Deviation

A protocol deviation is any change, divergence, or departure from the study design or procedures of a study protocol. In general, subjects associated with protocol deviations may remain in the study unless continuation in the study jeopardizes the subject's health, safety, or rights.

Investigators will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact GSK or its agents, if any, monitoring the study to request approval of a protocol deviation, as no authorized deviations are permitted. If the investigator feels a change to the protocol would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by

GVGH and a substantial amendment is approved by the IRB/EC and health authorities it cannot be implemented.

Any subject who becomes pregnant during the study, despite the protocol requirement for adequate contraception, should be encouraged to continue participating in the study for safety follow-up. The site must complete a Pregnancy Report CRF (initial report) as soon as possible after learning of pregnancy occurrence (see [section 7.1.6, Pregnancies](#) for further details). If the subject withdraws from the study for any of the above categories except death, the site will obtain permission from the subject to continue to remain in contact with her until the outcome of the pregnancy is known, even if the outcome is not known until after the subject reaches the end of follow-up period.

3.9 End of Study

Evaluation of the primary and/or secondary immunogenicity objectives requires the testing of biological samples from the study subjects, which can only be completed after all samples are collected. The last samples for the analysis of the primary and/or secondary objectives will be taken at visit 5.

For the purpose of this protocol, end of study (EoS) is defined as the completion of the testing of such biological samples, to be achieved no later than 8 months after collection of the last biological sample visit.

4. SELECTION OF STUDY POPULATION

4.1 Inclusion Criteria

In order to participate in this study, all subjects must meet ALL of the inclusion criteria described. Are included:

1. Males and females, aged 22 to 50 years, who were previously vaccinated, with either vaccine (3 doses) or placebo, in H03_01TP and who had undetectable antibody titers at baseline, or Males and females, aged 22 to 50 years, who were not part of H03_01TP.
2. Individuals who, after the nature of the study has been explained to them, and prior to any protocol specific procedures being performed, have given written consent according to local regulatory requirements.
3. Individuals in good health as determined by the outcome of medical history, physical examination, hematological blood tests and clinical judgment of the investigator.
4. If women of child-bearing potential, have a negative urinary pregnancy test prior study vaccination and willingness to use acceptable birth control measures for the entire study duration.
5. Individuals affiliated to a social security regimen.

4.2 Exclusion Criteria

Are excluded:

1. Individuals with behavioral or cognitive impairment or psychiatric disease that, in the opinion of the investigator, may interfere with the subject's ability to participate in the study.
2. Individuals with any progressive or severe neurological disorder, seizure disorder or Guillain-Barré syndrome.
3. Individuals who are not able to understand and to follow all required study procedures for the whole period of the study.
4. Individuals with known hepatitis B or C or suspected HIV infection or HIV related disease with history of an autoimmune disorder or any other known or suspected impairment /alteration of the immune system.
5. Progressive, unstable or uncontrolled clinical conditions.
6. Hypersensitivity, including allergy, to any component of vaccines, medicinal products or medical equipment whose use is foreseen in this study.
7. Individuals with a known bleeding diathesis, or any condition that may be associated with a prolonged bleeding time.
8. Clinical conditions representing a contraindication to intramuscular vaccination and blood draws.
9. Abnormal function of the immune system resulting from:
 - Clinical conditions;
 - Systemic administration of corticosteroids (PO/IV/IM) for more than 14 consecutive days within 90 days prior to informed consent;
 - Administration of antineoplastic and immunomodulating agents or radiotherapy within 90 days prior to informed consent.
10. Received immunoglobulins or any blood products within 180 days prior to informed consent.
11. Study personnel as an immediate family or household member.
12. Any other clinical condition that, in the opinion of the investigator, might interfere with the results of the study or pose additional risk to the subject due to participation in the study.
13. Individuals who have received an investigational product in another clinical trial 28 days prior to first study visit or intent to receive another investigational product at any time during the conduct of this study.

14. Individuals who received any other vaccines within 4 weeks prior to enrollment in this study or who are planning to receive any vaccine within the entire study duration. Inactivated influenza vaccine can be given, but only 4 weeks earlier or 4 weeks later than the date of immunization.
15. Individuals who have received blood, blood products, and/or plasma derivatives including parenteral immunoglobulin preparations in the past 12 weeks.
16. Individuals with body temperature > 38.0 degrees Celsius within 3 days of intended study vaccination.
17. Individuals with Body Mass Index (BMI) > 30 kg/m².
18. Individuals with history of substance or alcohol abuse within the past 2 years.
19. Women who are pregnant or are breast-feeding, or are of childbearing age who have not used or do not plan to use acceptable birth control measures, for the duration of the study.
20. Females with history of stillbirth, neonatal loss, or previous infant with anomaly.
21. Individuals who have a previously laboratory confirmed or suspected disease caused by *S. sonnei*.
22. Individuals who have had household contact with/and or intimate exposure to an individual with laboratory confirmed *S. sonnei*.
23. Any condition, which, in the opinion of the investigator may pose an increased and unreasonable safety risk to the subject if participating to the present study.
24. Individuals with a neutrophil count value lower than $1.8 \times 10^9/L$ at screening assessment.
25. Individuals with human leukocyte antigen (HLA)-B27 positive and/or with history of reactive arthritis.
26. Previous history of Benign Ethnic Neutropenia or drug related Neutropenia and/or concomitant treatment with neutropenic agents.

4.3 Criteria for Delay of Vaccination

There may be instances when individuals meet all eligibility criteria for vaccination yet have a transient clinical circumstance which may warrant delay of vaccination: body temperature elevation (≥ 38.0 °C within 3 days prior to intended study vaccination), or use of antipyretics and/or analgesic medications within 24 hours prior to vaccination. Under such circumstances, a subject may be considered eligible for study enrolment after the appropriate window for delay has passed and inclusion/exclusion criteria have been rechecked, and if the subject is confirmed to be eligible.

5. STUDY PROCEDURES

The sections that follow provide an overview of the procedures that are to be followed in enrolling, evaluating, and following subjects who participate in this clinical study. Visits can be either clinic visits or safety follow-up telephone calls, as specified in the Table below and in the [Time and Events Table 2](#).

Table 5 Study Procedures

Visit Category	Procedures
Pre-vaccination Clinic Visit(s)	Section 5.1 describes procedures to be followed prior to study vaccination: informed consent, screening, enrolment, and randomization
Vaccination Clinic Visit(s)	Section 5.2 describes procedures to be followed during each clinic visit involving vaccination: vaccination, post-vaccination procedures, and postvaccination reminders
Post-vaccination Visit(s)	Section 5.3 describes follow-up clinic visits and safety follow-up calls
Unscheduled Visit(s)	Section 5.4 describes possible procedures to be followed at unscheduled clinic visit
Study Termination Visit	Section 5.5 describes procedures to be followed at the last study visit for a subject (may include early termination visit)

5.1 Pre-vaccination Clinic Visit(s)

This section describes the procedures that must be performed for each potential subject prior to vaccination, including obtaining informed consent, screening, enrolment and randomization.

5.1.1 Informed Consent/Assent

"Informed consent" is the voluntary agreement of an individual or his/her legal guardian(s) to participate in research. Consent must be given with free will of choice, and without undue inducement. The individual must have sufficient knowledge and understanding of the nature of the proposed research, the anticipated risks and potential benefits, and the requirements of the research to be able to make an informed decision.

Informed consent following local IRB/EC guidance **must** be obtained before conducting any study-specific procedure (i.e., all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the subject source document in addition to maintaining a copy of the signed and dated informed consent. Additional specifics regarding the informed consent processes are located in [section 13.2, Informed Consent Procedures](#).

5.1.2 Screening

Subject identification numbers will be assigned sequentially to the subjects who have consented to participate in the study. The eligibility of the subject will be determined based on the inclusion and exclusion criteria listed in [section 4, Selection of Study Population](#) and evaluated during this screening procedure.

Prior to study enrolment, demographic data will be collected from the subject, including: age, gender, race and body mass index.

Medical history will also be collected, including but not limited to any medical history that may be relevant to subject eligibility for study participation such as prior vaccinations, concomitant medications, and previous and ongoing illnesses or injuries. Subject who participated in the H03_01TP parent trial will have their medical history since the last visit reviewed. Relevant medical history can also include any medical history that contributes to the understanding of an adverse event that occurs during study participation, if it represents an exacerbation of an underlying disease/pre-existing problem.

Review of systems is a structured interview that queries the subject as to any complaints the subject has experienced across each organ system. This will be performed before enrolment and used to guide physical examination.

Important prior and concomitant medications or vaccinations taken prior to start of study should be collected (refer to [section 6.5, Prior and Concomitant Medications and Vaccines](#) for further details).

Vital signs: heart rate, respiratory rate, diastolic and systolic blood pressure, temperature and also anthropometric measurements: height and weight will be collected

A general physical examination is to be performed by a qualified health care practitioner. “Qualified health care practitioner” refers to any licensed health care professional who is permitted by institutional policy to perform physical examinations and who is identified within the Study Staff Signature Log.

These data will be written in the source document (see [section 9.1, Source Documentation](#)).

Approximately 15 mL of blood will be obtained as part of the initial screening for hematology and serology testing (HIV, hepatitis B and C) and 25 mL for the same tests and HLA-B27 for naïve subjects. Another 20 mL of blood will be collected before vaccination on day 1 for baseline immunological testing (Refer to [section 3.5, Collection of Clinical Specimens](#)).

In the event that the individual is determined ineligible for study participation, he/she is considered a screen failure. The reason for screen failure must be documented in the

Screening and Enrolment log. If the individual is determined to be eligible for the study, he/she will be enrolled into the study.

5.1.3 Enrolment

After signing the informed form, if an individual is determined to be eligible for study participation, the investigator will enroll the subject.

5.1.4 Randomization

5.1.4.1 Randomization

This is a non-randomized study which is an extension of H03_01TP study done on the same setting. Enrolled subjects will be manually assigned a unique Subject ID; since 24 subjects to be enrolled are from the previous study (H03_01TP) database, so these will preserve their subject ID if they get enrolled. The subsequent 26 new recruits as explained on [section 3.1 overview of study design](#) will be assigned subject ID following the same order used in H03_01TP but starting from where last subject's ID ended. This will easier identify subjects who are on booster vaccine dose from subjects given one vaccine dose as per this study. The Subject ID will be the subject's unique identification number for all CRFs and associated study documentation that will be used for duration of the study. The Screening Number ceases to be used and remains in the Screening and Enrolment Log.

If for any reason, after enrolment the subject fails to undergo treatment/study procedures this is an Early Termination and the reason should be recorded in source document as specified in the Source Documentation Agreement Form (SDAF). The information on these Early Termination subjects should be kept distinct in the source documentation from subjects who are screen failures, as described in [section 5.1.2, Screening](#).

5.2 Vaccination Clinic Visit(s)

The vaccination will be performed on study day 1.

Ensure all serology samples are taken **prior** to vaccination.

Perform pregnancy testing in women of childbearing age ([section 3.5, Collection of Clinical Specimens](#) for guidance regarding the procedure). Informed consent process with any women of childbearing potential will include counseling about pregnancy including discussion of their commitment to practice acceptable birth control measures (defined as oral, injected or implantable contraceptives). Women of childbearing potential are defined as a post onset of menarche and pre-menopausal female capable of becoming pregnant. This does not include females who meet any of the following conditions: (1) menopause at least 2 years earlier, (2) tubal ligation at least 1 year earlier, (3) total hysterectomy or (4) post bilateral oophorectomy.

After completing the pre-vaccination procedures on day 1, administer the vaccine to the subject according to the procedures described in [section 6.3, Vaccine Preparation and Administration](#).

Prior to administration of vaccination, confirm that the subject is eligible for study vaccinations by checking his/her medical history, clinical examination, all inclusion/exclusion criteria and that the subject does not meet any criteria for delaying study vaccinations as described in [section 4, Selection of Study Population](#)

5.2.1 Post-vaccination Procedures

The following post-vaccination procedures will be performed on day 1:

After vaccination, the subject will be observed for at least 4 hour including observation for unsolicited adverse events, solicited adverse events, and body temperature and vital signs measurement. Record all safety data collected during this time in the subject's source document.

A Subject Diary will be used in this study to document solicited adverse events. The Subject Diary is the only source for collection of these data; therefore, it is critical that the subject completes the Subject Diary correctly. The subject should be trained on how and when to complete each field of the Subject Diary.

Subject Diary training should be directed at the individual(s) who will perform the measurements of adverse events and who will enter the information into the Subject Diary.

The same individual should complete the Subject Diary throughout the 7 days following vaccination.

Training of the subject on how to measure an injection site reaction should be performed while the subject is under observation after vaccination. The subject must understand that timely completion of the diary card on a daily basis is a critical component to study participation. The subject should also be instructed to write clearly and to complete the diary card in pen. Any corrections to the diary card that are performed by the person completing the diary card should include a single strikethrough line with a brief explanation for any change. No changes can be made to the diary card when it is returned to the clinic.

Starting on the day of vaccination, the subject will check in the evening for specific types of reactions at the injection site (solicited local reactions), any specific generalized symptoms (solicited systemic reactions), body temperature (taken preferably orally) any other symptoms or change in the subject's health status, and any medications taken (excluding vitamins and minerals).

The subject should be trained on how to self-measure local solicited adverse events and body temperature. The measurement of solicited local adverse events is to be performed using the ruler provided by the site.

Body temperature measurement is to be performed using the thermometer provided by the site. If the subject feels unusually hot or cold during the day, the subject should check body temperature. If the subject has fever, the highest body temperature observed that day should be recorded on the Diary Card. The collection of body temperature, solicited local adverse events, solicited systemic adverse events will continue for a total of 7 days on the Diary Card. The collection of unsolicited adverse events and medications will continue after the 7 days on the Diary Card.

At the end of the observation period, the site should schedule the next study visit with the subject. The subject will receive a study ID card to be used as a written reminder of the next planned study activity and to provide study staff contact details. The subject will be reminded to complete the Diary card daily and to contact the site if there are any questions and to contact the site immediately (or as soon as the subject is medically stable) if the subject has a medical condition that leads to a hospitalization or an emergency room visit.

All subjects presenting with a history of fever or any other sign or symptom judged by the investigator to be as a result of an infection within 21 days of vaccination will have a blood sample collected for a complete blood count to establish the absolute neutrophil count. If there is a neutropenia, the subject will be managed appropriately according to local and international requirements.

5.2.2 Post-vaccination Reminders

Reminder calls (or emails) are not intended to be an interview for collection of safety data. If the subject wishes to describe safety information, this information should only be collected by a healthcare professional at the site, and the safety data described must be written down in the subject's medical chart/source document.

Subject Diary Reminder Calls / Emails

Subject Diary reminder calls will be performed or email will be sent on day 3 and day 7 post vaccination. The purpose of this call or email is to remind the subject about completion of the Subject Diary. The call/email follow the Subject Diary Reminder Telephone Call/Email Scripts provided to the site. The subject should be reminded to contact the site via the telephone number provided in the informed consent to discuss medical questions. The safety data described by the subject on a telephone call must be written down in source documents and the subject should be reminded to write the information down in the diary card.

If the email is printed by study staff to document that the reminder was sent, all personal information such as name and email address of the subject, will be removed before printing.

5.3 Post-vaccination Visit(s)

5.3.1 Follow-up Clinic Visit(s)

Safety follow-up clinic visits will be performed on day 8, day 15, day 29 and day 85.

During visit 2, the Subject Diary will be reviewed. No changes to the information recorded within the Subject Diary are permissible. For details on the Subject Diary see [sections 3.4.2, Tools Used for Data Collection](#) and [5.2.1, Post-vaccination Procedures](#). The subject will be interviewed to determine if any unsolicited adverse events occurred and if any concomitant medications or vaccines were taken or received in the time since the last visit. This interview will follow a checklist which will facilitate the collection of relevant safety information. The healthcare professional reviewing these data will discuss the symptoms (if any) reported by the subject and will determine if any additional diagnoses and/or adverse events are present. Adverse events reported by the subject at this follow-up clinic visit must be recorded in the subject's source document and on an Adverse Events eCRF, as specified in [section 7.1, Safety Assessment](#), and not written on the checklist used for the interview.

Perform a brief symptom-directed physical examination if necessary according to symptoms the subject has reported. This is a physical examination that will include an examination of organ systems that are relevant to the investigator based on review of the subject's reported adverse events, concomitant medication use. The physical assessment must be performed by the investigator or designee of the investigator, who is qualified to perform a physical assessment in accordance with their institutional policy. Corresponding information is documented in the subject's source document.

The site should schedule the next study activity, i.e. the next clinic visit and reminder phone call/email with the subject. The subject will be reminded to contact the site if there are any questions and to contact the site immediately (or as soon as the subject is medically stable) if the subject has a medical condition that leads to a hospitalization or an emergency room visit.

5.3.2 Safety Follow-up Calls

No safety follow up call will be made in this study.

5.4 Unscheduled Visits

An unscheduled visit describes a non-routine study visit triggered by a specific event. These could include anticipated or unanticipated adverse events or interventions. Data obtained from such unscheduled visit should be record in a respective source document and eCRF. If a case of neutropenia is observed after vaccination and still prevalent on a subsequent visit, the results will be recorded in the Unscheduled Lab eCRF.

All individuals with a neutropenia, occurring at any time during the study, will have additional blood draws for complete blood count to be repeated on a weekly basis until the neutropenia resolves. If neutropenia occurs at the subject's last study visit, the complete blood count will be repeated on a regular basis until resolution. For classification of neutropenia during the trial, refer to [section 7.1.4.1 Adverse Events of Special Interest](#).

5.5 Study Termination Visit

The study termination visit will occur on day 85 (visit 5). The date of termination is the date of the last contact (clinic visit or telephone call) in which the subject's health status was assessed or, in cases where the subject does not agree to any further safety follow-up; it is the date consent is withdrawn. This date should be recorded on the termination eCRF page. For visit procedures to be performed for a subject whose planned study participation ends prematurely, please see [section 5.5.1, Early Termination Visit](#).

At the clinic visit or during the telephone call, the following procedures will be performed:

Review of systems, interview of subject to collect: medically attended adverse events, AEs leading to withdrawal, SAEs, AESIs, and new onset of chronic disease, interview of subject to collect concomitant medications in relation to these events, vaccinations, symptom-directed physical assessment and a check of general appearance, blood sampling for safety laboratory assessment (hematology testing) and immunogenicity, and a urine pregnancy test for women of childbearing potential.

The site will review with the subject the plan of when information relating to the subject's participation in the study may be available (i.e., study results, treatment assignments).

The site will complete the termination eCRF page and this will mark the completion of the subject's participation in the study.

5.5.1 Early Termination Visit

When a subject is withdrawn from treatment or withdraws from the study, the investigator will notify the Sponsor and, when possible, will perform the procedures listed below. The reason(s) for the early termination will be included in the subject's source documentation. If the Early Termination Visit is a telephone call, collect as much information as possible. Early Termination Visits include subjects who were enrolled but not treated.

At the clinic visit, the following procedures will be performed;

- Review of subject's medical records, source document and Diary Card,
- Review of systems, interview of subject to collect unsolicited adverse events, medically attended adverse events, AEs leading to withdrawal, SAEs, AESIs, and new onset of chronic disease,

- Interview of subject to collect concomitant medications/vaccinations,
- Symptom-directed physical assessment including measurement of vital signs and a check of general appearance,
- Blood sampling for safety laboratory assessment (no blood for immunogenicity assessment should be obtained unless this is agreed in advance with the Sponsor),
- Urine sample for pregnancy testing.

All individuals with neutropenia either ongoing or with onset at last study visit will have additional blood draws for complete blood count to be repeated on a regular basis until the neutropenia resolves (for classification of neutropenia during the trial, refer to [section 7.1.4.1 Adverse Events of Special Interest](#)). Laboratory results obtained after study termination will be maintained in subject medical records and not entered in the eCRF.

The site will review with the subject the plan of when information relating to the subject's participation in the study may be available (e.g., study results, treatment assignments). It will also be discussed how information relating to the subject's participation in the study will be shared with the subject's healthcare provider, if the subject chooses to share this information.

The site will complete the termination CRF page and this will mark the completion of the subject's participation in the study.

6. TREATMENT OF SUBJECTS

All vaccines associated with this study are to be stored separately from other vaccines and medications in a secure location under appropriate storage conditions with temperature monitoring. **All vaccines associated with this study must be checked for expiration date prior to use. Expired vaccines must not be administered to subjects.**

S6.1 Study Vaccine(s)

The term 'study vaccine' refers to those vaccines provided by the Sponsor, which will be evaluated as part of the study objectives. The study vaccine specific to this study is GVGH *S. sonnei* 1790GAHB vaccine. The GVGH GAHB-Diluent will be used as diluent for bedside mixing as described below.

The investigational agent is the GVGH *S. sonnei* vaccine. The vaccine consists of *S. sonnei* 1790-GMMA (200 µg/mL, measured by protein content) adsorbed to Alhydrogel®, (0.7 mg Al³⁺/mL) in Tris-buffered saline. The vaccine does not contain any preservative and is available as a liquid formulation in single dose vials with 0.7 mL of injectable solution containing approximately 140 µg of GMMA (as protein content), adsorbed onto 0.49 mg Al³⁺. It should be stored at +2/+8 °C.

A diluent, named GAHB-Diluent, visually matching the *S. sonnei* 1790GAHB vaccine, is also supplied for use in this clinical study as a diluent for bedside mixing. It contains the

same formulation ingredients as the active *S. sonnei* 1790GAHB vaccine, except for the Drug Substance antigen 1790-GMMA, and is provided in the same primary packaging as the *S. sonnei* 1790GAHB vaccine.

Aluminum hydroxide is well characterized and used as adjuvant in several licensed vaccines. In 1790GAHB, aluminum hydroxide is used as an adsorbent to reduce the reactogenicity of LPS and does not enhance the immunogenicity of the GMMA vaccine.

For further information of study vaccines refer to the Investigator Brochure.

6.2 Non-Study Vaccines

There will be no non-study vaccines to be used.

6.3 Vaccine Preparation and Administration

The investigator or designee will be responsible for oversight of the administration of vaccine to subjects enrolled in the study according to the procedures stipulated in this study protocol. All vaccines will be administered only by personnel who are qualified to perform that function under applicable local laws and regulations for the specific study site.

Detailed vaccine preparation and administration instructions will be provided to investigators in the bedside mixing checklist and instructions prior to study start.

A *S. sonnei* 1790GAHB vaccine volume of 0.5 mL will be administered intramuscularly after bedside mixing to make a 25 µg protein/0.5 mL dose. Bedside mixing, possibly necessary additional labeling of clinical study materials at the study site and vaccine administration will be performed according to Sponsor instructions and by trained site staff. The site staff responsible for these activities will be personnel who are respectively qualified according to applicable local laws and regulations. Sponsor will provide specific procedures and training for these activities.

PRECAUTIONS TO BE TAKEN IN ADMINISTERING STUDY VACCINE:

Prior to vaccination, subjects must be determined to be eligible for study vaccination and it must be clinically appropriate in the judgment of the investigator to vaccinate. Eligibility for vaccination prior to first study vaccine administration is determined by evaluating the entry criteria outlined in protocol [sections 4.1, Inclusion Criteria](#) and [4.2, Exclusion Criteria](#).

Study vaccines should not be administered to individuals with known hypersensitivity to any component of the vaccines.

Standard immunization practices are to be observed and care should be taken to administer the injection intramuscularly. Before administering vaccine, the vaccination site is to be

disinfected with a skin disinfectant (e.g., 70% alcohol). Allow the skin to dry. **DO NOT inject intravascularly.**

As with all injectable vaccines, trained medical personnel and appropriate medical treatment should be readily available in case of anaphylactic reactions following vaccine administration. For example, epinephrine 1:1000, diphenhydramine, and/or other medications for treating anaphylaxis should be available.

6.3.1 Replacement of unusable vaccines

In addition to the vaccine doses provided for the planned number of subjects (including extra doses to allow flexibility in enrolment at the different sites), at least 5% additional vaccine doses will be supplied to replace those that are unusable.

6.4 Vaccine Administration Error or Overdose of Vaccine

Vaccine administration error is defined as receiving a dose of study vaccine that was not prepared according to bedside mixing instructions or administered by a different route from the intended route of administration. An overdose of study vaccine (whether accidental or intentional) is defined when a dose higher than dose foreseen in this clinical study, i.e. 25 µg is administered in one dose of *Shigella sonnei* 1790GAHB study vaccine subjects.

Any vaccine administration error or overdose of study vaccine detailed in this protocol must be reported as an adverse event, and if the vaccine administration error or overdose is associated with a serious adverse event, it must be reported as such within 24 hours to the Sponsor.

6.5 Prior and Concomitant Medications and Vaccines

All relevant medications taken or received by the subject within 4 weeks prior to the start of the study are to be recorded on the Prior and Concomitant Medications eCRF.

In addition, the following are considered prior medications for this protocol:

all medication/vaccines described in the inclusion and exclusion criteria of this protocol including the use of antipyretics and/or analgesic medications within 24 hours prior to vaccination and ending 12 hours after vaccination must be identified and the reason for their use (prophylaxis versus treatment) must be described in the source document and Concomitant Medications CRF [Section 4.3, Criteria for Delay of Vaccination](#). Use of antipyretic, 24 hours before vaccination is a reason to delay vaccination.

Medications taken for prophylaxis are those intended to prevent the onset of symptoms. Medications taken for treatment are intended to reduce or eliminate the presence of symptoms that are present.

Concomitant medications include all medications (including vaccines) taken by/administered to the subject at and after enrolment and must be documented on the Concomitant Medications CRF.

When recording concomitant medications/vaccines, they should be checked against the study entry and continuation criteria in [section 4, Selection of Study Population](#) to ensure that the subject should be enrolled/continue in the study.

6.6 Vaccine Supply, Labeling, Storage and Tracking

Detailed vaccine supply, labeling, storage and tracking instructions will be provided to investigators prior to study start.

The Sponsor will ensure the following:

- Supply the study vaccine.
- Appropriate labeling of all study that complies with the country legal requirements.

The investigator must ensure the following:

- Acknowledge receipt of the study vaccines by a designated staff member at the site, including confirmation that the vaccines were received in good condition.
- Proper storage of the study vaccines, including:
 - Storage in a secure, locked, temperature-controlled location.
 - The study vaccine must be stored at the respective label storage temperature conditions in a safe and locked place. Access to the storage space should be limited to authorized study personnel. The storage conditions will be assessed during pre-study activities under the responsibility of the sponsor study contact.
 - Proper storage according to the instructions specified on the labels.
 - Appropriate record keeping and inventory of the study vaccines, including regular documentation of adequate storage temperature.
 - The storage temperature should be continuously monitored with calibrated (if not validated) temperature monitoring device(s) and recorded.
 - Temperature excursions must be reported in degree Celsius.
 - Any temperature excursion outside the range of +2.0 to +8.0 °C impacting investigational medicinal products (IMPs) must be reported to the Sponsor. The impacted IMPs must not be used and must be stored in quarantine at label temperature conditions until usage approval has been obtained from the Sponsor.
- Appropriate use of the study vaccines, including:
 - Use only in accordance with the approved protocol.

- Proper handling, including confirmation that the vaccine has not expired prior to administration.
- Appropriate documentation of administration of vaccines to study subjects including:
 - Date, dosage, batch/lot numbers, expiration dates, unique identifying numbers assigned to subjects and study vaccines, and time of vaccine administration. This information will be maintained in an accountability log that will be reviewed by the site monitor.
 - Reconciliation of all vaccines received from the Sponsor. Reconciliation is defined as maintaining records of which and how many vaccines were received, which vaccines were administered to subjects, which vaccines were destroyed at the site, and which vaccines were returned to the Sponsor, as applicable.
- Proper adherence to the local institutional policy with respect to destruction of study vaccines.
- Complete record keeping of vaccine use, wastage, return or destruction, including documentation of:
 - Copy of the site's procedure for destruction of hazardous material.
 - Copy of Destruction Certificate.

Vaccines that have been stored differently from the manufacturer's indications **must not** be used unless the Sponsor provides authorization for use. In the event that the use cannot be authorized, the Sponsor will make every effort to replace the vaccine supply. All vaccines used in conjunction with this protocol must be stored separately from normal hospital/practice stocks to prevent unintentional use of study vaccines outside of the clinical study setting.

Monitoring of vaccine accountability will be performed by the study monitor during site visits and at the completion of the study.

At the conclusion of the study, and as appropriate during the course of the study, the investigator must ensure that all unused study vaccines, packaging and supplementary labels are destroyed locally (upon approval from the Sponsor) or returned to the Sponsor.

7. ASSESSMENTS

7.1 Safety Assessment

The measures of safety used in this study are based on previous study data. They include a close vigilance for, and stringent reporting of selected local and systemic adverse events routinely monitored in vaccine studies as indicators of reactogenicity.

An adverse event (AE) is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product at any dose that does

not necessarily have to have a causal relationship with this treatment. Therefore, an AE can be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product. This definition includes intercurrent illnesses or injuries and exacerbation of pre-existing conditions.

For the purpose of this trial, AEs will be from the time the subject signs informed consent until Visit 4. AEs occurring after the informed consent form is signed but prior to receiving study vaccine will be documented as an adverse event and recorded within source document. However, any AEs occurring prior to receipt of any study vaccine will be analyzed separately from “treatment emergent” AEs (AEs occurring after administration of the first study vaccine). All adverse events that are serious, clinically significant as judged by the investigators, medically attended and AESI will be collected until study termination at visit 5.

Adverse events are collected as either solicited or unsolicited adverse events. Solicited events are derived from organized data collection systems, such as Subject Diaries or interview.

7.1.1 Solicited Adverse Events

The term “reactogenicity” refers to solicited signs and symptoms (“solicited adverse events”) occurring in the hours and days following a vaccination, to be collected by the subject for 7 consecutive days, using a pre-defined Subject Diary.

The following solicited adverse events are included in the Subject Diary. Each adverse event is to be assessed using the scoring system reported in parentheses below:

Solicited Local Adverse Events

These include erythema, induration and pain at injection site. They will be assessed using the scoring system reported in a table below. **Table 6 Grading of solicited local adverse events**

Solicited local adverse events	Grade 0 Absent	Present - Grading of Severity		
		Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe
Injection site Erythema (Captured as measurements in millimeters)	1-24 mm	25-50 mm	51-100 mm	> 100 mm
Injection site Induration (Captured as measurements in millimeters)	1-24 mm	25-50 mm	51-100 mm	> 100 mm

Injection site Pain	No pain	Present but does not interfere with activity	Interferes with activity	Prevents daily activity
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Solicited Systemic Adverse Events

These include headache, arthralgia, chills, fatigue, malaise, myalgia, and fever (body temperature measured orally). They will be assessed using the scoring system reported in a table below.

Table 7 Grading of solicited systemic adverse events

Solicited systemic adverse events	Grade 0 Absent	Present - Grading of Severity*		
		Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe
Headache	No headache	Present but does not interfere with activity	Interferes with activity	Prevents daily activity
Arthralgia	No arthralgia	Present but does not interfere with activity	Interferes with activity	Prevents daily activity
Chills	No chills	Present but does not interfere with activity	Interferes with activity	Prevents daily activity
Fatigue	No fatigue	No interference with activity	Some interference with activity	Significant; prevents daily activity
Malaise	No malaise	No interference with activity	Some interference with activity	Significant; prevents daily activity
Myalgia	No myalgia	Present but does not interfere with activity	Interferes with activity	Prevents daily activity
Fever as a Body temperature (Captured as measurements in degrees Celsius)	≤ 37.9 °C	≥ 38.0 – 38.9°C	≥ 39.0 – 39.9°C	≥ 40.0°C
	Oral Temperature: <35.5 °C to ≥38.0 °C			

Other Solicited Adverse Events

These include use of analgesics/antipyretics. It will be assessed using the scoring system reported in a table below.

Other Solicited adverse events	Grade 0 Absent	Present - Grading of Severity		
		Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe

Use of analgesics/ antipyretics	Categorized as “yes” or “no”
--------------------------------------------	------------------------------

The study staff must review the data entered into the Subject Diary as described in [section 3.4.2, Tools Used for Data Collection](#) and [section 5.3.1, Follow-up Clinic Visit\(s\)](#).

Note: Any solicited adverse event that meets any of the following criteria must be entered into subjects’ source document (see [section 9.1, Source Documentation](#)) and also as an adverse event on the Adverse Event CRF:

- Solicited local or systemic adverse event that continues beyond day 7 after vaccination.
- Solicited local or systemic adverse event that leads to a visit to a healthcare provider (medically attended adverse event, see [section 7.1.3, Evaluation of Adverse Events](#)).
- Solicited local or systemic adverse event leading to the subject withdrawing from the study or the subject being withdrawn from the study by the investigator (adverse event leading to withdrawal, see [section 7.1.3, Evaluation of Adverse Events](#)).
- Solicited local or systemic adverse event that otherwise meets the definition of a serious adverse event (see [section 7.1.4, Serious Adverse Events](#)).

7.1.2 Unsolicited Adverse Events

An unsolicited adverse event is an adverse event that was not solicited using a Subject Diary and that was spontaneously communicated by a subject who has signed the informed consent.

Potential unsolicited AEs may be medically attended (defined as symptoms or illnesses requiring hospitalization, or emergency room visit, or visit to/by a health care provider), or were of concern to the subject. In case of such events, subjects will be instructed to contact the site as soon as possible to report the event(s). The detailed information about the reported unsolicited AEs will be collected by the qualified site personnel during the interview and will be documented in the subject’s records.

Unsolicited AEs that are not medically attended nor perceived as a concern by subjects will be collected during interview with the subject and by review of available medical records at the next visit (see [section 5.3, Post-vaccination Visit\(s\)](#)).

7.1.3 Evaluation of Adverse Events

Every effort should be made by the investigator to evaluate safety information reported by a subject for an underlying diagnosis and to capture this diagnosis as the event in the AE page. In other words, the practice of reporting only symptoms (e.g., “cough” or “ear pain”) are better reported according to the underlying cause (e.g., “asthma exacerbation” or “otitis media”).

The severity of events reported on the Adverse Events CRF will be determined by the investigator as:

Mild: transient with no limitation in normal daily activity.
Moderate: some limitation in normal daily activity. Severe:
unable to perform normal daily activity.

The relationship of the study treatment to an AE will be determined by the investigator based on the following definitions:

1. Not Related

The AE is not related to an investigational vaccine if there is evidence that clearly indicates an alternative explanation. If the subject has not received the vaccine, the timing of the exposure to the vaccine and the onset of the AE are not reasonably related in time, or other facts, evidence or arguments exist that reasonably suggest an alternative explanation, then the AE is not related.

2. Possibly Related

The administration of the investigational vaccine and AE are considered reasonably related in time and the AE could be explained by exposure to the investigational vaccine or by other causes. 3. Probably Related

Exposure to the investigational vaccine and AE are reasonably related in time and no alternative explanation has been identified.

The relationship of the study treatment to an unsolicited AE will be determined by the investigator.

Note: solicited AEs will not be evaluated for relationship to study treatment. Grading for severity of solicited local and systemic AEs is described in [section 7.1.1, Solicited Adverse Events](#).

Adverse events will also be evaluated by the investigator for the co-existence of any of the other following conditions:

- “Medically attended adverse event”: an adverse event that leads to a visit to a healthcare provider.
- “New onset of chronic disease” (NOCD): an adverse event that represents a new diagnosis of a chronic medical condition that was not present or suspected in a subject prior to study enrolment.
- AEs leading to withdrawal: adverse events leading to study or vaccine withdrawal.

- Potential immune-mediated diseases (pIMDs): a subset of AEs that include autoimmune diseases and other inflammatory and/or neurologic disorders of interest which may or may not have an autoimmune aetiology. In this study, only the pIMDs reported in the table below will be collected. However if other pIMDs are discovered during development of the vaccine, the table will be revised and updated accordingly.

Musculoskeletal disorders	Spondyloarthritis, including ankylosing spondylitis, reactive arthritis (Reiter's Syndrome) and undifferentiated spondyloarthritis
Blood disorders	Autoimmune neutropenia

If solicited or unsolicited adverse events have been reported and the subject indicated that the symptoms required medical attendance or were of concern, the subject must be contacted for further information.

When the subject is contacted for any of these reasons, the contact must be documented in the subject's source documentation.

All AEs, regardless of severity, will be monitored until resolution or until the investigator assesses them as chronic or stable. All subjects experiencing AEs - whether considered associated with the use of the study vaccine or not - must be monitored until symptoms subside and any abnormal laboratory values have returned to baseline, or until there is a satisfactory explanation for the changes observed, or until death, in which case a full pathologist's report should be supplied, if possible. The investigator's assessment of ongoing Adverse Events at the time of each subject's last visit should be documented in the subject's medical chart.

7.1.4 Serious Adverse Events

A serious adverse event (SAE) is defined as any untoward medical occurrence that at any dose results in one or more of the following:

- Death.
- Is life-threatening (i.e., the subject was, in the opinion of the investigator, at immediate risk of death from the event as it occurred); it does not refer to an event which hypothetically might have caused death if it were more severe.
- Required or prolonged hospitalization.
- Persistent or significant disability/incapacity (i.e., the event causes a substantial disruption of a person's ability to conduct normal life functions).
- Congenital anomaly/birth defect.

- An important and significant medical event that may not be immediately life threatening or resulting in death or hospitalization but, based upon appropriate medical judgment, may jeopardize the subject or may require intervention to prevent one of the other outcomes listed above.

Adverse events which do not fall into these categories are defined as non-serious.

It should be noted that a severe adverse event need not be serious in nature and that a serious adverse event need not, by definition, be severe.

Serious adverse events will be captured both on the Vaccines Serious Adverse Event (VSAE) form as well as on the AE CRF. All SAEs will be evaluated by the investigator for relationship of the event to study vaccine. SAEs that are judged to be possibly or probably related to the study vaccine should be reported to the Sponsor as related events. The relationship of the study treatment to an SAE will be determined by the investigator based on the following definitions:

1. Related

The SAE is judged by the investigator to be possibly or probably related to the study vaccine on the AE CRF page (see [section 7.1.3, Evaluation of Adverse Events](#)).

2. Not Related

The SAE is not related if exposure to the study vaccine has not occurred, **or** the occurrence of the SAE is not reasonably related in time, **or** the SAE is considered unlikely to be related to use of the study vaccine, i.e., there are no facts (evidence) or arguments to suggest a causal relationship.

The relationship of the study vaccine to an SAE will be determined by the investigator.

In addition, SAEs will be evaluated by the Sponsor or designee for “expectedness.” An unexpected AE is one that is not listed in the current Summary of Product Characteristics or the Investigator’s Brochure or an event that is by nature more specific or more severe than a listed event.

In addition, a pre-existing event or condition that results in hospitalization should be recorded on the Medical History CRF. If the onset of an event occurred before the subject entered the study (e.g., any pre-planned hospitalization for conditions like cosmetic treatments or for non-emergency routine visits for a pre-existing condition), the hospitalization would not lead to an AE being classified as serious unless, in the view of the investigator, hospitalization was prolonged as a result of participation in the clinical study or was necessary due to a worsening of the pre-existing condition.

7.1.4.1 Adverse Events of Special Interest

Adverse events of special interest (AESIs) are predefined adverse events that will be specifically highlighted to the investigator and will be summarized separately. Only AESI meeting the definition of SAE will be categorized and reported as such in this study.

Reactive arthritis (ReA) or Neutropenia will be collected and analyzed as an AESI for this study.

Reactive arthritis is defined as non-purulent joint inflammation that develops in response to an infection in another part of the body. Since the inflammation is triggered by a previous condition, it is termed “reactive”. Intestinal pathogens that have been associated with reactive arthritis include *Campylobacter*, *Salmonella*, *Yersinia*, *Clostridium difficile*, and *Shigella*. If reactive arthritis is caused by an auto immune response, there is at least a possibility that it could be initiated by vaccination of susceptible people with the 1790GAHB vaccine.

For diagnosis of ReA, imaging and aspiration are not required (unless clinically indicated).

Neutropenia is defined as decrease of neutrophil count asymptotically or symptomatically with ANC $<1.8 \times 10^9/L$, occurring at 7 days after vaccination. Its graded from grade 1 to 4 basing on neutrophil counts as follows: Grade 1 ANC $1.5 - <1.8 \times 10^9/L$, Grade 2 ANC $<1.5 \times 10^9/L$, Grade 3 ANC $1.0 - 0.5 \times 10^9/L$, and Grade 4 $<0.5 \times 10^9/L$.

This is completely diagnosed by laboratory testing for complete blood count.

7.1.5 Methods for Recording Adverse Events and Serious Adverse Events

Findings regarding Adverse Events must be reported on an Adverse Events CRF, as specified in [section 7.1.1, Solicited Adverse Events](#), and on the VSAE form, if applicable, which is part of the Investigator Site File. All findings in subjects experiencing AEs must be reported also in the subject's source document.

All SAEs which occur during the course of the study, whether considered to be associated with the study vaccination or not and even if the information is incomplete, must be reported **within 24 hours of the site becoming aware of the event** to the Sponsor. Specific instructions and contact details for collecting and reporting SAEs will be provided to the investigator. Specifically, once an investigator becomes aware that a SAE has occurred in a study subject, the investigator (or designate) must complete a paper expedited Adverse Events report and forward it to the Sponsor **WITHIN 24 HOURS**. The report will always aimed to be completed as thoroughly as possible with all available details of the event and then dated and signed by the investigator (or designate). Even if the investigator does not have all information regarding a SAE, the report should still be completed and forwarded to the Sponsor within 24 hours. Once additional relevant information is received, the report should be updated and forwarded the Sponsor **WITHIN 24 HOURS**. The investigator will always provide an assessment of causality at the time of the initial report.

All SAEs are also to be documented on the Adverse Events CRF. Any medication or other therapeutic measures used to treat the AE will be recorded on the appropriate CRF(s) in addition to the outcome of the AE.

Only AESI meeting the definition of SAE will be categorized and reported as serious in this study by the investigator within 24 hours. However all other AESI irrespective of their grading will be recorded in the adverse event page of eCRF and the source documents.

After receipt of the initial report, representatives of the Sponsor or its designee will contact the investigator if it is necessary to obtain further information for assessment of the event. Of note, after the initial AE/SAE report, the investigator is required to proactively follow each subject and provide additional relevant information on the subject's condition to the Sponsor (within 24 hours for SAEs and Potential ImmuneMediated Disease pIMD, and within 2 weeks for pregnancies).

All SAEs must be reported by the investigator to his/her corresponding EC/IRB and/or applicable regulatory authorities in accordance with institutional policy/regulatory requirements and adequate documentation of this notification must be provided to the Sponsor.

GSK or its designee must also comply with the applicable regulatory requirement(s) related to the reporting of suspected unexpected serious adverse vaccine reactions (also known as SUSARs) to the regulatory authority(ies) and the IRB/EC. If a SUSAR or other safety signal relating to use of one of the study vaccines is reported to GSK or its designee, the Sponsor will communicate the information to the investigator and the investigator will be responsible for submitting this information to the EC/IRB and other relevant authorities.

7.1.5.1 Post-Study Events

Any SAE that occurs outside of the protocol-specified follow-up period and considered to be caused by the study vaccine must be reported to the Sponsor. These SAEs will be processed by the Sponsor as during the course of the study, until 3 months after last subject last visit. Instructions and contact details for collecting and reporting these suspected SAEs will be provided to the investigator.

7.1.6 Pregnancies

To ensure subjects' safety, each pregnancy in a subject after study vaccination must be reported to the Sponsor in due time of the site learning of its occurrence. If the subject agrees to submit this information, the pregnancy must be followed to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. This follow-up should occur even if intended duration of safety follow-up for the study has ended.

Pregnancy data must be recorded on a Pregnancy Report CRF (initial report) and Pregnancy Follow-Up CRF (outcome report) and reported to the Sponsor. Instructions and contact details for submitting the Pregnancy CRFs will be provided to the investigator.

Any pregnancy outcome meeting the definition of a SAE (see [section 7.1.4, Serious Adverse Events](#)) must also be reported on the VSAE Report Form. The following should always be considered as SAE.

- Spontaneous pregnancy loss, including:
 - spontaneous abortion, (spontaneous pregnancy loss before/at 22 weeks of gestation)
 - ectopic and molar pregnancy
 - Stillbirth (intrauterine death of foetus after 22 weeks of gestation).

Note: the 22 weeks cut-off in gestational age is based on WHO-ICD 10 noted in the EMA Guideline on pregnancy exposure (EMA, 2006). It is recognized that national regulations might be different.

- Any early neonatal death (i.e. death of a live born infant occurring within the first 7 days of life).
- Any congenital anomaly or birth defect (as per [[CDC MACDPJ guidelines](#)]) identified in the offspring of a study subject (either during pregnancy, at birth or later) regardless of whether the foetus is delivered dead or alive. This includes anomalies identified by prenatal ultrasound, amniocentesis or examination of the products of conception after elective or spontaneous abortion.

7.1.7 Safety Laboratory Measurements

For list of safety laboratory measurement, refer to synopsis [Table 2](#), Hematological Safety [Table 3](#).

Safety laboratory measurement will be performed as described in [Section 3.5, Collection of Clinical Specimens](#).

Significant alterations in hematology will be clinically assessed by the investigator's medical judgment based on interpretation of deviations from institution's normal values.

Any abnormality in laboratory measurements classified as clinically significant must be reported in the Adverse Event CRF form.

If a subject is to have blood drawn testing for safety laboratory for repeat safety assessment (i.e., in case of markedly abnormal safety laboratory parameter), investigator's medical judgment will be applied concerning values that would trigger reanalysis and frequency of repeats. If neutropenia is observed at a visit, a complete blood count will be repeated on a weekly basis until resolution.

Safety laboratory assessments will be performed at the site laboratory, and results of these tests will be recorded in the source documents and in the CRF.

7.2 Efficacy Assessment

This study has no efficacy endpoints.

7.3 Immunogenicity Assessment

The ELISA methodology used in this study has been adopted based on scientific consensus and has been deemed appropriate to describe the immune response against *Shigella sonnei* GMMA in this study.

The measure of immunogenicity used in this study is IgG ELISA against *Shigella sonnei* OAg. The serologic assays on clinical samples will be performed at GSK, Clinical Serology Laboratory, Marburg, Germany, or a delegated laboratory. [Section 3: Study Design](#).

For reference of visits the measurements are taken, refer to [section 3.5](#) and to the Clinical Specimen Laboratory Manual.

8. STATISTICAL CONSIDERATIONS

8.1 Endpoints

8.1.1 Primary Endpoint(s)

8.1.1.1 Primary Safety Endpoint(s)

This study has no primary safety endpoint.

8.1.1.2 Primary Efficacy Endpoint(s)

This study has no efficacy measurements.

8.1.1.3 Primary Immunogenicity Endpoint(s)

The primary immunogenicity endpoint which is memory response, against the OAg of *S. sonnei* will be evaluated by measuring IgG Geometric mean concentrations (GMCs) after vaccination as determined by ELISA with O-antigen containing LPS as coating antigen.

8.1.2 Secondary Endpoint(s)

8.1.2.1 Secondary Safety Endpoint(s)

The measures of safety will include:

- a. Numbers of subjects with deviations from normal values of hematological tests after vaccination.
- b. Numbers of subjects with solicited local and systemic reactions during 7 days following vaccination. Solicited local reactions include injection site erythema, injection site induration and injection site pain; solicited systemic reactions include headache, arthralgia, chills, fatigue, malaise, myalgia, and fever (as measured orally).
- c. Numbers of subjects with reported unsolicited adverse events (of any nature and severity) during 84 days following vaccination.
- d. Number of subjects with reported SAEs throughout the study duration.

8.1.2.2 Secondary Efficacy Endpoint(s)

The study has no secondary efficacy endpoint.

8.1.2.3 Secondary Immunogenicity Endpoint(s)

- a. IgG Geometric mean concentrations (GMCs) at 7, 14, 28 and 84 days after vaccination as determined by ELISA and applicable geometric mean ratios between post vaccination and baseline samples.

- b. Number and percentage of subjects with seroresponse for anti- LPS *S. sonnei* at 7, 14, 28 and 84 days after vaccination. Seroresponse is aimed to define a significant increase in post vaccination samples based on the biological performance of this specific serology assay and it is defined as follows:
- If the baseline value is greater than 50 ELISA Units (EU) then an increase of at least 50% in the post-vaccination sample as compared to baseline [i.e. $((\text{Post-vac minus baseline})/\text{baseline})100\% \geq 50\%$].
 - If the baseline value is less or equal to 50 EU then an increase of at least 25 EU in the post-vaccination sample as compared to baseline [i.e. $(\text{Postvac minus baseline}) \geq 25 \text{ EU}$].
- c. Number and percentage of subjects with titers post vaccination concentration ≥ 121 EU/ml for anti-LPS *S. sonnei* at 7, 14, 28 and 84 days after vaccination.

A post-vaccination concentration ≥ 121 anti-LPS serum IgG units in the GVGH ELISA with O-antigen containing LPS as coating antigen corresponds to a titer of 1:800 in the ELISA method used by Cohen et al. (1989 J. Clin. Microbiol. 27:162). This antibody level is the median antibody concentration of a set of 87 convalescent subjects previously infected by *S. sonnei*. The value of 121 anti-LPS serum IgG units in the GVGH ELISA was determined by calibration against the Cohen ELISA (i.e., the GVGH standard serum was tested in Cohen's lab using the Cohen's methodology).

The serologic assays on clinical samples will be performed at GSK, Clinical Laboratory Science (CLS), Marburg, Germany, or a delegated laboratory.

8.1.3 Exploratory Endpoint(s)

8.1.3.1 Exploratory Safety Endpoint(s)

The study has no exploratory safety endpoint(s).

8.1.3.2 Exploratory Efficacy Endpoint(s)

The study has no exploratory efficacy endpoint(s).

8.1.3.3 Exploratory Immunogenicity Endpoint(s)

Other assays, including serum secretory IgA, might be done to further characterize the immune response to the study vaccine. The analysis will be described in the statistical analysis plan.

8.2 Success Criteria

The study has no predefined success criteria. **8.2.1**

Success Criteria for Primary Objective(s) Not applicable.

8.2.1.1 Success Criteria for Primary Safety Objective(s)

Not applicable.

8.2.1.2 Success Criteria for Primary Efficacy Objective(s)

Not applicable.

8.2.1.3 Success Criteria for Primary Immunogenicity Objective(s)

Not applicable.

8.2.2 Success Criteria for Secondary Objective(s)

Not applicable.

8.2.2.1 Success Criteria for Secondary Safety Objective(s)

Not applicable.

8.2.2.2 Success Criteria for Secondary Efficacy Objective(s)

Not applicable.

8.2.2.3 Success Criteria for Secondary Immunogenicity Objective(s)

Not applicable.

8.3 Analysis Sets

8.3.1 All Enrolled Set

All screened subjects who provide informed consent and provide demographic and/or baseline screening assessments, regardless of the subject's randomization and treatment status in the study and received a Subject ID.

8.3.2 All Exposed Set

All subjects in the enrolled set who receive a study vaccination.

8.3.3 Safety Set

Solicited Safety Set (solicited local and systemic adverse events and other solicited adverse events)

All subjects in the Exposed Set with any solicited adverse event data and/or indicators of solicited adverse events.

Unsolicited Safety Set (unsolicited adverse events)

All subjects in the Exposed Set with unsolicited adverse event data.

Overall Safety Set

All subjects who are in the Solicited Safety Set and/or Unsolicited Safety Set.

8.3.4 Full Analysis Set (FAS) Efficacy/Immunogenicity Set

Full Analysis Set Efficacy

Not applicable.

Full Analysis Set Immunogenicity

All subjects in the Enrolled Population who:

- Receive a study vaccination AND provide at least one immunogenicity data at relevant time points.

The FAS will be the primary analysis set for the immunogenicity objective.

In case of vaccination error, subjects in the FAS sets will be analyzed “as randomized” (i.e., according to the study group a subject was assigned).

8.3.5 Per Protocol (PP) Immunogenicity Set

All subjects in the FAS / Immunogenicity who:

- Correctly receive the vaccine.
- Have no protocol deviations leading to exclusion (see [section 8.3.8, Protocol Deviations](#)) as defined prior to analysis.
- Are not excluded due to other reasons defined prior to analysis (see [section 8.3.8, Protocol Deviations](#)).

PPS are subsets of FAS and should be always defined even if the objectives do not require it.

Examples for subjects excluded due to other reasons than protocol deviations are

- Subjects who withdrew informed consent.

8.3.6 Other Analysis Sets

None.

8.3.7 Subgroups Not

applicable.

8.3.8 Protocol Deviations

A protocol deviation is any change, divergence, or departure from the study design or procedures of a study protocol. A protocol deviation may be a reason to remove data from an analysis set at the time of analysis. CSR-reportable protocol deviations will be defined as exclusionary from the analysis according to protocol objectives and endpoints, which will be specified in the statistical analysis plan. In some cases exclusion of data may be due to a reason other than a protocol deviation, i.e. early termination.

8.4 Statistical Analysis Plan

8.4.1 Analysis of Demographic and Baseline Characteristics

Descriptive statistics (mean, standard deviation, median, minimum and maximum) for age and BMI at enrolment will be calculated overall and by vaccine group.

Distributions of subjects by sex and ethnic origin will be summarized overall and by vaccine group.

8.4.2 Analysis of Primary Objective(s)

8.4.2.1 Analysis of Primary Safety Objective(s)

The study has no primary safety objective.

8.4.2.1.1 Analysis of Extent of Exposure

The frequencies and percentages of subjects with vaccination will be summarized overall and by study group. Data will be tabulated for the All Enrolled Set.

8.4.2.1.2 Analysis of Solicited Local, Systemic and Other Adverse Events

All solicited adverse events will be summarized according to defined severity grading scales.

Frequencies and percentages of subjects experiencing each adverse event will be presented for each symptom severity. Summary tables showing the occurrence of any local or systemic adverse event overall and at each time point will also be presented.

Post-vaccination solicited adverse events reported from day 1 to day 7 will be summarized for the intervals day 1-3, day 4-7, day 1-7 by maximal severity and by vaccine group, excluding the 30 minute and 4 hour measurement, which will be summarized separately. The severity of solicited local adverse events, including injectionsite erythema and induration will be summarized according to categories based on linear measurement: 25 to 50 mm, 51 to 100 mm, >100mm.

Injection site pain/tenderness and systemic adverse events (except fever) occurring up to 7 days after vaccination will be summarized according to “mild”, “moderate” or “severe”.

Each solicited local and systemic adverse event will also be further summarized as “none” versus “any”.

Implausible measurements (for further definition see statistical analysis plan) will be left out of the analysis.

Use of antipyretics and analgesics will be summarized by frequency, by type of use (prophylactic versus treatment) and percentage of subjects reporting use. The influence of antipyretics and analgesics use on the occurrence of specific adverse events (e.g., fever, pain) will be assessed.

Body temperature will be summarized by 0.5 °C and 1.0 °C increments from 36.0 °C up to ≥ 40 °C.

8.4.2.1.3 Analysis of Unsolicited Adverse Events

This analysis applies to all adverse events occurring during the study, judged either as probably related, possibly related, or not related to vaccination by the investigator, recorded in AE CRF, with a start date on or after the date of vaccination. AE starting prior to the vaccination will only be listed. The original verbatim terms used by investigators to identify adverse events in the CRFs will be mapped to preferred terms using the MedDRA dictionary. The adverse events will then be grouped by MedDRA preferred terms into frequency tables according to system organ class.

All reported adverse events, as well as adverse events judged by the investigator as at least possibly related to study vaccine, will be summarized according to system organ class and preferred term within system organ class. These summaries will be presented by vaccination group and by interval of study observation. When an adverse event occurs more than once for a subject, the maximal severity and strongest relationship to the vaccine group will be counted.

Separate summaries will be produced for the following categories:

- Serious adverse events
- Adverse events that are possibly or probably related to vaccine

- Adverse events of special interest
- New onset of chronic disease
- Potential immune-mediated diseases (pIMDs) adverse event leading to withdrawal •
Adverse events leading to a medically attended visit
- Adverse event by data source.

Data listings of all adverse events will be provided by subject. In addition, adverse events in the categories above will be provided as listed data.

8.4.2.1.4 Analysis of Safety Laboratory Values

The investigator must assess all safety laboratory results (see [section 7.1.7](#)). Clinically significant modifications in blood chemistry, hematology, and urinalysis test values will be assessed by medical judgment based on interpretation of deviations from the institution's normal values.

All laboratory safety data will be analyzed descriptively by study group. Safety laboratory data will be shown in a 3 x 3 table by visit using categorization of laboratory according to institutional normal reference range (below, within, above).

8.4.2.2 Analysis of Primary Efficacy Objective(s)

The study has no primary efficacy objective.

8.4.2.2.1 Statistical Hypotheses

This Phase 1 safety and immunogenicity trial is aimed to descriptively evaluate the safety and immunogenicity profiles of the study vaccines. No specific hypotheses are tested in this study.

8.4.2.2.2 Analysis Sets

For more details see ([section 8.3 Analysis Sets](#)).

8.4.2.2.3 Statistical Methods

Not applicable.

8.4.2.3 Analysis of Primary Immunogenicity Objective(s)

8.4.2.3.1 Statistical Hypotheses

This Phase 1 safety and immunogenicity trial is aimed to descriptively evaluate the safety and immunogenicity profiles of the study vaccines. No specific hypotheses are tested in this trial.

8.4.2.3.2 Analysis Sets

The modified FAS will be the primary analysis set for the immunogenicity objective (further details are given in [section 8.3, Analysis Sets](#)).

8.4.2.3.3 Statistical Methods

Analysis of continuous variables

The ELISA concentrations will be logarithmically transformed (base10) (to fulfil the normal distribution assumption). GMC will be calculated, with their associated two-sided 95% CIs, by exponentiating the corresponding log-transformed means and their 95% CI.

Additionally, within-subject GMRs will be computed for GMTs/GMCs at 7, 14, 28 and 84 days after vaccination versus baseline (day 1). The GMRs and 95% CIs will be constructed by exponentiating the mean within-subject differences in log-transformed titers and the corresponding 95% CIs.

Analysis of binary variables

The number and percentages of subjects with seroresponse from baseline and with high antibody level after vaccination (i.e. post vaccination antibody level ≥ 121 IgG units in the GVGH ELISA), will be summarized. Two-sided 95% Clopper-Pearson CIs for the percentages will be computed.

Titers below the limit of detection will be set to half that limit for the purposes of analysis. Missing values of immunogenicity will be excluded from analyses (i.e. complete-case analysis) since they are considered missing completely at random, i.e. not informative and with no impact on inferences

8.4.3 Analysis of Secondary Objective(s)

8.4.3.1 Analysis of Secondary Safety Objective(s)

For more details see [Section 8.4.2.1.2 Analysis of Solicited Local, Systemic and Other Adverse Events](#) and [8.4.2.1.3 Analysis of unsolicited adverse events](#).

8.4.3.1.1 Analysis of Extent of Exposure

For more details see [section 8.4.2.1.1 Analysis of Extent of Exposure](#).

8.4.3.1.2 Analysis of Solicited Local, Systemic and Other Adverse Events

For more details see [Section 8.4.2.1.2 Analysis of Solicited Local, Systemic and Other Adverse Events](#).

8.4.3.1.3 Analysis of Unsolicited Adverse Events

For more details see [8.4.2.1.3 Analysis of unsolicited adverse events](#).

8.4.3.1.4 Statistical Hypotheses

For more details see [section 8.4.2.2.1, Statistical Hypotheses](#).

8.4.3.1.5 Analysis Sets

For more details see [section 8.3, Analysis Sets](#).

8.4.3.1.6 Statistical Methods

For more details see [section 8.4.2.2.3, Statistical Methods](#).

8.4.3.2 Analysis of Secondary Efficacy Objective(s)

The study has no efficacy objective.

8.4.3.2.1 Statistical

Hypotheses Not applicable.

8.4.3.2.2 Analysis Sets

Not applicable.

8.4.3.2.3 Statistical Methods

Not applicable.

8.4.3.3 Analysis of Secondary Immunogenicity Objective(s)

8.4.3.3.1 Statistical Hypotheses

Not applicable.

8.4.3.3.2 Analysis Sets

For more details see [section 8.3, Analysis Sets](#).

8.4.3.3.3 Statistical Methods

For more details see [section 8.4.2.2.3, Statistical Methods](#).

8.4.4 Analysis of Exploratory Objectives

8.4.4.1 Analysis of Exploratory Safety Objective(s)

Not applicable.

8.4.4.2 Analysis of Exploratory Efficacy Objective(s)

Not applicable.

8.4.4.3 Analysis of Exploratory Immunogenicity Objective(s)

Other assays, including serum secretory IgA, might be done to further characterize the immune response to the study vaccine. The analysis will be described in the statistical analysis plan.

8.5 Sample Size and Power Considerations of Primary and Secondary Objectives

No formal statistical sample size and power computations are performed since the objectives of the study are to descriptively assess the immunogenicity and safety of the investigational vaccine.

8.6 Interim Analysis

No interim analysis of data from this study is planned.

9. SOURCE DOCUMENTATION, STUDY MONITORING AND AUDITING

Monitoring and auditing will be standardized and performed in accordance with GSK's or delegated contract research organization's (CRO) standard operating procedures and applicable regulatory requirements (e.g., FDA, EMA, and ICH guidelines).

Prior to enrolment of the first study subject, GSK or delegate will train investigators and/or their study staff on the study protocol, all applicable study procedures, documentation practices and all electronic systems. CRFs supplied by the Sponsor must be completed for each enrolled subject (see [section 8.3.1, All Enrolled Set](#) for definition of enrolled subject). For subjects not enrolled, information will be stored in source documents only. Documentation of screened but not enrolled subjects must be maintained at the site and made available for review by the site monitor. Data and documents will be checked by the Sponsor and/or monitor.

9.1 Source Documentation

Prior to the start of the study, the site staff participating in the study conduct will be instructed on what documents will be required for review as source documents. The kinds of documents that will serve as source documents will be agreed between Sponsor or delegate and investigator and designees and specified in the SDAF prior to subject enrolment.

In addition, source documentation **must** include all of the following: subject identification (on each page), eligibility and participation, proper informed consent procedures, dates of visits, adherence to protocol procedures, adequate reporting and follow-up of adverse events, documentation of prior/concomitant medication/vaccines, study vaccine receipt/dispensing/return records, study vaccine administration information, any data collected by a telephone conversation with the subject and date of completion and reason.

The subject must also allow access to the subject's medical records. Each subject must be informed of this prior to the start of the study and consent for access to medical records may be required in accordance with local regulations.

All safety data reported by subjects must be written down in source documents prior to entry of the data into CRFs. If there are multiple sources of information (e.g., Subject Diary, verbal report of the subject, telephone contact details, medical chart) supporting the diagnosis of an adverse event, these sources must be identified in the source documents, discrepancies between sources clarified, the ultimate diagnosis must be justified and written in the source documents, and this diagnosis must be captured in the Adverse Event CRF (AE CRF).

9.2 Study Monitoring, Auditing and Source Data Verification

Prior to enrolment of the first study subject, the Sponsor or its designee (e.g., a CRO) will develop a Clinical Monitoring Plan to specify how centralized and/or on-site monitoring, including clinical specimens reconciliation, will be performed for the study. Study progress will be monitored by the Sponsor or its designee as frequently as necessary to ensure:

- That the rights and well-being of human subjects are protected,
- The reported study data are accurate, complete, and verifiable from the source documents and
- The conduct of the study is in compliance with the current approved protocol/amendment(s), GCP and applicable regulatory requirements.

Contact details for the Sponsor team or its designee involved in study monitoring will be provided to the investigator. Study data recorded on CRFs will be verified by checking the CRF entries against source documents in order to ensure data completeness and accuracy as required by study protocol except for those parameters which are specifically described in [section 7, Assessment](#) being entered directly into the EDC system.

Data verification may also be performed through a centralized review of data (e.g., checking for outliers or other anomalies). Additional documents such as the investigator site file, pharmacy records, and informed consent documentation must also be available for review if requested. Arrangements for monitoring visits will be made in advance in accordance with the monitoring plan, except in case of emergency.

The investigator and/or site staff must make source documents of subjects enrolled in this study available for inspection by GSK Bio or its representative at the time of each monitoring visit and Sponsor audits, when applicable. These documents must also be available for inspection, verification and copying, as required by regulations, by officials of the regulatory health authorities (e.g., FDA, EMA and others) and/or ECs/IRBs. The investigator and study site staff must comply with applicable privacy, data protection and medical confidentiality laws for use and disclosure of information related to the study and enrolled subjects.

10. DATA MANAGEMENT

10.1 Data Entry and Management

In this study, all clinical data (including, but not limited to, AE/SAEs, concomitant medications, medical history, and physical assessments), safety data will be entered onto case report forms (CRFs) in a timely fashion by the investigator and/or the investigator's dedicated site staff. Data entered onto CRFs are stored on a secure website. The data collected on this secure website are assimilated into an electronic data capture (EDC) system, which is compliant with Title 21 Part 11 policies of the Code of Federal Regulations ([FDA 1997](#)). The data system includes password protection and internal quality checks. The EDC system will be designed and validated by the Sponsor prior to activation for data entry by sites. The investigator or designated delegate must review data entered and electronically sign the CRFs to verify their accuracy.

Access to the EDC system for data entry or review will require training and distinct individual access code assignments to those site staff members who will be entering study data and those involved in study oversight who may review study data. Data are collected within the EDC system, to which the Sponsor and site monitors have exclusively "read only" access.

10.2 Data Clarification

As part of the conduct of the trial, the Sponsor may have questions about the data entered by the site, referred to as queries. The monitors, the Sponsor and delegated DM are the only parties that can generate a query. All corrections and clarifications will be entered into the EDC system and will be identified by the person entering the information, the reason for the change, as well as the time of the changes made. If changes are made to a previously and electronically signed CRF, the investigator must confirm and endorse the changes.

10.3 Data Protection

The Sponsor respect the subjects' rights to privacy and will ensure the confidentiality of their medical information in accordance with all applicable laws and regulations.

The Sponsor as Data Controller according to the European Directive on the protection of individuals with regard to the processing of personal data and on the free movement of such data ([95/46/EC](#)) confirms herewith compliance to Directive [95/46/EC](#) in all stages of Data Management.

11. RECORD RETENTION

Following closure of the study, the investigator must maintain all site study records (except for those required by local regulations to be maintained elsewhere) in a safe and secure location. The records must be easily accessible, when needed (e.g. audit or inspection), and must be available for review in conjunction with assessment of the facility, supporting systems, and staff. Where permitted by applicable laws/regulations or institutional policy, some or all of these records can be maintained in a validated format other than hard copy (e.g. microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken. The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure that an acceptable back-up of the reproductions exists and that there is an acceptable quality control procedure in place for making these reproductions.

The Sponsor will inform the investigator/institution of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to a particular site, as dictated by ICH GCP, any institutional requirements, applicable laws or regulations, or GSK standards/procedures, otherwise, the minimum retention period will default to 25 years after completion of the study report.

The investigator/institution must notify the Sponsor of any changes in the archival arrangements, including, but not limited to archival at an off-site facility, transfer of ownership of the records in the event the investigator leaves the site. The principles for the storage of laboratory samples are provided below:

Collected samples will be stored for a maximum of 20 years (counting from when the last subject performed the last study visit), unless local rules, regulations or guidelines require different timeframes or different procedures, which will then be in line with the subject consent. These extra requirements need to be communicated formally to and discussed and agreed with the Sponsor.

12. USE OF INFORMATION AND PUBLICATION

GSK assures that key results of this clinical study will be posted in a publicly accessible database within the required time-frame from the end of study as defined in [section 3.9, End of Study](#).

In accordance with standard editorial, ethical practices and current guidelines of Good Publication Practice ([Graf 2009](#)), GSK will generally support publication of multicenter studies only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement prior to the start of the study. The coordinating investigator will also sign the clinical study report on behalf of the principal investigators ([CPMP/EWP/2747/00](#)). Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of GSK personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate GSK personnel.

The Sponsor must be notified of any intent to publish data collected from the study and prior approval from the Sponsor must be obtained prior to submission for publication.

13. ETHICAL CONSIDERATIONS

13.1 Regulatory and Ethical Compliance

The study will be conducted in compliance with the protocol, GCP and applicable regulatory requirement(s).

This clinical study was designed and shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations including [European Directive 2001/20/EC](#), GSK codes on protection of human rights, and with the ethical principles laid down in the Declaration of Helsinki ([European Council 2001](#), [US Code of Federal Regulations](#), [ICH 1997](#)).

The Sponsor will have an account for the trial in the French national database (VRB – Volontaires pour la Recherche Biomédicale) where investigator will register each volunteer at the day of enrollment.

After the end of the study, each subject will receive a monetary compensation for a total of 530 euros to cover for the time spent and any inconvenience due to the study participation. This indemnification will be proportional to the number of visits completed as follows:

- 50 euros: screening visit
- 120 euros: vaccination visit
- 90 euros: follow up visit

13.2 Informed Consent Procedures

Eligible subjects may only be included in the study after providing written informed consent, as described in [section 5.1.1, Informed Consent/Assent](#). Before the start of the study, the investigator will have the informed consent and any other materials that will be provided to the subjects reviewed and approved by the IRB/EC. This review and approval will be documented and stored with other study documents. The investigator or designee must fully inform the subject of all pertinent aspects of the study. A copy of the written informed consent will be given to the subject. The subject must be allowed ample time to ask about the details of the study and to make a decision as to whether or not to participate in the study. The subject **must** sign the consent form indicating their agreement to participate in the study before any study-related procedures are conducted. The informed consent process may be conducted up to 21 days prior to vaccination on day 1. If the subject is unable to read and write, a witness must be present during the informed consent discussion and at the time of informed consent signature.

Prior to the start of the study, the Sponsor will provide to investigators a proposed informed consent form that complies with the ICH GCP guideline and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form

suggested by the investigator must be agreed to by the Sponsor before submission to the IRB/EC and a copy of the approved version must be provided to the Sponsor monitor after IRB/EC approval.

Women of childbearing potential should be informed that taking the study medication may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirements indicated in the protocol for the duration of the study. If case of doubts on the ability of a subject to adhere to these requirements, that subject should not be allowed in the study

13.3 Responsibilities of the Investigator and IRB/EC

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted IRB/EC before study start. Properly constituted IRB/EC is defined in ICH Guideline for Good Clinical Practice E6 (R1), Section 3 ([ICH 1997](#)). A signed and dated statement that the protocol and informed consent have been approved by the IRB/EC must be given to GSK before study initiation. Prior to study start and at any time the protocol is amended during study conduct, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to GSK monitors, auditors, GSK Clinical Quality Assurance representatives, designated agents of GSK, IRBs/ECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform GSK immediately that this request has been made. The investigator also responsible for the following:

- Maintaining a list of appropriately qualified persons to whom the investigator has delegated significant study-related duties
- Demonstrating the capability of recruiting the required number of suitable subjects within the recruitment period
- Demonstrating sufficient time and staffing to properly conduct and complete the study within the agreed study period
- Ensuring that all persons assisting with the study are adequately informed about the protocol, the investigational product(s), and their study-related duties and functions
- Ensuring that appropriately trained health care professionals are responsible for all study-related medical decisions and for ensuring appropriate medical care of subjects experiencing any adverse event related to the study
- If permission to do so is given by the subject, ensuring that the subject's primary healthcare provider is informed of the subject's participation in the study.

The investigator should not implement any deviation from, or changes of the protocol without agreement by the Sponsor and prior review and documented approval/favourable

opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to study subjects, or when the change(s) involves only logistical or administrative aspects of the study (e.g., change in monitor(s), change of telephone number(s)). In addition, the investigator, or person designated by the investigator, should document and explain any deviation from the approved protocol.

The investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to study subjects without prior IRB/IEC approval/favourable opinion. As soon as possible, the implemented deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendment(s) should be submitted:

- (a) To the IRB/IEC for review and approval/favourable opinion,
- (b) To GVGH for agreement and, if required,
- (c) To the regulatory authority(ies).

13.4 Protocol Amendments

An amendment is a written description of change(s) to or formal clarification of a study protocol which may impact on the conduct of the clinical study, potential benefit of the clinical study, or may affect subject safety, including changes of study objectives, study design, subject population, sample sizes, study procedures, or significant administrative aspects. An administrative change of a study protocol is a minor correction or clarification that has no significant impact on the way the clinical study is to be conducted and no effect on subject safety (e.g., change of telephone number(s), logistical changes). Protocol amendments must be approved by the Sponsor, health authorities where required, and the IRB/EC. In cases when the amendment is required in order to protect the subject safety, the amendment can be implemented prior to IRB/EC approval. Notwithstanding, the need for formal approval of a protocol amendment, the investigator is expected to take any immediate action required for the safety of any subject included in this study, even if this action represents a deviation from the protocol. In such cases, the Sponsor should be notified of this action, the IRB/EC at the study site, and, if required by local regulations, the relevant health authority) should be informed within 10 working days.

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Appendix 1: Investigator Agreement

I agree:

- To conduct the study in compliance with this protocol, any future protocol amendments or protocol administrative changes, with the terms of the clinical trial agreement and with any other study conduct procedures and/or study conduct documents provided by GSK.
- To assume responsibility for the proper conduct of the study at this site.
- That I am aware of, and will comply with, 'Good Clinical Practice' (GCP) and all applicable regulatory requirements.
- To ensure that all persons assisting me with the study are adequately informed about the GSK study vaccine(s)/product(s) and other study-related duties and functions as described in the protocol.
- To acquire the reference ranges for laboratory tests performed locally and, if required by local regulations, obtain the laboratory's current certification or Quality Assurance procedure manual.
- To ensure that no clinical samples (including serum samples) are retained onsite or elsewhere without the approval of GSK and the express written informed consent of the subject and/or the subject's legally acceptable representative.
- To perform no other biological assays on the clinical samples except those described in the protocol or its amendment(s).
- To co-operate with a representative of GSK in the monitoring process of the study and in resolution of queries about the data.
- That I have been informed that certain regulatory authorities require the sponsor to obtain and supply, as necessary, details about the investigator's ownership interest in the sponsor or the investigational vaccine(s)/product(s), and more generally about his/her financial ties with the sponsor. GSK Biologicals 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 course of the study and for one year following completion of the study.
- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.

- Agree to provide GSK with an updated Curriculum Vitae and other documents required by regulatory agencies for this study.

eTrack study number and
Abbreviated Title

205905 (S SONNEI MONO GMMA SBVGH-005
EXT: 001 SUPP (H03_01E1TP)

EudraCT number

EudraCT No. 2016-004178-16

Date of protocol

Version 1: 12 October 2016

Detailed Title

A Phase 1, open label, non-randomized, single center study to evaluate the safety and immunogenicity of 1 booster vaccination with GVGH *Shigella sonnei* 1790GAHB vaccine administered intramuscularly in healthy adults previously primed with three doses of the same vaccine in study H03_01TP compared to 1 vaccination with 1790GAHB administered intramuscularly either to subjects who received placebo in the H03_01TP study or naïve subjects who were not part of H03_01TP study.

Investigator name

Signature

Date



CLINICAL STUDY PROTOCOL H03_01E1TP

Amendment 1 of 06 February 2017

Version

2

A Phase 1, open label, non-randomized, single center study to evaluate the safety and immunogenicity of 1 booster vaccination with GVGH *Shigella sonnei* 1790GAHB vaccine administered intramuscularly in healthy adults previously primed with three doses of the same vaccine in study H03_01TP compared to 1 vaccination with 1790GAHB administered intramuscularly either to subjects who received placebo in the H03_01TP study or naïve subjects who were not part of H03_01TP study

Shigella sonnei GMMA vaccine in healthy French adult extension Phase I vaccine trial

Property of GlaxoSmithKline Biologicals SA (hereafter referred to as GSK Bio)

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PROTOCOL SYNOPSIS [H03_01E1TP, Version 2]		

Name of Sponsor: GlaxoSmithKline Biologicals SA (GSK Bio)	Protocol number: H03_01E1TP	Generic name of study vaccine(s): GVGH <i>Shigella sonnei</i> 1790GAHB vaccine
Title of Study: A Phase 1, open label, non-randomized, single center study to evaluate the safety and immunogenicity of 1 booster vaccination with GVGH <i>Shigella sonnei</i> 1790GAHB vaccine administered intramuscularly in healthy adults previously primed with three doses of the same vaccine in study H03_01TP compared to 1 vaccination with 1790GAHB administered intramuscularly either to subjects who received placebo in the H03_01TP study or naïve subjects who were not part of H03_01TP study.		
Study Period: Each subject will be followed-up for 84 days (approximately 3 months) after vaccination		Clinical Phase: Phase 1
<p>Background and Rationale: The trial H03_01TP evaluated the safety and immunogenicity profile of 5 different doses of GVGH <i>Shigella sonnei</i> 1790GAHB vaccine (1 µg to 100 µg) compared to placebo, when administered in 3 injections to 50 healthy adults. The immunogenicity was evaluated at baseline, 28 days after each vaccination and at 168 days after third vaccination, by measuring the anti-LPS <i>S. sonnei</i> serum IgG. Overall, an antibody response was observed across all the vaccine groups. However, at most of the time points, the response was higher in subjects who received higher antigen doses (e.g., 25 µg, 50 µg, and 100 µg) than those who received lower doses (e.g., 1 µg and 5µg). More specifically, a vaccine dose of 25 µg was very well tolerated and induced median antibody concentrations above 121 EU/mL at all post vaccination time points. Since 121 EU/mL is the median antibody titer in a panel of 87 convalescents previously exposed to <i>S. sonnei</i> infection and therefore protected against re-infection from the same serotype, a vaccine dose of 25 µg has the potential to be protective when included in a vaccine against <i>S. sonnei</i>.</p> <p>After unblinding the immunogenicity database, it was observed that the trial subjects could be classified in 2 groups based on <i>S. sonnei</i> antibody concentration at baseline, with approximately 50% having undetectable and the other 50% having detectable antiLPS <i>S. sonnei</i> serum IgG antibody concentrations. Therefore, for a better understanding of the immunological response induced by the vaccine in naïve and primed subjects and for a better planning of new clinical studies, additional analyses were carried out. To mitigate the small size of study groups, subjects who received vaccines containing 1 µg and 5 µg antigen/dose were combined into a single group and then stratified by the presence or absence of detectable antibodies at baseline. Same was done for subjects who received vaccines containing 25 µg, 50 µg, and 100 µg antigen/dose. As shown in</p>		

Name of Sponsor:	Protocol number:	Generic name of study vaccine(s):
GlaxoSmithKline Biologicals SA (GSK Bio)	H03_01E1TP	GVGH <i>Shigella</i> <i>sonnei</i> 1790GAHB vaccine

Figure 1 below, subjects vaccinated with 25 µg, 50 µg and 100 µg vaccines, with detectable antibody concentrations at baseline, showed, at all-time points (1 month after the first, second and the third vaccinations and 6 months after the third vaccination), median antibody concentrations far higher than 121 EU/mL. Subjects vaccinated with 1 µg and 5 µg vaccines, with detectable antibody concentrations at baseline, showed median antibody concentrations slightly higher than 121 EU/mL only at 1 month after the third vaccination.

Figure 1: Median anti-LPS *S. sonnei* IgG ELISA concentrations and interquartile range in subjects with detectable antibodies at baseline (subjects with data at all visits)

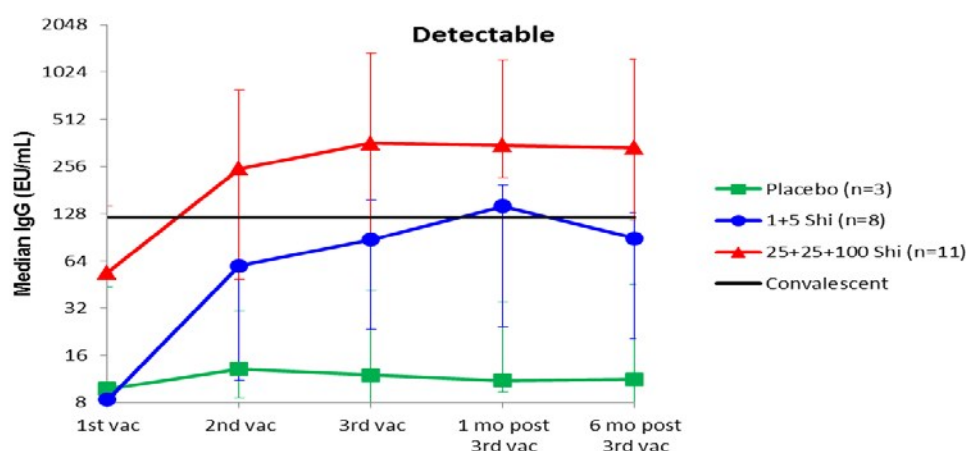
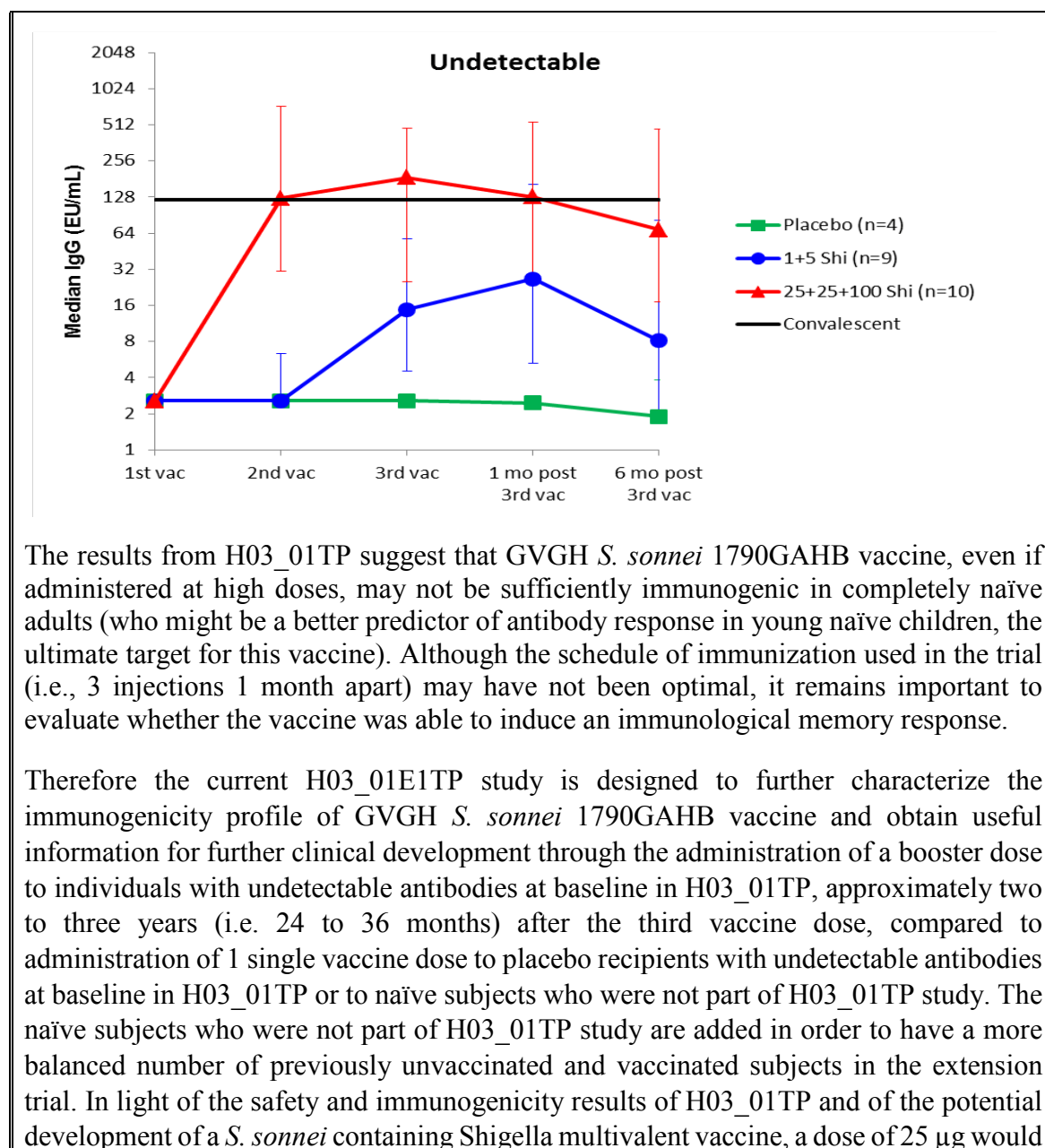


Figure 2 below, with subjects vaccinated with 25 µg, 50 µg and 100 µg vaccines, with undetectable antibody concentrations at baseline, showed median antibody concentrations higher than 121 EU/mL at 1 month after the first, second and the third vaccination, while at 6 months after the third vaccination the median antibody concentration was less than 121 EU/mL. Subjects vaccinated with 1 µg and 5 µg vaccines, with undetectable antibody concentrations at baseline, did not reach the 121 EU/mL threshold at any time point.

Figure 2: Median anti-LPS *S. sonnei* IgG ELISA concentrations and interquartile range in subjects with undetectable antibodies at baseline (subjects with data at all visits)

Name of Sponsor:	Protocol number:	Generic name of study vaccine(s):
GlaxoSmithKline Biologicals SA (GSK Bio)	H03_01E1TP	GVGH <i>Shigella sonnei</i> 1790GAHB vaccine



be preferable for further development. Therefore, the use of this antigen dose is proposed for immunization of all subjects to provide further useful information for a more complete characterization of this vaccine strength.

Study Objectives:

Name of Sponsor:	Protocol number:	Generic name of study vaccine(s):
GlaxoSmithKline Biologicals SA (GSK Bio)	H03_01E1TP	GVGH <i>Shigella</i> <i>sonnei</i> 1790GAHB vaccine

Primary Objective(s):

To evaluate the memory response, as measured by anti-LPS *S. sonnei* serum IgG, 7 days after vaccination with a booster dose of GVGH *S. sonnei* 1790GAHB vaccine in individuals who had undetectable antibody titers at baseline in H03_01TP, approximately two to three years after the third vaccine dose, compared to administration of 1 single vaccine dose to placebo recipients with undetectable antibody titers at baseline in H03_01TP or naïve subjects who were not part of H03_01TP study.

Secondary Objective(s):

1) Safety:

- a. To evaluate the safety profile of one dose of GVGH *S. sonnei* 1790GAHB vaccine in subjects who previously received three vaccinations with 1790GAHB and in subjects receiving one dose 1790GAHB for the first time (either placebo recipients in H03_01TP or naïve subjects who were not part of H03_01TP study).
- b. To evaluate the safety profile of one dose of GVGH *S. sonnei* 1790GAHB vaccine in subjects receiving one dose 1790GAHB for the first time and having detectable antibodies at baseline of the extension trial.

2) Immunogenicity:

- a. To evaluate the immunogenicity profile 7, 14, 28 and 84 days after vaccination with one dose of GVGH *S. sonnei* 1790GAHB vaccine in subjects with undetectable antibody titers at baseline who previously received three vaccinations of GVGH *S. sonnei* 1790GAHB vaccine in H03_01TP and in placebo recipients with undetectable antibody titers at baseline in H03_01TP or naïve subjects who were not part of H03_01TP study.
- b. To evaluate the immunogenicity profile of one dose of GVGH *S. sonnei* 1790GAHB vaccine in subjects receiving one dose 1790GAHB for the first time and having detectable antibodies at baseline of the extension trial.
- c. To evaluate the persistence of anti-LPS *S. sonnei* serum IgG antibody titers approximately two to three years after the third vaccination with 1790GAHB. 3)

Exploratory:

Other immunological assays might be performed to further characterize the immune response to the study vaccine including serum secretory IgA.

Study Design:

Name of Sponsor: GlaxoSmithKline Biologicals SA (GSK Bio)	Protocol number: H03_01E1TP	Generic name of study vaccine(s): GVGH <i>Shigella sonnei</i> 1790GAHB vaccine
This is an open label, non-randomized, single center, Phase 1 clinical trial. The study includes a screening visit (performed at study Days -21to -1), one clinical visit with vaccination (performed at study Day 1), 4 clinical visits (performed 7, 14, 28 and 84 days after vaccination), and 2 phone calls (performed 2 and 6 days after the vaccination).		
Table 1 H03_01TP Study Design		
H03_01TP		H03_01E1TP
Vaccine group	No. subjects*	New enrolled subjects No. subjects Vaccine group
1790GAHB – 1 µg**	5	5 1790GAHB – 25 µg
1790GAHB – 5 µg	4	4 1790GAHB – 25 µg
1790GAHB – 25 µg	2	2 1790GAHB – 25 µg
1790GAHB – 50 µg	4	4 1790GAHB – 25 µg
1790GAHB – 100 µg	5	5 1790GAHB – 25 µg
Placebo	4	4 1790GAHB – 25 µg
Total H03_01TP	24	Naïve subjects 26 1790GAHB – 25 µg
Grand total		50
*only subjects with undetectable antibodies at baseline. ** µg of total protein		

Number of Subjects planned:

Up to 50 subjects will be enrolled into this trial. Up to 24 subjects are eligible from the parent H03_01TP trial. With respect to naïve subjects who were not part of H03_01TP study, considering that in the original H03_01TP population 50% of subjects did not have detectable antibodies at baseline, with 26 subjects, approximately 13 subjects should not have detectable antibodies. This number combined with that of placebo recipients in H03_01TP should be sufficient to allow a balanced contribution of previously unvaccinated and vaccinated subjects in the extension trial. Subjects withdrawn or lost to follow up will not be replaced. The sample size is not driven by any statistical hypothesis, but by availability of subjects from H03_01TP study and fulfilling inclusion criteria.

Study Population and Subject Characteristics:

The study population will consist of adult healthy volunteer subjects meeting all inclusion and no exclusion criteria.

The list of inclusion and exclusion criteria is included in protocol [section 4, Selection of](#)

Name of Sponsor:	Protocol number:	Generic name of study vaccine(s):
GlaxoSmithKline Biologicals SA (GSK Bio)	H03_01E1TP	GVGH <i>Shigella sonnei</i> 1790GAHB vaccine
Study Population.		

Study Procedures:

Before any study procedure is performed, informed consent will be obtained; subjects will be enrolled only after their eligibility for participation is confirmed by the investigator. Safety procedures:

All subjects providing informed consent will undergo review of medical history, a general physical examination including vital signs measurement (temperature, respiratory rate, heart rate, blood systolic and diastolic pressure) at the screening visit (study Days -21 to -1) and at Visit 1 (Day 1) for evaluation of the general health status by clinical assessment and verification of inclusion and exclusion criteria. At clinic Visit 2 and at subsequent visits, a brief symptom-directed physical examination (if necessary according to symptoms the subject has reported) will be performed. Throughout the study it will be checked whether continued participation in the study is in the subject best interest in terms of safety. For all women of childbearing potential before vaccination at visit 1, a urine pregnancy test will be conducted and will also be repeated at visit 5 (Day 85). Women with positive test or refusing to perform the test will be immediately excluded from the study. Female subjects must use acceptable (defined as oral, injected or implantable contraceptives) birth control measures during study participation.

Blood Draw Procedure:

Approximately 15 mL blood draw will be obtained for hematological and serological (HIV, hepatitis B and C) for subjects who were part of the parent trial (H03_01TP). For naïve subjects however 25 mL of blood draw will be obtained for the same hematological and serological test mentioned above and in addition HLA-B27 testing as part of the initial screening. One additional blood draw of 6 mL for hematological tests will be obtained at 7 days (Visit 2) and 84 days (Visit 5) after vaccination (see [Table 2](#)). Each subject will have 20 mL of blood drawn for immunological studies before and 7, 14, 28 and 84 days after vaccination. For the purpose of creating a standard reference serum for the serological assay, volunteers will be asked to provide an additional blood sample of 20 mL at 28 days after vaccination (Visit 4).

Clinically significant modifications in hematology will be assessed by medical judgment based on interpretation of deviations from institution's normal values and recommendations from [CBER FDA GUIDANCE FOR INDUSTRY](#): Toxicity Grading

Name of Sponsor:	Protocol number:	Generic name of study vaccine(s):
GlaxoSmithKline Biologicals SA (GSK Bio)	H03_01E1TP	GVGH <i>Shigella sonnei</i> 1790GAHB vaccine

Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials.

Vaccination Procedure:

All eligible subjects will receive one intramuscular vaccination (into the deltoid area of the non-dominant arm) with GVGH *S. sonnei* 1790GAHB vaccine containing 25µg/dose. Subjects will be observed at the clinic site for 4 hours after vaccination.

Procedure for Collection of Solicited AEs:

Beginning in the evening following study vaccine administration (approximately 6 hours), and daily during the following 6 days following vaccination, diary cards will be used to collect solicited local and systemic adverse events including other reactions (i.e. body temperature measurements and use of analgesics/antipyretics). A reminder phone call will be performed or an email will be sent by the site staff to the subject 2 and 6 days following vaccination to remind subjects that the diary card should be completed (no update on the status of the subject's health will be solicited during these contacts that are not intended for safety data collection).

Seven days following vaccination, a clinical visit (Visit 2) will be performed at the study site and all information recorded in the diary card will be reported on e-CRF in order to document all safety data occurred during the one week follow-up post vaccination.

In addition to the solicited adverse events data, any unsolicited AE, solicited local and systemic AE that continue at 7 days after study vaccination (Visit 2), will be collected and recorded at V2, V3 and V4 by clinical study staff in the subject's source document. All Serious Adverse Events (SAEs), all AEs leading to vaccine/study withdrawal, all Adverse Events of Special Interest (AESI, see below) and all concomitant medications associated with those events, will be collected and recorded in the subject's source document and on an Adverse Events CRF(s) from the time of vaccination (visit 1) to study termination (visit 5). These data will be captured through interview of the subject and by review of available medical records.

Reactive arthritis and neutropenia will be collected and analyzed as AESIs for this study.

A summary of the main medical and safety data to be collected into the e-CRF during the study is provided in [Table 2](#).

Name of Sponsor: GlaxoSmithKline Biologicals SA (GSK Bio)	Protocol number: H03_01E1TP	Generic name of study vaccine(s): GVGH <i>Shigella sonnei</i> 1790GAHB vaccine
<p>Study Vaccines: GVGH <i>S. sonnei</i> (1790GAHB) vaccine</p> <p>The investigational agent is the GVGH <i>S. sonnei</i> 1790GAHB vaccine. The vaccine consists of <i>S. sonnei</i> OAg containing 1790-GMMA (approximately 200 µg/mL measured by protein content) adsorbed to Alhydrogel, (0.7 mg Al³⁺/mL) in Trisbuffered saline. The vaccine does not contain any preservative and is available in a liquid formulation as a single dose vials with 0.7 mL of injectable solution containing approximately 140 µg of GMMA (as protein content), adsorbed onto 0.49 mg Al³⁺.</p> <p>The vaccine will be used at a dose of 25 µg and will be obtained by bed-side mixing. Following dilution, the volume administered by intramuscular route will be 0.5 mL.</p> <p>Therefore, each 0.5 mL dose of GVGH <i>S. sonnei</i> 1790GAHB vaccine will contain 3+. approximately 25 µg of GMMA total protein and 0.35 mg of Al</p>		

Primary Endpoint(s):

This study has no primary efficacy or safety endpoints.

Primary Immunogenicity Endpoint(s)

Memory response, against the OAg of *S. sonnei* will be evaluated by measuring IgG Geometric mean concentrations (GMCs) after vaccination as determined by ELISA with O-antigen containing LPS as coating antigen.

Secondary safety endpoint(s):

The measures of safety will include:

- a. Numbers of subjects with deviations from normal values of hematological tests after vaccination.
- b. Numbers of subjects with solicited local and systemic reactions during 7 days following vaccination. Solicited local reactions include injection site erythema, injection site induration and injection site pain; solicited systemic reactions include headache, arthralgia, chills, fatigue, malaise, myalgia, and fever (as measured orally).
- c. Numbers of subjects with reported unsolicited adverse events (of any nature and severity) during 84 days following vaccination.
- d. Number of subjects with reported SAEs throughout the study duration.

Name of Sponsor:	Protocol number:	Generic name of study vaccine(s):
GlaxoSmithKline Biologicals SA (GSK Bio)	H03_01E1TP	GVGH <i>Shigella sonnei</i> 1790GAHB vaccine

Secondary Immunogenicity Endpoint(s)

- a. IgG Geometric mean concentrations (GMCs) at 7, 14, 28 and 84 days after vaccination as determined by ELISA and applicable geometric mean ratios between post vaccination and baseline samples.
- b. Number and percentage of subjects with seroresponse for anti- LPS *S. sonnei* at 7, 14, 28 and 84 days after vaccination. Seroresponse is aimed to define a significant increase in post vaccination samples based on the biological performance of this specific serology assay and it is defined as follows:
 - If the baseline value is greater than 50 ELISA Units (EU) then an increase of at least 50% in the post-vaccination sample as compared to baseline [i.e. $((\text{Post-vac minus baseline})/\text{baseline})100\% \geq 50\%$].
 - If the baseline value is less or equal to 50 EU then an increase of at least 25 EU in the post-vaccination sample as compared to baseline [i.e. $(\text{Postvac minus baseline}) \geq 25 \text{ EU}$].
- c. Number and percentage of subjects with titers post vaccination concentration ≥ 121 EU/ml for anti-LPS *S. sonnei* at 7, 14, 28 and 84 days after vaccination.

A post-vaccination concentration ≥ 121 anti-LPS serum IgG units in the GVGH ELISA with O-antigen containing LPS as coating antigen corresponds to a titer of 1:800 in the ELISA method used by Cohen et al. (1989 *J. Clin. Microbiol.* 27:162). This antibody level is the median antibody concentration of a set of 87 convalescent subjects previously infected by *S. sonnei*. The value of 121 anti-LPS serum IgG units in the GVGH ELISA was determined by calibration against the Cohen ELISA (i.e., the GVGH standard serum was tested in Cohen's lab using the Cohen's methodology).

The serologic assays on clinical samples will be performed at GSK, Clinical Laboratory Science (CLS), Marburg, Germany, or a delegated laboratory.

Exploratory Immunogenicity Endpoint(s):

Other assays, including serum secretory IgA, might be done to further characterize the immune response to the study vaccine. The analysis will be described in the statistical analysis plan.

Statistical Analyses:

Name of Sponsor:	Protocol number:	Generic name of study vaccine(s):
GlaxoSmithKline Biologicals SA (GSK Bio)	H03_01E1TP	GVGH <i>Shigella sonnei</i> 1790GAHB vaccine

This Phase 1 safety and immunogenicity extension trial is aimed to descriptively evaluate the safety and immunogenicity profiles of the study vaccine, used either a booster (4th dose) or as a first dose. No specific hypotheses are tested in this trial. Descriptive analyses will be performed to describe and summarize the data (e.g. mean, median, min and max).

Interim Analysis: No interim analysis is planned for this trial.

Data Monitoring Committee:

No ad hoc DSMB will be established for this trial as no interim assessment of safety data is anticipated.

Table 2 Time and Event Table- Treatment Period

Visit Type		Clinic Visit	Clinic Visit	Phone Call	Clinic Visit	Clinic Visit	Clinic Visit	Clinic Visit
			1	3, 7 V1+2 days; V1+6 days	8 V1+7 days	15 V1+14 days	29 V1+28 days	85 V1+84 days
		Study Day						
		Visit Window (Days)	-21 to -1	n/a	n/a	0 to +1	0 to +4	-3 to +4
Visit Number		Screening	1		2	3	4	5
Study Event	References							
Study Treatment								
Vaccination	Section 5.2		X					
Screening and Safety								
Informed Consent ^a	Section 5.1.1	X						
Medical History	Sections 5.1.2	X						
Physical Exam ^b	Sections 5.1.2 and 5.1.3	X	X					
Symptom-directed physical Exam ^b	Section 5.3.1				X	X	X	X

Vital signs (temperature, respiratory rate, heart rate, blood systolic and diastolic pressure)	Sections 5.1.2 Screening and 5.2.1 Post-vaccination Procedures	X	X					
Safety blood draw (Hematology) ^e	Sections 3.5 and 7.1.7	X			X			X

	Visit Type	Clinic Visit	Clinic Visit	Phone Call	Clinic Visit	Clinic Visit	Clinic Visit	Clinic Visit
	Study Day		1	3, 7 V1+2 days; V1+6 days	8 V1+7 days	15 V1+14 days	29 V1+28 days	85 V1+84 days
	Visit Window (Days)	-21 to -1	n/a	n/a	0 to +1	0 to +4	-3 to +4	-3 to +7
	Visit Number	Screening	1		2	3	4	5
Study Event	References							
Serology (HIV, hepatitis B and C, and HLA-B27 testing only for naïve subjects) ^d	Section 3.5 and 5.1.2	X						
Pregnancy Test	Sections 3.5 and 5.1.2		X					X
Exclusion/Inclusion Criteria	Section 4	X						
Post Injection Assessment ^e	Section 5.2.1		X					
Subject Diary Dispensed with Training	Section 5.2.1		X					

Subject Diary Reminder Call	Section 5.2.2			X				
Subject Diary Reviewed and Collected	Section 5.3.1				X			
Assess all AEs	Section 7.1	X	X		X	X	X	
Assess SAEs	Section 7.1.4	X	X		X	X	X	X
Assess for NOCDs, medically attended AEs, AEs leading to withdrawal, and AESIs	Sections 7.1.4.1 and 7.1.3		X		X	X	X	X

Number	Visit Type	Clinic Visit	Clinic Visit	Phone Call	Clinic Visit	Clinic Visit	Clinic Visit	Clinic Visit
	Study Day		1	3, 7 V1+2 days; V1+6 days	8 V1+7 days	15 V1+14 days	29 V1+28 days	85 V1+84 days
	Visit (Days)							
	Window	-21 to -1	n/a	n/a	0 to +1	0 to +4	-3 to +4	-3 to +7
Study Event	Visit	Screening	1		2	3	4	5
	References							
	Assess relevant medications	Sections 5.1.2 and 6.5	X	X		X	X	X
	Immunogenicity							
Serology blood draw	Section 3.5		X		X	X	X	X

Additional blood draw for preparation of standard serum	Section 3.5						X	
Study Completion Procedures								
Study Termination ^f	Section 5.5							X
<p>Notes:</p> <p>^a Informed Consent to be confirmed (oral confirmation) on Visit 1 prior to vaccination</p> <p>^b Physical examination must be performed by a qualified health professional in accordance with local regulations and licensing requirements designated within the Site Responsibility Delegation Log.</p> <p>^c In case of neutropenia, Complete Blood Count to be repeated on a weekly basis until resolution. If neutropenia occurs at the last study visit, Complete Blood Count to be repeated on a regular basis until resolution.</p> <p>^d The serology tests that are performed at screening are HIV, hepatitis B and hepatitis C and they are conducted for subjects in the parent trial and for the naïve subjects. HLA-B27 testing is performed at screening only for the naïve subjects.</p> <p>^e A post-injection local and systemic adverse event and body temperature and vital signs measurement will be performed approximately 30 minutes and 4 hours after vaccination. ^f Subjects who terminate the study early are recommended to complete certain study-related procedures. See protocol section 5.5 for further details.</p>								

Table 3 Safety Tests Table

HEMATOLOGY
White Blood Cells (WBC)
Red Blood Cells (RBC)
Haemoglobin
Haematocrit
Platelets
Eosinophils
Basophils

Neutrophils
Monocytes
Lymphocytes
Prothrombin time*
SEROLOGY
HIV antibodies*
HbsAg*
Hepatitis C antibodies*
HLA-B27 testing**
PREGNANCY TEST
Human chorionic gonadotropin (hCG) in urine

* Performed at screening only ** Performed at screening only for naïve subjects.

LIST OF ABBREVIATIONS

AE	Adverse Event
AESI	Adverse Events of Special Interest
AP	(Statistical) Analysis Plan
ANC	Absolute Neutrophil Count
BMI	Body mass index
CBC	Complete Blood Count
CI	Confidence Interval
CLS	Clinical Laboratory Science
CRF	Case Report Form
CRO	Contract Research Organization
DM	Data Management
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ELISA	Enzyme-linked Immunosorbent Assay
EMA	European Medicines Agency
EoS	End of Study
EU	ELISA Unit
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practices
GMC	Geometric Mean Concentration
GMMA	Generalized Modules for Membrane Antigens
GMR	Geometric Mean Ratio
GMT	Geometric Mean Titer
GVGH	GSK Vaccines Institute for Global Health
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IRB	Institutional Review Board
ITT	Intention-To-Treat
MSD	Moderate to Severe Diarrhea
LPS	Lipopolysaccharide
LSLV	Last Subject Last Visit
MedDRA	Medical Dictionary for Regulatory Activities
NOCD	New onsets of chronic diseases
OAg	O antigen (of <i>Shigella sonnei</i>)
pIMD	Potential Immuno-Mediated Diseases

PP	Per Protocol
ReA	Reactive arthritis
SAE	Serious Adverse Event
SDA	Source Data Agreement
SDAF	Source Documentation Agreement Form
SOC	System Organ Class
SOP	Standard Operating Procedure
SPC	Summary of Product Characteristics
WHO	World Health Organization

1. BACKGROUND AND RATIONALE

1.1 Background

Shigellosis remains a major health problem in developing countries with approximately 100 million cases per year mostly in children ≤ 5 years (Kotloff et al., 1999). Antibiotic resistance of *Shigella* is increasing and no vaccine is currently available against shigellosis. Livio et al showed that a quadrivalent vaccine containing *S. sonnei* and 3 serotype/subserotypes of *S. flexneri* (*S. flexneri* 2a, *S. flexneri* 3a, and *S. flexneri* 6) can provide broad coverage against *Shigella* serotypes (up to 65%) (Livio et al., 2014), which cause shigellosis in the developing world, and can also provide broad coverage for travelers.

In this view, GSK Vaccines Institute for Global Health (GVGH) developed the *S. sonnei* 1790GAHB vaccine that has been tested in two Phase 1 trials in European adult population: one trial of the trials (protocol H03_01TP), looking at the intramuscular (IM) administration was conducted in France. In that study different antigen doses were evaluated and showed to be safe and well tolerated. More specifically, the trial evaluated the safety and immunogenicity profile of 5 different doses of GVGH *Shigella sonnei* 1790GAHB vaccine (1 μ g to 100 μ g) compared to placebo, when administered in 3 injections 1 month apart to 50 healthy adults. The immunogenicity was evaluated at baseline, 28 days after each vaccination and at 168 days after third vaccination, by measuring the anti-LPS *S. sonnei* serum IgG. Overall, an antibody response was observed across all the vaccine groups. However, at most of the time points, the response was higher in subjects who received higher antigen doses (i.e., 25 μ g, 50 μ g, and 100 μ g) than those who received lower doses (i.e., 1 μ g and 5 μ g).

More specifically, a vaccine dose of 25 μ g was very well tolerated and induced median antibody concentrations above 121 EU/mL at all post vaccination time points. Since 121 EU/mL is the median antibody titer in a panel of 87 convalescents previously exposed to *S. sonnei* infection and therefore protected against re-infection from the same serotype (Cohen et al, 1989), a vaccine dose of 25 μ g has the potential to be protective when included in a vaccine against *S. sonnei*. After unblinding the immunogenicity database, it was observed that the trial subjects could be grouped in 2 groups based on *S. sonnei* antibody concentration at baseline, with 50% having undetectable and 50% having detectable anti-LPS *S. sonnei* serum IgG antibody concentrations. Therefore, for a better understanding of the immunological response induced by the vaccine in naïve and primed subjects and for a better planning of new clinical studies, additional analyses were carried out. To mitigate the small size of study groups, subjects who received vaccines containing 1 μ g and 5 μ g antigen/dose were combined into a single group in which those with detectable antibody concentrations at baseline, showed median antibody concentrations slightly higher than 121 EU/mL only at 1 month after the third vaccination. Same was done for subjects who received vaccines containing 25 μ g, 50 μ g, and 100 μ g antigen/dose, among whom those with detectable antibody concentrations at baseline, showed, at all-time points (1 month

after the first, second and the third vaccinations and 6 months after the third vaccination), median antibody concentrations far higher than 121 EU/mL.

Based on the results from this trial, it has been decided to proceed with further development using only the IM route of immunization and a dose of 25 µg was selected as the lowest dose that in phase 1 induced antibody titers comparable to antibodies in a population of convalescent subjects after natural infection already after the first vaccination.

The results from H03_01TP suggest that 1790GAHB, even if administered at high doses, may not be sufficiently immunogenic in completely naïve adults (who might be a better predictor of antibody response in young naïve children, the ultimate target for this vaccine). Although the schedule of immunization used in the trial (i.e., 3 injections 1 month apart) may have not been optimal, it remains important to evaluate whether the vaccine was able to induce an immunological memory response.

1.2 Rationale

The current H03_01E1TP study is designed to further characterize the immunogenicity profile of GVGH *S. sonnei* 1790GAHB vaccine and obtain useful information for further clinical development through the administration of a booster dose to individuals with undetectable antibodies at baseline in H03_01TP, approximately two to three years (i.e., 24 to 36 months) after the third vaccine dose, compared to administration of 1 single vaccine dose to placebo recipients with undetectable antibodies at baseline in H03_01TP or to naïve subjects who were not part of H03_01TP study. The naïve subjects who were not part of H03_01TP study are added in order to have a more balanced number of previously unvaccinated and vaccinated subjects in the extension trial. In light of the safety and immunogenicity results of H03_01TP and of the potential development of a *S. sonnei* containing Shigella multivalent vaccine, a dose of 25 µg would be preferable for further development. Therefore, the use of this antigen dose is proposed for immunization of all subjects to provide further useful information for a more complete characterization of this vaccine strength.

2. OBJECTIVES

2.1 Primary Objective(s)

Primary Safety Objective(s)

This study has no primary safety objective

Primary Efficacy Objective(s)

This study has no primary efficacy objective

Primary Immunogenicity Objective(s)

To evaluate the memory response, as measured by anti-LPS *S. sonnei* serum IgG, 7 days after vaccination with a booster dose of GVGH *S. sonnei* 1790GAHB vaccine in individuals who had undetectable antibody titers at baseline in H03_01TP, approximately two to three years after the third vaccine dose, compared to administration of 1 single vaccine dose to placebo recipients with undetectable antibody titers at baseline in H03_01TP or naïve subjects who were not part of H03_01TP study.

2.2 Secondary Objective(s)

Secondary Safety Objective(s)

- a. To evaluate the safety profile of one dose of GVGH *S. sonnei* 1790GAHB vaccine in subjects who previously received three vaccinations with 1790GAHB and in subjects receiving one dose 1790GAHB for the first time (either placebo recipients in H03_01TP or naïve subjects who were not part of H03_01TP study).
- b. To evaluate the safety profile of one dose of GVGH *S. sonnei* 1790GAHB vaccine in subjects receiving one dose 1790GAHB for the first time and having detectable antibodies at baseline of the extension trial. **Secondary Efficacy Objective(s)**

This study has no secondary efficacy objectives.

Secondary Immunogenicity Objective(s)

- a. To evaluate the immunogenicity profile 7, 14, 28 and 84 days after vaccination with one dose of GVGH *S. sonnei* 1790GAHB in subjects with undetectable antibody titers at baseline who previously received three vaccinations of 1790GAHB in H03_01TP and in placebo recipients with undetectable antibody titers at baseline in H03_01TP or naïve subjects who were not part of H03_01TP study.
- b. To evaluate the immunogenicity profile of one dose of GVGH *S. sonnei* 1790GAHB vaccine in subjects receiving one dose 1790GAHB for the first time and having detectable antibodies at baseline of the extension trial.
- c. To evaluate the persistence of anti-LPS *S. sonnei* serum IgG antibody titers approximately two to three years after the third vaccination with 1790GAHB.

2.3 Exploratory Objective(s)

Other immunological assays might be performed to further characterize the immune response to the study vaccine including serum secretory IgA.

3. STUDY DESIGN

3.1 Overview of Study Design

This is an open label, non-randomized, single center, Phase 1 clinical trial designed to further characterize the immunogenicity profile of GVGH *S. sonnei* 1790GAHB vaccine through the administration of a booster dose to individuals with undetectable antibodies at baseline in H03_01TP parent study, approximately two to three years (i.e., 24 to 36 months) after the third vaccine dose, compared to administration of 1 single vaccine dose to placebo recipients with undetectable antibodies at baseline in H03_01TP parent study or to naïve subjects who were not part of H03_01TP study. The study includes a screening visit (performed at study Days -21 to -1), one clinical visit with vaccination (performed at study Day 1), 4 clinical visits (performed 7, 14, 28 and 84 days after vaccination), and 2 phone calls or email contacts (performed 2 and 6 days after the vaccination). No subject or study staff will be blinded for any study procedure.

During the screening period, subjects giving informed consent will be screened for general health status. No pharmacokinetic tests will be performed as evaluation of pharmacokinetic properties is not required for vaccines unless new delivery systems are employed or when the vaccine contains novel adjuvants or excipients ([Berlanda Scorza et al., 2012](#)). Subjects who meet all inclusion criteria and none of the exclusion criteria, with screening tests within normal values and women of child bearing potential with negative urine pregnancy test at V1 will be eligible for enrollment. Female subjects of child bearing potential must use birth control measures during study participation.

Up to 50 subjects will be enrolled into this trial. 24 subjects are eligible from the parent H03_01TP trial. With respect to naïve subjects who were not part of H03_01TP study, considering that in the original H03_01TP population 50% of subjects did not have detectable antibodies at baseline, with 26 subjects, it is anticipated that at least 13 subjects should not have detectable antibodies. This number combined with that of placebo recipients in H03_01TP should be sufficient to allow a balanced contribution of previously unvaccinated and vaccinated subjects in the extension trial. Subjects withdrawn or lost to follow up will not be replaced. The sample size is not driven by any statistical hypothesis, but by availability of subjects from H03_01TP study and fulfilling inclusion criteria. Subjects will be recruited as detailed in [table 1](#).

No randomization will be required since all subjects will receive the same dose of the same vaccine.

Screening/baseline clinical safety labs will take place before Visit 1 (from -21 up to -1 day). All subjects providing informed consent will undergo review of medical history, a complete physical examination including vital signs measurement (temperature, respiratory rate, heart rate, blood systolic and diastolic pressure) at the screening visit (study Day -21 to -1) and at visit 1 (Day 1) for evaluation of the general health status by clinical assessment and verification of inclusion and exclusion criteria. At clinic visit 2 and at subsequent visits, a

brief symptom-directed physical examination (if necessary according to symptoms the subject has reported) will be performed.

A blood sample will be obtained as part of the initial screening for hematology and serology (HIV, hepatitis B and C, and for HLA-B27 testing only for naïve subjects). Blood will be collected for hematology also on day 8 and 85 (visit 2 and 5 respectively). Each consented subject will have blood collected before vaccination on day 1 for baseline immunological testing and on day 8, 15, 29 and 85 (visit 2, 3, 4, and 5 respectively) post vaccination for immunological. Additional blood draw for preparation of standard serum will be done on day 29 post vaccination (visit 4). Urine pregnancy test will be done at visit 1 prior to vaccination and at visit 5. All individuals with neutropenia occurring at any time during the study will have additional blood draws to repeat complete blood count on a weekly basis until the neutropenia resolves. If neutropenia occurs at the last study visit, Complete Blood Count to be repeated on a regular basis until resolution (for classification of neutropenia during the trial, refer to [Section 5.4 Unscheduled Visits](#)).

Subjects will be observed at the clinic for 4 hour after vaccination on visit 1. Vital signs will be collected before vaccination and at 30 minutes and 4 hours post vaccination. Before leaving the clinic, they will be given a paper dairy card and trained to record in any adverse events occurring before visit 2 and will be reminded by phone call or email on day 3 and 7 post vaccination. These dairy cards will be collected and reviewed on day 8 post vaccination (visit 2).

Any unsolicited AE until visit 4, SAEs until study termination, all AEs leading to study withdrawal, reactive arthritis and severe neutropenia (AESI) and all concomitant medications associated with those events, will be collected and recorded in the subject's source document and in the eCRF. Further details on study procedure are found in [sections 5, Study Procedures and 7, Assessments](#).

3.2 Study Period

Each subject should expect to participate in the study for 85 days, from the time of enrolment through the last study visit.

3.3 Blinding Procedures

No blinding procedures will be applied for this study.

3.4 Data Collection

3.4.1 Data Collected from Subjects

The following data will be collected from each subject over the duration of their study participation:

- Demographic Information

- Medical History
- Post-vaccination immediate reactions
- Vital signs including but not limited to body temperature
- Adverse Events
- Concomitant Medications

All data collected must only be identified using the GSK Subject ID and Subject code, as described in [section 5.1.4, Randomization](#).

3.4.2 Tools Used for Data Collection

Subject Diary

Paper Diaries, hereafter referred to as Subject Diaries will be the only source document allowed for solicited local and systemic adverse events (including body temperature measurements), starting approximately 6 hours post-vaccination and collected by the subject. The following additional rules apply to documentation of safety information collected in the Subject Diary.

The Investigator or delegated staff should monitor the Subject's Diary status throughout the study for compliance and any solicited local and systemic adverse events that were of concern to the subject.

1. No corrections or additions to the information recorded by the subject within the Subject Diary will be allowed after it is delivered to the site.
2. Any blank or illegible fields on the Subject Diary must be described as missing in the CRF.

Case Report Forms

An electronic data capture (EDC) system (e.g., Inform™) will be used to expedite the entry of data. A qualified site staff member(s) will enter data in English into the web enable EDC system in a timely manner; the data will be stored in GSK clinical database management system. eCRF data will be reviewed routinely by GSK Data Management (DM) Group and GSK clinical monitors or representatives.

The information from the diary will be entered in the eCRF at visit 2. All data not recorded directly on the eCRFs must be verified by checking eCRF entries against source documents in order to ensure that the data have been completely and accurately reported as required by the study protocol.

Source data verification will be performed and recorded following GSK internal SOP. The subject must also allow access to his/her medical records. Each subject will be informed of this prior to the start of the study.

The following additional rules apply to documentation of Subject Diary information collected in the CRFs:

1. The site must enter all readable entries from the Subject Diary into the eCRF, including those values that may be biologically implausible (e.g. body temperature: 400°C).
2. Any illegible or implausible data should be reviewed with the subject. If an underlying solicited or unsolicited adverse event is described on review with the subject, this should be described in the source document and reported as an unsolicited adverse event in the Adverse Event CRF (e.g., if the subject above confirms body temperature of 40°C on the day in which body temperature: 400°C was written into his/her Subject Diary, this fever of 40°C should be recorded in the Adverse Event CRF).
3. Any newly described safety information (including a solicited adverse event) must not be written into the Subject Diary and must be described in the study file (studyspecific workbook) as a verbally reported adverse event. Any adverse event reported in this fashion must be described as an unsolicited adverse event and therefore entered on the Adverse Event CRF.

3.5 Collection of Clinical Specimens

Collected samples will be used for protocol mandated research and purposes related to the improvement, development and quality assurance of the laboratory tests described in this protocol. This may include the management of the quality of these tests, the maintenance or improvement of these tests, the development of new test methods, as well as making sure that new tests are comparable to previous methods and work reliably.

It is also possible that future findings may make it desirable to use the samples acquired in this study for future research, not described in this protocol. Therefore, all subjects in countries where this is allowed/all subjects will be asked to give a specific consent to allow the Sponsor or a contracted partner to use the samples for future research. Future research will be subject to the laws and regulations in France and will only be performed once an independent Ethics Committee or Review Board has approved this research. Information on further investigations and their rationale can be obtained from GSK.

Any sample testing will be done in line with the consent of the individual subject. If additional testing is performed, the marker priority ranking given in the table below may be changed.

Table 4 Blood For Immunological purposes

Blood sampling timepoint		Subset	No. subjects	Component	Components priority rank
Type of contact and timepoint	Sampling timepoint	/Subcohort Name			
Screening (Day -21 to 1)	Pre-Vacc	All subjects	50	HIV*	NA
		All subjects	50	anti-HBsAg*	
		All subjects	50	Hepatitis C*	

		Naïve subjects	26	HLA-B27	
Visit 1 (Day 1)	Pre-Vacc		50	Anti LPS IgG ELISA	NA
Visit 2 (Day 8)	Post-Vacc 1		50	Anti LPS IgG ELISA	NA
Visit 3 (Day 15)	Post-Vacc 2		50	Anti LPS IgG	NA
Visit 4 (Day 29)	Post-Vacc 3		50	Anti LPS IgG	1
	Standard Serum		50	Standard pool for ELISA	2
Visit 5 (Day 85)	Post-Vacc 4		50	Anti LPS IgG	NA

* The results of this testing might potentially impact the subject medical care

Processing of each specimen should be completed by a qualified site member and in accordance with the study-specific laboratory manual. Testing of clinical specimens will be performed by GSK Clinical Laboratory Science (CLS), Marburg, (Germany) or a delegated laboratory. Refer to the study-specific laboratory manual for additional details.

Blood Specimens

Approximately 15 mL blood draw will be obtained for hematological and serological (HIV, hepatitis B and C for subjects who were in the parent study. Naïve subjects will however have 25mL of blood drawn for HLA-B27 testing in addition of the hematological and serological (HIV, hepatitis B and C) tests as part of the initial screening. One additional blood draw of 6 mL for hematological tests will be obtained at 8 days (Visit 2) and 85 days (Visit 5) after vaccination (see [Table 2](#)). Each subject will have 20 mL of blood drawn for immunological studies before vaccination at Day 1 and 8, 15, 29 and 85 days after vaccination. For the purpose of creating a standard reference serum for the serological assay, study subjects will provide an additional blood sample of 20 ml at 29 days after vaccination.

All individuals with neutropenia occurring at any time during the study will have additional 6mL blood draws to repeat complete blood count on a weekly basis until the neutropenia resolves.

Clinically significant modifications in hematology will be assessed by medical judgment based on interpretation of deviations from institution's normal values and recommendations from [CBER FDA GUIDANCE FOR INDUSTRY: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials](#).

The total amount of blood collected over the study period per subject will be approximately 157 mL including screening for HLA for a subject who was not part of the parent study and the additional blood sample at day 29 for the standard pool serum for immunogenicity and excluding possible repeats of hematological tests in case of neutropenia.

Serum samples will be stored frozen below -20°C. The sera aliquots will be shipped according to guidelines provided by GSK to the laboratories for analysis. The serologic assays will be conducted at the GSK Clinical Laboratory Science, Marburg, (Germany) or a delegated laboratory.

Aliquots of sera will be archived for 20 years at the GSK laboratory in Marburg (Germany) for future research on immunogenicity of the *Shigella* vaccines. Study-related future research may include additional evaluation of immunogenicity on *Shigella sonnei* (i.e. IgM, IgA against the O antigen or IgG against other antigens of *Shigella sonnei*). It may not be possible to contact individual participants in the future in order to disseminate results obtained from research conducted on archived samples. However, these results, if relevant, will be published in peer-reviewed journals and disseminated to the scientific community. An archival time of 20 years should cover the entire vaccine development time, including the possibility to address potential questions from regulators during the registration time.

Complete instructions for processing, labeling, storage and shipping of samples are included in the Clinical Specimen Laboratory Manual provided to the investigators and available in the Investigator Site File.

Blood samples must be collected in the appropriate manner, using exclusively materials and guidelines supplied by GSK. The investigator must ensure that his/her personnel and the laboratory(ies) under his/her supervision comply with this requirement. The results of safety testing will be recorded in the source document and eCRF.

Urine Specimens

In this study urine samples will be collected from women of childbearing potential only for pregnancy testing before vaccination at Day 1 (visit1) and at study termination (visit 5).

3.6 Stopping/Pausing Guidelines

There are no predetermined stopping rules in this study. Subjects may be withdrawn from the study according to investigator discretion as described in [section 3.8, Premature Withdrawal from Study](#).

3.7 Data Monitoring Committee

No Data Monitoring Committee will be established for this study.

3.8 Premature Withdrawal from Study

Subjects may withdraw at any time, or be dropped from the study at the discretion of the investigator should any untoward effects occur and/or for safety reasons. In addition, a subject may be withdrawn by the investigator or Sponsor if he/she violates the study plan

or for administrative reasons. The investigator or study coordinator must notify the Sponsor immediately when a subject has been withdrawn due to an adverse event.

The circumstances above are referred to as premature withdrawal from the study, and the reason for premature withdrawal should be clearly documented and detailed in the source documentation. The investigator should make every attempt to evaluate the subject's safety, including resolution of ongoing AEs, at the time of premature withdrawal. If a subject wants to withdraw from the study prior to the last planned study visit, the subject will be asked to be followed for safety for the duration of the study. When a subject withdraws, or is withdrawn, from the study, the procedures described in [section 5.5.1, Early Termination Visit](#) should be completed if possible.

The reasons for premature withdrawal from the study include: Adverse event, death, withdrawal of consent, lost to follow-up, administrative reason, and protocol deviation. These reasons are described in greater detail below.

Adverse Event

For any subject withdrawn from study participation prior to the planned Study Termination Visit, it is important to determine if an AE was associated with the reason for discontinuing the study. This AE must be identified on the AE CRF page by indicating "Withdrawn from study due to AE". Any ongoing AEs at the time of study withdrawal must be followed until resolution or stabilization.

Death

For any subject withdrawn from study participation due to death, this should be noted on the Study Termination CRF page and the associated SAE that led to the death must be reported.

Withdrawal of consent

The subject can withdraw consent for participation in the study at any time without penalty or loss of benefit to which the subject is otherwise entitled. Reason for early termination should be deemed as "withdrawal of consent" if the subject withdraws from participation due to a non-medical reason (i.e., reason other than AE). If the subject intends to withdraw consent from the study, the investigator should clarify if the subject will withdraw completely from the study or if the subject will continue study participation for safety, or a subset of other study procedures. If the subject requests complete withdrawal from the study, no further study interventions will be performed with the subject.

Lost to Follow-Up

For subjects who fail to show up for final visits (clinic or telephone contacts), or for three consecutive visits, study staff are encouraged to make at least three documented attempts to contact the subject by telephone and at least one documented written attempt to contact

the subject to encourage the completion of study termination procedures. These efforts to contact the subject should be recorded in the source document. The termination date for the subject to be captured on the Study Termination CRF page is the date of the last successful contact (clinic visit or telephone) with the subject.

Administrative Reason

Examples for subjects withdrawn from the study due to administrative reason can include: Sponsor decision to terminate the study, subject meeting a pre-specified withdrawal criterion, subject discontinuation for insurance issues, moving, no time, etc. This reason should be noted in the Study Termination CRF page and any ongoing AEs at the time of study withdrawal must be followed until resolution/stabilization.

If the clinical study is prematurely terminated by the Sponsor, the investigator is to promptly inform the study subjects and local EC/IRB and should assure appropriate therapy and follow up for the subjects. All procedures and requirements pertaining to the archiving of study documents should be followed. All other study materials (study medication/vaccines, etc.) must be returned to the Sponsor.

For subjects who are withdrawn from the study due to receipt of an excluded medication/vaccination or due to significant protocol non-compliance, this reason should be noted in the Study Termination CRF page.

Subjects should submit the diary card data at day 8 (visit 2). Subject must be contacted by phone if they fail to submit the diary card on visit 2 and proper arrangement be made for collection of diary.

Protocol Deviation

A protocol deviation is any change, divergence, or departure from the study design or procedures of a study protocol. In general, subjects associated with protocol deviations may remain in the study unless continuation in the study jeopardizes the subject's health, safety, or rights.

Investigators will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact GSK or its agents, if any, monitoring the study to request approval of a protocol deviation, as no authorized deviations are permitted. If the investigator feels a change to the protocol would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by GSK and a substantial amendment is approved by the IRB/EC and health authorities it cannot be implemented.

Any subject who becomes pregnant during the study, despite the protocol requirement for adequate contraception, should be encouraged to continue participating in the study for safety follow-up. The site must complete a Pregnancy Report CRF (initial report) as soon

as possible after learning of pregnancy occurrence (see [section 7.1.6, Pregnancies](#) for further details). If the subject withdraws from the study for any of the above categories except death, the site will obtain permission from the subject to continue to remain in contact with her until the outcome of the pregnancy is known, even if the outcome is not known until after the subject reaches the end of follow-up period.

3.9 End of Study

Evaluation of the primary and/or secondary immunogenicity objectives requires the testing of biological samples from the study subjects, which can only be completed after all samples are collected. The last samples for the analysis of the primary and/or secondary objectives will be taken at visit 5.

For the purpose of this protocol, end of study (EoS) is defined as the completion of the testing of such biological samples, to be achieved no later than 8 months after collection of the last biological sample visit.

4. SELECTION OF STUDY POPULATION

4.1 Inclusion Criteria

In order to participate in this study, all subjects must meet ALL of the inclusion criteria described. Are included:

1. Males and females, aged 22 to 50 years, who were previously vaccinated, with either vaccine (3 doses) or placebo, in H03_01TP and who had undetectable antibody titers at baseline, or Males and females, aged 22 to 50 years, who were not part of H03_01TP.
2. Individuals who, after the nature of the study has been explained to them, and prior to any protocol specific procedures being performed, have given written consent according to local regulatory requirements.
3. Individuals in good health as determined by the outcome of medical history, physical examination, hematological blood tests and clinical judgment of the investigator.
4. If women of child-bearing potential, have a negative urinary pregnancy test prior study vaccination and willingness to use acceptable birth control measures for the entire study duration.
5. Individuals affiliated to a social security regimen.

4.2 Exclusion Criteria

Are excluded:

1. Individuals with behavioral or cognitive impairment or psychiatric disease that, in the opinion of the investigator, may interfere with the subject's ability to participate in the study.
2. Individuals with any progressive or severe neurological disorder, seizure disorder or Guillain-Barré syndrome.
3. Individuals who are not able to understand and to follow all required study procedures for the whole period of the study.
4. Individuals with known hepatitis B or C or suspected HIV infection or HIV related disease with history of an autoimmune disorder or any other known or suspected impairment /alteration of the immune system.
5. Progressive, unstable or uncontrolled clinical conditions.
6. Hypersensitivity, including allergy, to any component of vaccines, medicinal products or medical equipment whose use is foreseen in this study.
7. Individuals with a known bleeding diathesis, or any condition that may be associated with a prolonged bleeding time.
8. Clinical conditions representing a contraindication to intramuscular vaccination and blood draws.
9. Abnormal function of the immune system resulting from:
 - Clinical conditions;
 - Systemic administration of corticosteroids (PO/IV/IM) for more than 14 consecutive days within 90 days prior to informed consent;
 - Administration of antineoplastic and immunomodulating agents or radiotherapy within 90 days prior to informed consent.
10. Received immunoglobulins or any blood products within 180 days prior to informed consent.
11. Study personnel as an immediate family or household member.
12. Any other clinical condition that, in the opinion of the investigator, might interfere with the results of the study or pose additional risk to the subject due to participation in the study.
13. Individuals who have received an investigational product in another clinical trial 28 days prior to first study visit or intent to receive another investigational product at any time during the conduct of this study.
14. Individuals who received any other vaccines within 4 weeks prior to enrollment in this study or who are planning to receive any vaccine within the entire study duration. Inactivated influenza vaccine can be given, but only 4 weeks earlier or 4 weeks later than the date of immunization.

15. Individuals who have received blood, blood products, and/or plasma derivatives including parenteral immunoglobulin preparations in the past 180 days.
16. Individuals with body temperature > 38.0 degrees Celsius within 3 days of intended study vaccination.
17. Individuals with Body Mass Index (BMI) > 30 kg/m².
18. Individuals with history of substance or alcohol abuse within the past 2 years.
19. Women who are pregnant or are breast-feeding, or are of childbearing age who have not used or do not plan to use acceptable birth control measures, for the duration of the study.
20. Females with history of stillbirth, neonatal loss, or previous infant with anomaly.
21. Individuals who have a previously laboratory confirmed or suspected disease caused by *S. sonnei*.
22. Individuals who have had household contact with/and or intimate exposure to an individual with laboratory confirmed *S. sonnei*.
23. Any condition, which, in the opinion of the investigator may pose an increased and unreasonable safety risk to the subject if participating to the present study.
24. Individuals with a neutrophil count value lower than $1.8 \times 10^9/L$ at screening assessment.
25. Individuals with human leukocyte antigen (HLA)-B27 positive and/or with history of reactive arthritis.
26. Previous history of Benign Ethnic Neutropenia or drug related Neutropenia and/or concomitant treatment with neutropenic agents.

4.3 Criteria for Delay of Vaccination

There may be instances when individuals meet all eligibility criteria for vaccination yet have a transient clinical circumstance which may warrant delay of vaccination: body temperature elevation ($\geq 38.0^\circ\text{C}$ within 3 days prior to intended study vaccination), or use of antipyretics and/or analgesic medications within 24 hours prior to vaccination. Under such circumstances, a subject may be considered eligible for study enrolment after the appropriate window for delay has passed and inclusion/exclusion criteria have been rechecked, and if the subject is confirmed to be eligible.

5. STUDY PROCEDURES

The sections that follow provide an overview of the procedures that are to be followed in enrolling, evaluating, and following subjects who participate in this clinical study. Visits can be either clinic visits or safety follow-up telephone calls, as specified in the Table below and in the [Time and Events Table 2](#).

Table 5 Study Procedures

Visit Category	Procedures
Pre-vaccination Clinic Visit(s)	Section 5.1 describes procedures to be followed prior to study vaccination: informed consent, screening, enrolment, and randomization
Vaccination Clinic Visit(s)	Section 5.2 describes procedures to be followed during each clinic visit involving vaccination: vaccination, post-vaccination procedures, and postvaccination reminders
Post-vaccination Visit(s)	Section 5.3 describes follow-up clinic visits and safety follow-up calls
Unscheduled Visit(s)	Section 5.4 describes possible procedures to be followed at unscheduled clinic visit
Study Termination Visit	Section 5.5 describes procedures to be followed at the last study visit for a subject (may include early termination visit)

5.1 Pre-vaccination Clinic Visit(s)

This section describes the procedures that must be performed for each potential subject prior to vaccination, including obtaining informed consent, screening, enrolment and randomization.

5.1.1 Informed Consent/Assent

"Informed consent" is the voluntary agreement of an individual or his/her legal guardian(s) to participate in research. Consent must be given with free will of choice, and without undue inducement. The individual must have sufficient knowledge and understanding of the nature of the proposed research, the anticipated risks and potential benefits, and the requirements of the research to be able to make an informed decision.

Informed consent following local IRB/EC guidance **must** be obtained before conducting any study-specific procedure (i.e., all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the subject source document in addition to maintaining a copy of the signed and dated informed consent. Additional specifics regarding the informed consent processes are located in [section 13.2, Informed Consent Procedures](#).

5.1.2 Screening

Subject identification numbers will be assigned sequentially to the subjects who have consented to participate in the study. The eligibility of the subject will be determined based on the inclusion and exclusion criteria listed in [section 4, Selection of Study Population](#) and evaluated during this screening procedure.

Prior to study enrolment, demographic data will be collected from the subject, including: age, gender, race and body mass index.

Medical history will also be collected, including but not limited to any medical history that may be relevant to subject eligibility for study participation such as prior vaccinations, concomitant medications, and previous and ongoing illnesses or injuries. Subject who participated in the H03_01TP parent trial will have their medical history since the last visit reviewed. Relevant medical history can also include any medical history that contributes to the understanding of an adverse event that occurs during study participation, if it represents an exacerbation of an underlying disease/pre-existing problem.

Review of systems is a structured interview that queries the subject as to any complaints the subject has experienced across each organ system. This will be performed before enrolment and used to guide physical examination.

Important prior and concomitant medications or vaccinations taken prior to start of study should be collected (refer to [section 6.5, Prior and Concomitant Medications and Vaccines](#) for further details).

Vital signs: heart rate, respiratory rate, diastolic and systolic blood pressure, temperature and also anthropometric measurements: height and weight will be collected

A general physical examination is to be performed by a qualified health care practitioner. “Qualified health care practitioner” refers to any licensed health care professional who is permitted by institutional policy to perform physical examinations and who is identified within the Study Staff Signature Log.

These data will be written in the source document (see [section 9.1, Source Documentation](#)).

Approximately 15 mL of blood will be obtained as part of the initial screening for hematology and serology testing (HIV, hepatitis B and C) and 25 mL for the same tests and HLA-B27 for naïve subjects. Another 20 mL of blood will be collected before vaccination on day 1 for baseline immunological testing (Refer to [section 3.5, Collection of Clinical Specimens](#)).

In the event that the individual is determined ineligible for study participation, he/she is considered a screen failure. The reason for screen failure must be documented in the

Screening and Enrolment log. If the individual is determined to be eligible for the study, he/she will be enrolled into the study.

5.1.3 Enrolment

After signing the informed form, if an individual is determined to be eligible for study participation, the investigator will enroll the subject.

5.1.4 Randomization

5.1.4.1 Randomization

This is a non-randomized study which is an extension of H03_01TP study done on the same setting. Enrolled subjects will be manually assigned a unique Subject ID; since 24 subjects to be enrolled are from the previous study (H03_01TP) database, so these will preserve their subject ID if they get enrolled. The subsequent 26 new recruits as explained on [section 3.1 overview of study design](#) will be assigned subject ID following the same order used in H03_01TP but starting from where last subject's ID ended. This will easier identify subjects who are on booster vaccine dose from subjects given one vaccine dose as per this study. The Subject ID will be the subject's unique identification number for all CRFs and associated study documentation that will be used for duration of the study. The Screening Number ceases to be used and remains in the Screening and Enrolment Log.

If for any reason, after enrolment the subject fails to undergo treatment/study procedures this is an Early Termination and the reason should be recorded in source document as specified in the Source Documentation Agreement Form (SDAF). The information on these Early Termination subjects should be kept distinct in the source documentation from subjects who are screen failures, as described in [section 5.1.2, Screening](#).

5.2 Vaccination Clinic Visit(s)

The vaccination will be performed on study day 1.

Ensure all serology samples are taken **prior** to vaccination.

Perform pregnancy testing in women of childbearing age ([section 3.5, Collection of Clinical Specimens](#) for guidance regarding the procedure). Informed consent process with any women of childbearing potential will include counseling about pregnancy including discussion of their commitment to practice acceptable birth control measures (defined as oral, injected or implantable contraceptives). Women of childbearing potential are defined as a post onset of menarche and pre-menopausal female capable of becoming pregnant. This does not include females who meet any of the following conditions: (1) menopause at least 2 years earlier, (2) tubal ligation at least 1 year earlier, (3) total hysterectomy or (4) post bilateral oophorectomy.

After completing the pre-vaccination procedures on day 1, administer the vaccine to the subject according to the procedures described in [section 6.3, Vaccine Preparation and Administration](#).

Prior to administration of vaccination, confirm that the subject is eligible for study vaccinations by checking his/her medical history, clinical examination, all inclusion/exclusion criteria and that the subject does not meet any criteria for delaying study vaccinations as described in [section 4, Selection of Study Population](#)

5.2.1 Post-vaccination Procedures

The following post-vaccination procedures will be performed on day 1:

After vaccination, the subject will be observed for at least 4 hour including observation for unsolicited adverse events, solicited adverse events, and body temperature and vital signs measurement. Record all safety data collected during this time in the subject's source document.

A Subject Diary will be used in this study to document solicited adverse events. The Subject Diary is the only source for collection of these data; therefore, it is critical that the subject completes the Subject Diary correctly. The subject should be trained on how and when to complete each field of the Subject Diary.

Subject Diary training should be directed at the individual(s) who will perform the measurements of adverse events and who will enter the information into the Subject Diary.

The same individual should complete the Subject Diary throughout the 7 days following vaccination.

Training of the subject on how to measure an injection site reaction should be performed while the subject is under observation after vaccination. The subject must understand that timely completion of the diary card on a daily basis is a critical component to study participation. The subject should also be instructed to write clearly and to complete the diary card in pen. Any corrections to the diary card that are performed by the person completing the diary card should include a single strikethrough line with a brief explanation for any change. No changes can be made to the diary card when it is returned to the clinic.

Starting on the day of vaccination, the subject will check in the evening for specific types of reactions at the injection site (solicited local reactions), any specific generalized symptoms (solicited systemic reactions), body temperature (taken preferably orally) any other symptoms or change in the subject's health status, and any medications taken (excluding vitamins and minerals).

The subject should be trained on how to self-measure local solicited adverse events and body temperature. The measurement of solicited local adverse events is to be performed using the ruler provided by the site.

Body temperature measurement is to be performed using the thermometer provided by the site. If the subject feels unusually hot or cold during the day, the subject should check body temperature. If the subject has fever, the highest body temperature observed that day should be recorded on the Diary Card. The collection of body temperature, solicited local adverse events, solicited systemic adverse events will continue for a total of 7 days on the Diary Card. Unsolicited adverse events and medications will be collected by the site staff on the source document at the next planned visit based on subject's interview or when reported by the subject to the site staff by phone/unplanned visits.

At the end of the observation period, the site should schedule the next study visit with the subject. The subject will receive a study ID card to be used as a written reminder of the next planned study activity and to provide study staff contact details. The subject will be reminded to complete the Diary card daily and to contact the site if there are any questions and to contact the site immediately (or as soon as the subject is medically stable) if the subject has a medical condition that leads to a hospitalization or an emergency room visit.

The site staff/doctor should instruct the subject to contact the study doctor immediately in case of fever. All subjects presenting with a history of fever or any other sign or symptom judged by the investigator to be as a result of an infection within 21 days of vaccination will have a blood sample collected for a complete blood count to establish the absolute neutrophil count. If there is a neutropenia, the subject will be managed appropriately according to local and international requirements.

5.2.2 Post-vaccination Reminders

Reminder calls (or emails) are not intended to be an interview for collection of safety data. If the subject wishes to describe safety information, this information should only be collected by a healthcare professional at the site, and the safety data described must be written down in the subject's medical chart/source document.

Subject Diary Reminder Calls / Emails

Subject Diary reminder calls will be performed or email will be sent on day 3 and day 7 post vaccination. The purpose of this call or email is to remind the subject about completion of the Subject Diary. The call/email follow the Subject Diary Reminder Telephone Call/Email Scripts provided to the site. The subject should be reminded to contact the site via the telephone number provided in the informed consent to discuss medical questions. The safety data described by the subject on a telephone call must be written down in source documents and the subject should be reminded to write the information down in the diary card, as applicable.

If the email is printed by study staff to document that the reminder was sent, all personal information such as name and email address of the subject, will be removed before printing.

5.3 Post-vaccination Visit(s)

5.3.1 Follow-up Clinic Visit(s)

Safety follow-up clinic visits will be performed on day 8, day 15, day 29 and day 85.

During visit 2, the Subject Diary will be reviewed. No changes to the information recorded within the Subject Diary are permissible. For details on the Subject Diary see [sections 3.4.2, Tools Used for Data Collection](#) and [5.2.1, Post-vaccination Procedures](#). The subject will be interviewed to determine if any unsolicited adverse events occurred and if any concomitant medications or vaccines were taken or received in the time since the last visit. This interview will follow a checklist which will facilitate the collection of relevant safety information. The healthcare professional reviewing these data will discuss the symptoms (if any) reported by the subject and will determine if any additional diagnoses and/or adverse events are present. Adverse events reported by the subject at this follow-up clinic visit must be recorded in the subject's source document and on an Adverse Events eCRF, as specified in [section 7.1, Safety Assessment](#), and not written on the checklist used for the interview.

Perform a brief symptom-directed physical examination if necessary according to symptoms the subject has reported. This is a physical examination that will include an examination of organ systems that are relevant to the investigator based on review of the subject's reported adverse events, concomitant medication use. The physical assessment must be performed by the investigator or designee of the investigator, who is qualified to perform a physical assessment in accordance with their institutional policy. Corresponding information is documented in the subject's source document.

The site should schedule the next study activity, i.e. the next clinic visit and reminder phone call/email with the subject. The subject will be reminded to contact the site if there are any questions and to contact the site immediately (or as soon as the subject is medically stable) if the subject has a medical condition that leads to a hospitalization or an emergency room visit.

5.3.2 Safety Follow-up Calls

No safety follow up call will be made in this study. **5.4**

Unscheduled Visits

An unscheduled visit describes a non-routine study visit triggered by a specific event. These could include anticipated or unanticipated adverse events or interventions. Data obtained from such unscheduled visit should be record in a respective source document and eCRF.

If a case of neutropenia is observed after vaccination and still prevalent on a subsequent visit, the results will be recorded in the Unscheduled Lab eCRF.

All individuals with a neutropenia, occurring at any time during the study, will have additional blood draws for complete blood count to be repeated on a weekly basis until the neutropenia resolves. If neutropenia occurs at the subject's last study visit, the complete blood count will be repeated on a regular basis until resolution. For classification of neutropenia during the trial, refer to [section 7.1.4.1 Adverse Events of Special Interest](#).

5.5 Study Termination Visit

The study termination visit will occur on day 85 (visit 5). The date of termination is the date of the last contact (clinic visit or telephone call) in which the subject's health status was assessed or, in cases where the subject does not agree to any further safety follow-up; it is the date consent is withdrawn. This date should be recorded on the termination eCRF page. For visit procedures to be performed for a subject whose planned study participation ends prematurely, please see [section 5.5.1, Early Termination Visit](#).

At the clinic visit or during the telephone call, the following procedures will be performed:

Review of systems, interview of subject to collect: medically attended adverse events, AEs leading to withdrawal, SAEs, AESIs, and new onset of chronic disease, interview of subject to collect concomitant medications in relation to these events, vaccinations, symptom-directed physical assessment and a check of general appearance, blood sampling for safety laboratory assessment (hematology testing) and immunogenicity, and a urine pregnancy test for women of childbearing potential.

The site will review with the subject the plan of when information relating to the subject's participation in the study may be available (i.e., study results, treatment assignments).

The site will complete the termination eCRF page and this will mark the completion of the subject's participation in the study.

5.5.1 Early Termination Visit

When a subject is withdrawn from treatment or withdraws from the study, the investigator will notify the Sponsor and, when possible, will perform the procedures listed below. The reason(s) for the early termination will be included in the subject's source documentation. If the Early Termination Visit is a telephone call, collect as much information as possible. Early Termination Visits include subjects who were enrolled but not treated.

At the clinic visit, the following procedures will be performed;

- Review of subject's medical records, source document and Diary Card,

- Review of systems, interview of subject to collect unsolicited adverse events, medically attended adverse events, AEs leading to withdrawal, SAEs, AESIs, and new onset of chronic disease,
- Interview of subject to collect concomitant medications/vaccinations,
- Symptom-directed physical assessment including measurement of vital signs and a check of general appearance,
- Blood sampling for safety laboratory assessment (no blood for immunogenicity assessment should be obtained unless this is agreed in advance with the Sponsor),
- Urine sample for pregnancy testing.

All individuals with neutropenia either ongoing or with onset at last study visit will have additional blood draws for complete blood count to be repeated on a regular basis until the neutropenia resolves (for classification of neutropenia during the trial, refer to [section 7.1.4.1 Adverse Events of Special Interest](#)). Laboratory results obtained after study termination will be maintained in subject medical records and not entered in the eCRF.

The site will review with the subject the plan of when information relating to the subject's participation in the study may be available (e.g., study results, treatment assignments). It will also be discussed how information relating to the subject's participation in the study will be shared with the subject's healthcare provider, if the subject chooses to share this information.

The site will complete the termination CRF page and this will mark the completion of the subject's participation in the study.

6. TREATMENT OF SUBJECTS

All vaccines associated with this study are to be stored separately from other vaccines and medications in a secure location under appropriate storage conditions with temperature monitoring. **All vaccines associated with this study must be checked for expiration date prior to use. Expired vaccines must not be administered to subjects.**

6.1 Study Vaccine(s)

The term 'study vaccine' refers to those vaccines provided by the Sponsor, which will be evaluated as part of the study objectives. The study vaccine specific to this study is GVGH *S. sonnei* 1790GAHB vaccine. The GVGH GAHB-Placebo will be used as diluent for bedside mixing as described below.

The investigational agent is the GVGH *S. sonnei* vaccine. The vaccine consists of *S. sonnei* 1790-GMMA (200 µg/mL, measured by protein content) adsorbed to Alhydrogel®, (0.7 mg Al³⁺/mL) in Tris-buffered saline. The vaccine does not contain any preservative and is available as a liquid formulation in single dose vials with 0.7 mL of injectable

solution containing approximately 140 µg of GMMA (as protein content), adsorbed onto 0.49 mg Al₃+. It should be stored at +2/+8 °C.

A diluent, named GAHB-Placebo, visually matching the *S. sonnei* 1790GAHB vaccine, is also supplied for use in this clinical study as a diluent for bedside mixing. It contains the same formulation ingredients as the active *S. sonnei* 1790GAHB vaccine, except for the Drug Substance antigen 1790-GMMA, and is provided in the same primary packaging as the *S. sonnei* 1790GAHB vaccine.

Aluminum hydroxide is well characterized and used as adjuvant in several licensed vaccines. In 1790GAHB, aluminum hydroxide is used as an adsorbent to reduce the reactogenicity of LPS and does not enhance the immunogenicity of the GMMA vaccine. For further information of study vaccines refer to the Investigator Brochure. **6.2 Non-Study Vaccines**

There will be no non-study vaccines to be used.

6.3 Vaccine Preparation and Administration

The investigator or designee will be responsible for oversight of the administration of vaccine to subjects enrolled in the study according to the procedures stipulated in this study protocol. All vaccines will be administered only by personnel who are qualified to perform that function under applicable local laws and regulations for the specific study site.

Detailed vaccine preparation and administration instructions will be provided to investigators in the bedside mixing checklist and instructions prior to study start.

A *S. sonnei* 1790GAHB vaccine volume of 0.5 mL will be administered intramuscularly after bedside mixing to make a 25 µg protein/0.5 mL dose. Bedside mixing, possibly necessary additional labeling of clinical study materials at the study site and vaccine administration will be performed according to Sponsor instructions and by trained site staff. The site staff responsible for these activities will be personnel who are respectively qualified according to applicable local laws and regulations. Sponsor will provide specific procedures and training for these activities.

PRECAUTIONS TO BE TAKEN IN ADMINISTERING STUDY VACCINE:

Prior to vaccination, subjects must be determined to be eligible for study vaccination and it must be clinically appropriate in the judgment of the investigator to vaccinate. Eligibility for vaccination prior to first study vaccine administration is determined by evaluating the entry criteria outlined in protocol [sections 4.1, Inclusion Criteria](#) and [4.2, Exclusion Criteria](#).

Study vaccines should not be administered to individuals with known hypersensitivity to any component of the vaccines.

Standard immunization practices are to be observed and care should be taken to administer the injection intramuscularly. Before administering vaccine, the vaccination site is to be disinfected with a skin disinfectant (e.g., 70% alcohol). Allow the skin to dry. **DO NOT inject intravascularly.**

As with all injectable vaccines, trained medical personnel and appropriate medical treatment should be readily available in case of anaphylactic reactions following vaccine administration. For example, epinephrine 1:1000, diphenhydramine, and/or other medications for treating anaphylaxis should be available.

6.3.1 Replacement of unusable vaccines

In addition to the vaccine doses provided for the planned number of subjects (including extra doses to allow flexibility in enrolment at the different sites), at least 5% additional vaccine doses will be supplied to replace those that are unusable.

6.4 Vaccine Administration Error or Overdose of Vaccine

Vaccine administration error is defined as receiving a dose of study vaccine that was not prepared according to bedside mixing instructions or administered by a different route from the intended route of administration. An overdose of study vaccine (whether accidental or intentional) is defined when a dose higher than dose foreseen in this clinical study, i.e. 25 µg is administered in one dose of *Shigella sonnei* 1790GAHB study vaccine subjects.

Any vaccine administration error or overdose of study vaccine detailed in this protocol must be reported as an adverse event, and if the vaccine administration error or overdose is associated with a serious adverse event, it must be reported as such within 24 hours to the Sponsor.

6.5 Prior and Concomitant Medications and Vaccines

All relevant medications taken or received by the subject within 4 weeks prior to the start of the study are to be recorded on the Prior and Concomitant Medications eCRF.

In addition, the following are considered prior medications for this protocol:

all medication/vaccines described in the inclusion and exclusion criteria of this protocol including the use of antipyretics and/or analgesic medications within 24 hours prior to vaccination and ending 12 hours after vaccination must be identified and the reason for their use (prophylaxis versus treatment) must be described in the source document and Concomitant Medications CRF [Section 4.3, Criteria for Delay of Vaccination](#). Use of antipyretic, 24 hours before vaccination is a reason to delay vaccination.

Medications taken for prophylaxis are those intended to prevent the onset of symptoms. Medications taken for treatment are intended to reduce or eliminate the presence of symptoms that are present.

Concomitant medications include all medications (including vaccines) taken by/administered to the subject at and after enrolment and must be documented on the Concomitant Medications CRF.

When recording concomitant medications/vaccines, they should be checked against the study entry and continuation criteria in [section 4, Selection of Study Population](#) to ensure that the subject should be enrolled/continue in the study.

6.6 Vaccine Supply, Labeling, Storage and Tracking

Detailed vaccine supply, labeling, storage and tracking instructions will be provided to investigators prior to study start.

The Sponsor will ensure the following:

- Supply the study vaccine.
- Appropriate labeling of all study that complies with the country legal requirements.

The investigator must ensure the following:

- Acknowledge receipt of the study vaccines by a designated staff member at the site, including confirmation that the vaccines were received in good condition.
- Proper storage of the study vaccines, including:
 - Storage in a secure, locked, temperature-controlled location.
 - The study vaccine must be stored at the respective label storage temperature conditions in a safe and locked place. Access to the storage space should be limited to authorized study personnel. The storage conditions will be assessed during pre-study activities under the responsibility of the sponsor study contact.
 - Proper storage according to the instructions specified on the labels.
 - Appropriate record keeping and inventory of the study vaccines, including regular documentation of adequate storage temperature.
 - The storage temperature should be continuously monitored with calibrated (if not validated) temperature monitoring device(s) and recorded.
 - Temperature excursions must be reported in degree Celsius.
 - Any temperature excursion outside the range of +2.0 to +8.0 °C impacting investigational medicinal products (IMPs) must be reported to the Sponsor. The impacted IMPs must not be used and must be stored in quarantine at label temperature conditions until usage approval has been obtained from the Sponsor.
- Appropriate use of the study vaccines, including:
 - Use only in accordance with the approved protocol.

- Proper handling, including confirmation that the vaccine has not expired prior to administration.
- Appropriate documentation of administration of vaccines to study subjects including:
 - Date, dosage, batch/lot numbers, expiration dates, unique identifying numbers assigned to subjects and study vaccines, and time of vaccine administration. This information will be maintained in an accountability log that will be reviewed by the site monitor.
 - Reconciliation of all vaccines received from the Sponsor. Reconciliation is defined as maintaining records of which and how many vaccines were received, which vaccines were administered to subjects, which vaccines were destroyed at the site, and which vaccines were returned to the Sponsor, as applicable.
- Proper adherence to the local institutional policy with respect to destruction of study vaccines.
- Complete record keeping of vaccine use, wastage, return or destruction, including documentation of:
 - Copy of the site's procedure for destruction of hazardous material. - Copy of Destruction Certificate.

Vaccines that have been stored differently from the manufacturer's indications **must not** be used unless the Sponsor provides authorization for use. In the event that the use cannot be authorized, the Sponsor will make every effort to replace the vaccine supply. All vaccines used in conjunction with this protocol must be stored separately from normal hospital/practice stocks to prevent unintentional use of study vaccines outside of the clinical study setting.

Monitoring of vaccine accountability will be performed by the study monitor during site visits and at the completion of the study.

At the conclusion of the study, and as appropriate during the course of the study, the investigator must ensure that all unused study vaccines, packaging and supplementary labels are destroyed locally (upon approval from the Sponsor) or returned to the Sponsor.

7. ASSESSMENTS

7.1 Safety Assessment

The measures of safety used in this study are based on previous study data. They include a close vigilance for, and stringent reporting of selected local and systemic adverse events routinely monitored in vaccine studies as indicators of reactogenicity.

An adverse event (AE) is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product at any dose that does not necessarily have to have a causal relationship with this treatment. Therefore, an AE can be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product. This definition includes intercurrent illnesses or injuries and exacerbation of pre-existing conditions.

For the purpose of this trial, AEs will be from the time the subject signs informed consent until Visit 4. AEs occurring after the informed consent form is signed but prior to receiving study vaccine will be documented as an adverse event and recorded within source document. However, any AEs occurring prior to receipt of any study vaccine will be analyzed separately from “treatment emergent” AEs (AEs occurring after administration of the first study vaccine). All adverse events that are serious, clinically significant as judged by the investigators, medically attended and AESI will be collected until study termination at visit 5.

Adverse events are collected as either solicited or unsolicited adverse events. Solicited events are derived from organized data collection systems, such as Subject Diaries or interview.

7.1.1 Solicited Adverse Events

The term “reactogenicity” refers to solicited signs and symptoms (“solicited adverse events”) occurring in the hours and days following a vaccination, to be collected by the subject for 7 consecutive days, using a pre-defined Subject Diary.

The following solicited adverse events are included in the Subject Diary. Each adverse event is to be assessed using the scoring system reported in parentheses below:

Solicited Local Adverse Events

These include erythema, induration and pain at injection site. They will be assessed using the scoring system reported in a table below. **Table 6 Grading of solicited local adverse events**

Solicited local adverse events	Grade 0 Absent	Present - Grading of Severity		
		Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe
Injection site Erythema (Captured as measurements in millimeters)	1-24 mm	25-50 mm	51-100 mm	> 100 mm

Injection site Induration (Captured as measurements in millimeters)	1-24 mm	25-50 mm	51-100 mm	> 100 mm
Injection site Pain	No pain	Present but does not interfere with activity	Interferes with activity	Prevents daily activity

Solicited Systemic Adverse Events

These include headache, arthralgia, chills, fatigue, malaise, myalgia, and fever (body temperature measured orally). They will be assessed using the scoring system reported in a table below.

Table 7 Grading of solicited systemic adverse events

Solicited systemic adverse events	Grade 0 Absent	Present - Grading of Severity*		
		Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe
Headache	No headache	Present but does not interfere with activity	Interferes with activity	Prevents daily activity
Arthralgia	No arthralgia	Present but does not interfere with activity	Interferes with activity	Prevents daily activity
Chills	No chills	Present but does not interfere with activity	Interferes with activity	Prevents daily activity
Fatigue	No fatigue	No interference with activity	Some interference with activity	Significant; prevents daily activity
Malaise	No malaise	No interference with activity	Some interference with activity	Significant; prevents daily activity
Myalgia	No myalgia	Present but does not interfere with activity	Interferes with activity	Prevents daily activity
Fever as a Body temperature (Captured as measurements in degrees Celsius)	≤ 37.9 °C	≥ 38.0 – 38.9°C	≥ 39.0 – 39.9°C	≥ 40.0°C
	Oral Temperature: <35.5 °C to ≥38.0 °C			

Other Solicited Adverse Events

These include use of analgesics/antipyretics. It will be assessed using the scoring system reported in a table below.

Other Solicited adverse events	Grade 0 Absent	Present - Grading of Severity		
		Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe
Use of analgesics/antipyretics	Categorized as “yes” or “no”			

The study staff must review the data entered into the Subject Diary as described in [section 3.4.2, Tools Used for Data Collection](#) and [section 5.3.1, Follow-up Clinic Visit\(s\)](#).

Note: Any solicited adverse event that meets any of the following criteria must be entered into subjects’ source document (see [section 9.1, Source Documentation](#)) and also as an adverse event on the Adverse Event CRF:

- Solicited local or systemic adverse event that continues beyond day 7 after vaccination.
- Solicited local or systemic adverse event that leads to a visit to a healthcare provider (medically attended adverse event, see [section 7.1.3, Evaluation of Adverse Events](#)).
- Solicited local or systemic adverse event leading to the subject withdrawing from the study or the subject being withdrawn from the study by the investigator (adverse event leading to withdrawal, see [section 7.1.3, Evaluation of Adverse Events](#)).
- Solicited local or systemic adverse event that otherwise meets the definition of a serious adverse event (see [section 7.1.4, Serious Adverse Events](#)).

7.1.2 Unsolicited Adverse Events

An unsolicited adverse event is an adverse event that was not solicited using a Subject Diary and that was spontaneously communicated by a subject who has signed the informed consent.

Potential unsolicited AEs may be medically attended (defined as symptoms or illnesses requiring hospitalization, or emergency room visit, or visit to/by a health care provider), or were of concern to the subject. In case of such events, subjects will be instructed to contact the site as soon as possible to report the event(s). The detailed information about the reported unsolicited AEs will be collected by the qualified site personnel during the interview and will be documented in the subject’s records.

Unsolicited AEs that are not medically attended nor perceived as a concern by subjects will be collected during interview with the subject and by review of available medical records at the next visit (see [section 5.3, Post-vaccination Visit\(s\)](#)).

7.1.3 Evaluation of Adverse Events

Every effort should be made by the investigator to evaluate safety information reported by a subject for an underlying diagnosis and to capture this diagnosis as the event in the AE page. In other words, the practice of reporting only symptoms (e.g., “cough” or “ear pain”)

are better reported according to the underlying cause (e.g., “asthma exacerbation” or “otitis media”).

The severity of events reported on the Adverse Events CRF will be determined by the investigator as:

Mild: transient with no limitation in normal daily activity.

Moderate: some limitation in normal daily activity. Severe:

unable to perform normal daily activity.

The relationship of the study treatment to an AE will be determined by the investigator based on the following definitions:

1. Not Related

The AE is not related to an investigational vaccine if there is evidence that clearly indicates an alternative explanation. If the subject has not received the vaccine, the timing of the exposure to the vaccine and the onset of the AE are not reasonably related in time, or other facts, evidence or arguments exist that reasonably suggest an alternative explanation, then the AE is not related.

2. Possibly Related

The administration of the investigational vaccine and AE are considered reasonably related in time and the AE could be explained by exposure to the investigational vaccine or by other causes. 3. Probably Related

Exposure to the investigational vaccine and AE are reasonably related in time and no alternative explanation has been identified.

The relationship of the study treatment to an unsolicited AE will be determined by the investigator.

Note: solicited AEs will not be evaluated for relationship to study treatment. Grading for severity of solicited local and systemic AEs is described in [section 7.1.1, Solicited Adverse Events](#).

Adverse events will also be evaluated by the investigator for the co-existence of any of the other following conditions:

- “Medically attended adverse event”: an adverse event that leads to a visit to a healthcare provider.
- “New onset of chronic disease” (NOCD): an adverse event that represents a new diagnosis of a chronic medical condition that was not present or suspected in a subject prior to study enrolment.

- AEs leading to withdrawal: adverse events leading to study or vaccine withdrawal.
- Potential immune-mediated diseases (pIMDs): a subset of AEs that include autoimmune diseases and other inflammatory and/or neurologic disorders of interest which may or may not have an autoimmune aetiology. In this study, only the pIMDs reported in the table below will be collected. However if other pIMDs are discovered during development of the vaccine, the table will be revised and updated accordingly.

Musculoskeletal disorders	Spondyloarthritis, including ankylosing spondylitis, reactive arthritis (Reiter's Syndrome) and undifferentiated spondyloarthritis
Blood disorders	Autoimmune neutropenia

If solicited or unsolicited adverse events have been reported and the subject indicated that the symptoms required medical attendance or were of concern, the subject must be contacted for further information.

When the subject is contacted for any of these reasons, the contact must be documented in the subject's source documentation.

All AEs, regardless of severity, will be monitored until resolution or until the investigator assesses them as chronic or stable. All subjects experiencing AEs - whether considered associated with the use of the study vaccine or not - must be monitored until symptoms subside and any abnormal laboratory values have returned to baseline, or until there is a satisfactory explanation for the changes observed, or until death, in which case a full pathologist's report should be supplied, if possible. The investigator's assessment of ongoing Adverse Events at the time of each subject's last visit should be documented in the subject's medical chart.

7.1.4 Serious Adverse Events

A serious adverse event (SAE) is defined as any untoward medical occurrence that at any dose results in one or more of the following:

- Death.
- Is life-threatening (i.e., the subject was, in the opinion of the investigator, at immediate risk of death from the event as it occurred); it does not refer to an event which hypothetically might have caused death if it were more severe.
- Required or prolonged hospitalization.
- Persistent or significant disability/incapacity (i.e., the event causes a substantial disruption of a person's ability to conduct normal life functions).
- Congenital anomaly/birth defect.

- An important and significant medical event that may not be immediately life threatening or resulting in death or hospitalization but, based upon appropriate medical judgment, may jeopardize the subject or may require intervention to prevent one of the other outcomes listed above.

Adverse events which do not fall into these categories are defined as non-serious.

It should be noted that a severe adverse event need not be serious in nature and that a serious adverse event need not, by definition, be severe.

Serious adverse events will be captured both on the Vaccines Serious Adverse Event (VSAE) form as well as on the AE CRF. All SAEs will be evaluated by the investigator for relationship of the event to study vaccine. SAEs that are judged to be possibly or probably related to the study vaccine should be reported to the Sponsor as related events. The relationship of the study treatment to an SAE will be determined by the investigator based on the following definitions:

1. Related

The SAE is judged by the investigator to be possibly or probably related to the study vaccine on the AE CRF page (see [section 7.1.3, Evaluation of Adverse Events](#)).

2. Not Related

The SAE is not related if exposure to the study vaccine has not occurred, **or** the occurrence of the SAE is not reasonably related in time, **or** the SAE is considered unlikely to be related to use of the study vaccine, i.e., there are no facts (evidence) or arguments to suggest a causal relationship.

The relationship of the study vaccine to an SAE will be determined by the investigator.

In addition, SAEs will be evaluated by the Sponsor or designee for “expectedness.” An unexpected AE is one that is not listed in the current Summary of Product Characteristics or the Investigator’s Brochure or an event that is by nature more specific or more severe than a listed event.

In addition, a pre-existing event or condition that results in hospitalization should be recorded on the Medical History CRF. If the onset of an event occurred before the subject entered the study (e.g., any pre-planned hospitalization for conditions like cosmetic treatments or for non-emergency routine visits for a pre-existing condition), the hospitalization would not lead to an AE being classified as serious unless, in the view of the investigator, hospitalization was prolonged as a result of participation in the clinical study or was necessary due to a worsening of the pre-existing condition.

7.1.4.1 Adverse Events of Special Interest

Adverse events of special interest (AESIs) are predefined adverse events that will be specifically highlighted to the investigator and will be summarized separately. Only AESI meeting the definition of SAE will be categorized and reported as such in this study.

Reactive arthritis (ReA) or Neutropenia will be collected and analyzed as an AESI for this study.

Reactive arthritis is defined as non-purulent joint inflammation that develops in response to an infection in another part of the body. Since the inflammation is triggered by a previous condition, it is termed “reactive”. Intestinal pathogens that have been associated with reactive arthritis include Campylobacter, Salmonella, Yersinia, Clostridium difficile, and Shigella. If reactive arthritis is caused by an auto immune response, there is at least a possibility that it could be initiated by vaccination of susceptible people with the 1790GAHB vaccine.

For diagnosis of ReA, imaging and aspiration are not required (unless clinically indicated).

Neutropenia is defined as decrease of neutrophil count asymptotically or symptomatically with ANC $<1.8 \times 10^9/L$, occurring at 7 days after vaccination. Its graded from grade 1 to 4 basing on neutrophil counts as follows: Grade 1 ANC $1.5 - <1.8 \times 10^9/L$, Grade 2 ANC $<1.5 \times 10^9/L$, Grade 3 ANC $1.0 - 0.5 \times 10^9/L$, and Grade 4 $<0.5 \times 10^9/L$.

This is completely diagnosed by laboratory testing for complete blood count.

7.1.5 Methods for Recording Adverse Events and Serious Adverse Events

Findings regarding Adverse Events must be reported on an Adverse Events CRF, as specified in [section 7.1.1, Solicited Adverse Events](#), and on the VSAE form, if applicable, which is part of the Investigator Site File. All findings in subjects experiencing AEs must be reported also in the subject's source document.

All SAEs which occur during the course of the study, whether considered to be associated with the study vaccination or not and even if the information is incomplete, must be reported **within 24 hours of the site becoming aware of the event** to the Sponsor. Specific instructions and contact details for collecting and reporting SAEs will be provided to the investigator. Specifically, once an investigator becomes aware that a SAE has occurred in a study subject, the investigator (or designate) must complete a paper expedited Adverse Events report and forward it to the Sponsor **WITHIN 24 HOURS**. The report will always aimed to be completed as thoroughly as possible with all available details of the event and then dated and signed by the investigator (or designate). Even if the investigator does not have all information regarding a SAE, the report should still be completed and forwarded to the Sponsor within 24 hours. Once additional relevant information is received, the report should be updated and forwarded the Sponsor **WITHIN 24 HOURS**. The investigator will always provide an assessment of causality at the time of the initial report.

All SAEs are also to be documented on the Adverse Events CRF. Any medication or other therapeutic measures used to treat the AE will be recorded on the appropriate CRF(s) in addition to the outcome of the AE.

Only AESI meeting the definition of SAE will be categorized and reported as serious in this study by the investigator within 24 hours. However all other AESI irrespective of their grading will be recorded in the adverse event page of eCRF and the source documents.

After receipt of the initial report, representatives of the Sponsor or its designee will contact the investigator if it is necessary to obtain further information for assessment of the event. Of note, after the initial AE/SAE report, the investigator is required to proactively follow each subject and provide additional relevant information on the subject's condition to the Sponsor (within 24 hours for SAEs and Potential ImmuneMediated Disease pIMD, and within 2 weeks for pregnancies).

All SAEs must be reported by the investigator to his/her corresponding EC/IRB and/or applicable regulatory authorities in accordance with institutional policy/regulatory requirements and adequate documentation of this notification must be provided to the Sponsor.

GSK or its designee must also comply with the applicable regulatory requirement(s) related to the reporting of suspected unexpected serious adverse vaccine reactions (also known as SUSARs) to the regulatory authority(ies) and the IRB/EC. If a SUSAR or other safety signal relating to use of one of the study vaccines is reported to GSK or its designee, the Sponsor will communicate the information to the investigator and the investigator will be responsible for submitting this information to the EC/IRB and other relevant authorities.

7.1.5.1 Post-Study Events

Any SAE that occurs outside of the protocol-specified follow-up period and considered to be caused by the study vaccine must be reported to the Sponsor. These SAEs will be processed by the Sponsor as during the course of the study, until 3 months after last subject last visit. Instructions and contact details for collecting and reporting these suspected SAEs will be provided to the investigator.

7.1.6 Pregnancies

To ensure subjects' safety, each pregnancy in a subject after study vaccination must be reported to the Sponsor in due time of the site learning of its occurrence. If the subject agrees to submit this information, the pregnancy must be followed to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. This follow-up should occur even if intended duration of safety follow-up for the study has ended.

Pregnancy data must be recorded on a Pregnancy Report CRF (initial report) and Pregnancy Follow-Up CRF (outcome report) and reported to the Sponsor. Instructions and contact details for submitting the Pregnancy CRFs will be provided to the investigator.

Any pregnancy outcome meeting the definition of a SAE (see [section 7.1.4, Serious Adverse Events](#)) must also be reported on the VSAE Report Form. The following should always be considered as SAE.

- Spontaneous pregnancy loss, including:
 - spontaneous abortion, (spontaneous pregnancy loss before/at 22 weeks of gestation)
 - ectopic and molar pregnancy
 - Stillbirth (intrauterine death of foetus after 22 weeks of gestation).

Note: the 22 weeks cut-off in gestational age is based on WHO-ICD 10 noted in the EMA Guideline on pregnancy exposure (EMA, 2006). It is recognized that national regulations might be different.

- Any early neonatal death (i.e. death of a live born infant occurring within the first 7 days of life).
- Any congenital anomaly or birth defect (as per [[CDC MACDPJ guidelines](#)]) identified in the offspring of a study subject (either during pregnancy, at birth or later) regardless of whether the foetus is delivered dead or alive. This includes anomalies identified by prenatal ultrasound, amniocentesis or examination of the products of conception after elective or spontaneous abortion.

7.1.7 Safety Laboratory Measurements

For list of safety laboratory measurement, refer to synopsis [Table 2](#), Hematological Safety [Table 3](#).

Safety laboratory measurement will be performed as described in [Section 3.5, Collection of Clinical Specimens](#).

Significant alterations in hematology will be clinically assessed by the investigator's medical judgment based on interpretation of deviations from institution's normal values.

Any abnormality in laboratory measurements classified as clinically significant must be reported in the Adverse Event CRF form.

If a subject is to have blood drawn testing for safety laboratory for repeat safety assessment (i.e., in case of markedly abnormal safety laboratory parameter), investigator's medical judgment will be applied concerning values that would trigger reanalysis and frequency of repeats. If neutropenia is observed at a visit, a complete blood count will be repeated on a weekly basis until resolution.

Safety laboratory assessments will be performed at the site laboratory, and results of these tests will be recorded in the source documents and in the CRF.

7.2 Efficacy Assessment

This study has no efficacy endpoints.

7.3 Immunogenicity Assessment

The ELISA methodology used in this study has been adopted based on scientific consensus and has been deemed appropriate to describe the immune response against *Shigella sonnei* GMMA in this study.

The measure of immunogenicity used in this study is IgG ELISA against *Shigella sonnei* OAg. The serologic assays on clinical samples will be performed at GSK, Clinical Serology Laboratory, Marburg, Germany, or a delegated laboratory. [Section 3: Study Design](#).

For reference of visits the measurements are taken, refer to [section 3.5](#) and to the Clinical Specimen Laboratory Manual.

8. STATISTICAL CONSIDERATIONS

8.1 Endpoints

8.1.1 Primary Endpoint(s)

8.1.1.1 Primary Safety Endpoint(s)

This study has no primary safety endpoint.

8.1.1.2 Primary Efficacy Endpoint(s) This study has no efficacy measurements.

8.1.1.3 Primary Immunogenicity Endpoint(s)

The primary immunogenicity endpoint which is memory response, against the OAg of *S. sonnei* will be evaluated by measuring IgG Geometric mean concentrations (GMCs) after vaccination as determined by ELISA with O-antigen containing LPS as coating antigen.

8.1.2 Secondary Endpoint(s)

8.1.2.1 Secondary Safety

Endpoint(s) The measures of safety will include:

- a. Numbers of subjects with deviations from normal values of hematological tests after vaccination.
- b. Numbers of subjects with solicited local and systemic reactions during 7 days following vaccination. Solicited local reactions include injection site erythema, injection site induration and injection site pain; solicited systemic reactions include headache, arthralgia, chills, fatigue, malaise, myalgia, and fever (as measured orally).
- c. Numbers of subjects with reported unsolicited adverse events (of any nature and severity) during 84 days following vaccination.
- d. Number of subjects with reported SAEs throughout the study duration.

8.1.2.2 Secondary Efficacy Endpoint(s)

The study has no secondary efficacy endpoint.

8.1.2.3 Secondary Immunogenicity Endpoint(s)

- a. IgG Geometric mean concentrations (GMCs) at 7, 14, 28 and 84 days after vaccination as determined by ELISA and applicable geometric mean ratios between post vaccination and baseline samples.
- b. Number and percentage of subjects with seroresponse for anti- LPS *S. sonnei* at 7, 14, 28 and 84 days after vaccination. Seroresponse is aimed to define a significant

increase in post vaccination samples based on the biological performance of this specific serology assay and it is defined as follows:

- If the baseline value is greater than 50 ELISA Units (EU) then an increase of at least 50% in the post-vaccination sample as compared to baseline [i.e. $((\text{Post-vac} - \text{baseline}) / \text{baseline}) \times 100\% \geq 50\%$].
- If the baseline value is less or equal to 50 EU then an increase of at least 25 EU in the post-vaccination sample as compared to baseline [i.e. $(\text{Postvac} - \text{baseline}) \geq 25$ EU]. Number and percentage of subjects with titers post vaccination concentration ≥ 121 EU/ml for anti-LPS *S. sonnei* at 7, 14, 28 and 84 days after vaccination.

A post-vaccination concentration ≥ 121 anti-LPS serum IgG units in the GVGH ELISA with O-antigen containing LPS as coating antigen corresponds to a titer of 1:800 in the ELISA method used by Cohen et al. (1989 J. Clin. Microbiol. 27:162). This antibody level is the median antibody concentration of a set of 87 convalescent subjects previously infected by *S. sonnei*. The value of 121 anti-LPS serum IgG units in the GVGH ELISA was determined by calibration against the Cohen ELISA (i.e., the GVGH standard serum was tested in Cohen's lab using the Cohen's methodology).

The serologic assays on clinical samples will be performed at GSK, Clinical Laboratory Science (CLS), Marburg, Germany, or a delegated laboratory.

8.1.3 Exploratory Endpoint(s)

8.1.3.1 Exploratory Safety Endpoint(s)

The study has no exploratory safety endpoint(s).

8.1.3.2 Exploratory Efficacy Endpoint(s)

The study has no exploratory efficacy endpoint(s).

8.1.3.3 Exploratory Immunogenicity Endpoint(s)

Other assays, including serum secretory IgA, might be done to further characterize the immune response to the study vaccine. The analysis will be described in the statistical analysis plan.

8.2 Success Criteria

The study has no predefined success criteria. **8.2.1**

Success Criteria for Primary Objective(s) Not applicable.

8.2.1.1 Success Criteria for Primary Safety Objective(s)

Not applicable.

8.2.1.2 Success Criteria for Primary Efficacy Objective(s)

Not applicable.

8.2.1.3 Success Criteria for Primary Immunogenicity Objective(s)

Not applicable.

8.2.2 Success Criteria for Secondary Objective(s)

Not applicable.

8.2.2.1 Success Criteria for Secondary Safety Objective(s)

Not applicable.

8.2.2.2 Success Criteria for Secondary Efficacy Objective(s)

Not applicable.

8.2.2.3 Success Criteria for Secondary Immunogenicity Objective(s)

Not applicable.

8.3 Analysis Sets

8.3.1 All Enrolled Set

All screened subjects who provide informed consent and provide demographic and/or baseline screening assessments, regardless of the subject's randomization and treatment status in the study and received a Subject ID.

8.3.2 All Exposed Set

All subjects in the enrolled set who receive a study vaccination.

8.3.3 Safety Set

Solicited Safety Set (solicited local and systemic adverse events and other solicited adverse events)

All subjects in the Exposed Set with any solicited adverse event data and/or indicators of solicited adverse events.

Unsolicited Safety Set (unsolicited adverse events)

All subjects in the Exposed Set with unsolicited adverse event data.

Overall Safety Set

All subjects who are in the Solicited Safety Set and/or Unsolicited Safety Set.

8.3.4 Full Analysis Set (FAS) Efficacy/Immunogenicity Set

Full Analysis Set Efficacy

Not applicable.

Full Analysis Set Immunogenicity

All subjects in the Enrolled Population who:

- Receive a study vaccination AND provide at least one immunogenicity data at relevant time points.

The FAS will be the primary analysis set for the immunogenicity objective.

In case of vaccination error, subjects in the FAS sets will be analyzed “as randomized” (i.e., according to the study group a subject was assigned).

8.3.5 Per Protocol (PP) Immunogenicity Set

All subjects in the FAS / Immunogenicity who:

- Correctly receive the vaccine.
- Have no protocol deviations leading to exclusion (see [section 8.3.8, Protocol Deviations](#)) as defined prior to analysis.
- Are not excluded due to other reasons defined prior to analysis (see [section 8.3.8, Protocol Deviations](#)).

PPS are subsets of FAS and should be always defined even if the objectives do not require it.

Examples for subjects excluded due to other reasons than protocol deviations are

- Subjects who withdrew informed consent.

8.3.6 Other Analysis Sets

None.

8.3.7 Subgroups Not

applicable.

8.3.8 Protocol Deviations

A protocol deviation is any change, divergence, or departure from the study design or procedures of a study protocol. A protocol deviation may be a reason to remove data from an analysis set at the time of analysis. CSR-reportable protocol deviations will be defined as exclusionary from the analysis according to protocol objectives and endpoints, which will be specified in the statistical analysis plan. In some cases exclusion of data may be due to a reason other than a protocol deviation, i.e. early termination.

8.4 Statistical Analysis Plan

8.4.1 Analysis of Demographic and Baseline Characteristics

Descriptive statistics (mean, standard deviation, median, minimum and maximum) for age and BMI at enrolment will be calculated overall and by vaccine group.

Distributions of subjects by sex and ethnic origin will be summarized overall and by vaccine group.

8.4.2 Analysis of Primary Objective(s)

8.4.2.1 Analysis of Primary Safety Objective(s)

The study has no primary safety objective.

8.4.2.1.1 Analysis of Extent of Exposure

The frequencies and percentages of subjects with vaccination will be summarized overall and by study group. Data will be tabulated for the All Enrolled Set.

8.4.2.1.2 Analysis of Solicited Local, Systemic and Other Adverse Events

All solicited adverse events will be summarized according to defined severity grading scales.

Frequencies and percentages of subjects experiencing each adverse event will be presented for each symptom severity. Summary tables showing the occurrence of any local or systemic adverse event overall and at each time point will also be presented.

Post-vaccination solicited adverse events reported from day 1 to day 7 will be summarized for the intervals day 1-3, day 4-7, day 1-7 by maximal severity and by vaccine group, excluding the 30 minute and 4 hour measurement, which will be summarized separately. The severity of solicited local adverse events, including injection site erythema and induration will be summarized according to categories based on linear measurement: 25 to 50 mm, 51 to 100 mm, >100mm.

Injection site pain/tenderness and systemic adverse events (except fever) occurring up to 7 days after vaccination will be summarized according to “mild”, “moderate” or “severe”.

Each solicited local and systemic adverse event will also be further summarized as “none” versus “any”.

Implausible measurements (for further definition see statistical analysis plan) will be left out of the analysis.

Use of antipyretics and analgesics will be summarized by frequency, by type of use (prophylactic versus treatment) and percentage of subjects reporting use. The influence of antipyretics and analgesics use on the occurrence of specific adverse events (e.g., fever, pain) will be assessed.

Body temperature will be summarized by 0.5 °C and 1.0 °C increments from 36.0 °C up to ≥ 40 °C.

8.4.2.1.3 Analysis of Unsolicited Adverse Events

This analysis applies to all adverse events occurring during the study, judged either as probably related, possibly related, or not related to vaccination by the investigator, recorded in AE CRF, with a start date on or after the date of vaccination. AE starting prior to the vaccination will only be listed. The original verbatim terms used by investigators to identify adverse events in the CRFs will be mapped to preferred terms using the MedDRA dictionary. The adverse events will then be grouped by MedDRA preferred terms into frequency tables according to system organ class.

All reported adverse events, as well as adverse events judged by the investigator as at least possibly related to study vaccine, will be summarized according to system organ class and preferred term within system organ class. These summaries will be presented by vaccination group and by interval of study observation. When an adverse event occurs more than once for a subject, the maximal severity and strongest relationship to the vaccine group will be counted.

Separate summaries will be produced for the following categories:

- Serious adverse events
- Adverse events that are possibly or probably related to vaccine

- Adverse events of special interest
- New onset of chronic disease
- Potential immune-mediated diseases (pIMDs) adverse event leading to withdrawal •
Adverse events leading to a medically attended visit
- Adverse event by data source.

Data listings of all adverse events will be provided by subject. In addition, adverse events in the categories above will be provided as listed data.

8.4.2.1.4 Analysis of Safety Laboratory Values

The investigator must assess all safety laboratory results (see [section 7.1.7](#)). Clinically significant modifications in hematology test values will be assessed by medical judgment based on interpretation of deviations from the institution's normal values.

All laboratory safety data will be analyzed descriptively by study group. Safety laboratory data will be shown in a 3 x 3 table by visit using categorization of laboratory according to institutional normal reference range (below, within, above).

8.4.2.2 Analysis of Primary Efficacy Objective(s)

The study has no primary efficacy objective.

8.4.2.2.1 Statistical Hypotheses

This Phase 1 safety and immunogenicity trial is aimed to descriptively evaluate the safety and immunogenicity profiles of the study vaccines. No specific hypotheses are tested in this study.

8.4.2.2.2 Analysis Sets

For more details see ([section 8.3 Analysis Sets](#)).

8.4.2.2.3 Statistical Methods

Not applicable.

8.4.2.3 Analysis of Primary Immunogenicity Objective(s)

8.4.2.3.1 Statistical Hypotheses

This Phase 1 safety and immunogenicity trial is aimed to descriptively evaluate the safety and immunogenicity profiles of the study vaccines. No specific hypotheses are tested in this trial.

8.4.2.3.2 Analysis Sets

The modified FAS will be the primary analysis set for the immunogenicity objective (further details are given in [section 8.3, Analysis Sets](#)).

8.4.2.3.3 Statistical Methods

Analysis of continuous variables

The ELISA concentrations will be logarithmically transformed (base10) (to fulfil the normal distribution assumption). GMC will be calculated, with their associated two-sided 95% CIs, by exponentiating the corresponding log-transformed means and their 95% CI.

Additionally, within-subject GMRs will be computed for GMTs/GMCs at 7, 14, 28 and 84 days after vaccination versus baseline (day 1). The GMRs and 95% CIs will be constructed by exponentiating the mean within-subject differences in log-transformed titers and the corresponding 95% CIs. Analysis of binary variables

The number and percentages of subjects with seroresponse from baseline and with high antibody level after vaccination (i.e. post vaccination antibody level ≥ 121 IgG units in the GVGH ELISA), will be summarized. Two-sided 95% Clopper-Pearson CIs for the percentages will be computed.

Titers below the limit of detection will be set to half that limit for the purposes of analysis. Missing values of immunogenicity will be excluded from analyses (i.e. complete-case analysis) since they are considered missing completely at random, i.e. not informative and with no impact on inferences

8.4.3 Analysis of Secondary Objective(s)

8.4.3.1 Analysis of Secondary Safety Objective(s)

For more details see [Section 8.4.2.1.2 Analysis of Solicited Local, Systemic and Other Adverse Events](#) and [8.4.2.1.3 Analysis of unsolicited adverse events](#).

8.4.3.1.1 Analysis of Extent of Exposure

For more details see [section 8.4.2.1.1 Analysis of Extent of Exposure](#).

8.4.3.1.2 Analysis of Solicited Local, Systemic and Other Adverse Events

For more details see [Section 8.4.2.1.2 Analysis of Solicited Local, Systemic and Other Adverse Events](#).

8.4.3.1.3 Analysis of Unsolicited Adverse Events

For more details see [8.4.2.1.3 Analysis of unsolicited adverse events](#).

8.4.3.1.4 Statistical Hypotheses

For more details see [section 8.4.2.2.1, Statistical Hypotheses](#).

8.4.3.1.5 Analysis Sets

For more details see [section 8.3, Analysis Sets](#).

8.4.3.1.6 Statistical Methods

For more details see [section 8.4.2.2.3, Statistical Methods](#).

8.4.3.2 Analysis of Secondary Efficacy Objective(s)

The study has no efficacy objective.

8.4.3.2.1 Statistical

Hypotheses Not applicable.

8.4.3.2.2 Analysis Sets Not

applicable.

8.4.3.2.3 Statistical Methods

Not applicable.

8.4.3.3 Analysis of Secondary Immunogenicity Objective(s)

8.4.3.3.1 Statistical Hypotheses

Not applicable.

8.4.3.3.2 Analysis Sets

For more details see [section 8.3, Analysis Sets](#).

8.4.3.3.3 Statistical Methods

For more details see [section 8.4.2.2.3, Statistical Methods](#).

8.4.4 Analysis of Exploratory Objectives

8.4.4.1 Analysis of Exploratory Safety Objective(s)

Not applicable.

8.4.4.2 Analysis of Exploratory Efficacy Objective(s)

Not applicable.

8.4.4.3 Analysis of Exploratory Immunogenicity Objective(s)

Other assays, including serum secretory IgA, might be done to further characterize the immune response to the study vaccine. The analysis will be described in the statistical analysis plan.

8.5 Sample Size and Power Considerations of Primary and Secondary Objectives

No formal statistical sample size and power computations are performed since the objectives of the study are to descriptively assess the immunogenicity and safety of the investigational vaccine.

8.6 Interim Analysis

No interim analysis of data from this study is planned.

9. SOURCE DOCUMENTATION, STUDY MONITORING AND AUDITING

Monitoring and auditing will be standardized and performed in accordance with GSK's or delegated contract research organization's (CRO) standard operating procedures and applicable regulatory requirements (e.g., FDA, EMA, and ICH guidelines).

Prior to enrolment of the first study subject, GSK or delegate will train investigators and/or their study staff on the study protocol, all applicable study procedures, documentation practices and all electronic systems. CRFs supplied by the Sponsor must be completed for each enrolled subject (see [section 8.3.1, All Enrolled Set](#) for definition of enrolled subject). For subjects not enrolled, information will be stored in source documents only. Documentation of screened but not enrolled subjects must be maintained at the site and made available for review by the site monitor. Data and documents will be checked by the Sponsor and/or monitor.

9.1 Source Documentation

Prior to the start of the study, the site staff participating in the study conduct will be instructed on what documents will be required for review as source documents. The kinds of documents that will serve as source documents will be agreed between Sponsor or delegate and investigator and designees and specified in the SDAF prior to subject enrolment.

In addition, source documentation **must** include all of the following: subject identification (on each page), eligibility and participation, proper informed consent procedures, dates of visits, adherence to protocol procedures, adequate reporting and follow-up of adverse

events, documentation of prior/concomitant medication/vaccines, study vaccine receipt/dispensing/return records, study vaccine administration information, any data collected by a telephone conversation with the subject and date of completion and reason.

The subject must also allow access to the subject's medical records. Each subject must be informed of this prior to the start of the study and consent for access to medical records may be required in accordance with local regulations.

All safety data reported by subjects must be written down in source documents prior to entry of the data into CRFs. If there are multiple sources of information (e.g., Subject Diary, verbal report of the subject, telephone contact details, medical chart) supporting the diagnosis of an adverse event, these sources must be identified in the source documents, discrepancies between sources clarified, the ultimate diagnosis must be justified and written in the source documents, and this diagnosis must be captured in the Adverse Event CRF (AE CRF).

9.2 Study Monitoring, Auditing and Source Data Verification

Prior to enrolment of the first study subject, the Sponsor or its designee (e.g., a CRO) will develop a Clinical Monitoring Plan to specify how centralized and/or on-site monitoring, including clinical specimens reconciliation, will be performed for the study. Study progress will be monitored by the Sponsor or its designee as frequently as necessary to ensure:

- That the rights and well-being of human subjects are protected,
- The reported study data are accurate, complete, and verifiable from the source documents and
- The conduct of the study is in compliance with the current approved protocol/amendment(s), GCP and applicable regulatory requirements.

Contact details for the Sponsor team or its designee involved in study monitoring will be provided to the investigator. Study data recorded on CRFs will be verified by checking the CRF entries against source documents in order to ensure data completeness and accuracy as required by study protocol except for those parameters which are specifically described in [section 7, Assessment](#) being entered directly into the EDC system.

Data verification may also be performed through a centralized review of data (e.g., checking for outliers or other anomalies). Additional documents such as the investigator site file, pharmacy records, and informed consent documentation must also be available for review if requested. Arrangements for monitoring visits will be made in advance in accordance with the monitoring plan, except in case of emergency.

The investigator and/or site staff must make source documents of subjects enrolled in this study available for inspection by GSK Bio or its representative at the time of each monitoring visit and Sponsor audits, when applicable. These documents must also be available for inspection, verification and copying, as required by regulations, by officials

of the regulatory health authorities (e.g., FDA, EMA and others) and/or ECs/IRBs. The investigator and study site staff must comply with applicable privacy, data protection and medical confidentiality laws for use and disclosure of information related to the study and enrolled subjects.

10. DATA MANAGEMENT

10.1 Data Entry and Management

In this study, all clinical data (including, but not limited to, AE/SAEs, concomitant medications, medical history, and physical assessments), safety data will be entered onto case report forms (CRFs) in a timely fashion by the investigator and/or the investigator's dedicated site staff. Data entered onto CRFs are stored on a secure website. The data collected on this secure website are assimilated into an electronic data capture (EDC) system, which is compliant with Title 21 Part 11 policies of the Code of Federal Regulations (FDA 1997). The data system includes password protection and internal quality checks. The EDC system will be designed and validated by the Sponsor prior to activation for data entry by sites. The investigator or designated delegate must review data entered and electronically sign the CRFs to verify their accuracy.

Access to the EDC system for data entry or review will require training and distinct individual access code assignments to those site staff members who will be entering study data and those involved in study oversight who may review study data. Data are collected within the EDC system, to which the Sponsor and site monitors have exclusively "read only" access.

10.2 Data Clarification

As part of the conduct of the trial, the Sponsor may have questions about the data entered by the site, referred to as queries. The monitors, the Sponsor and delegated DM are the only parties that can generate a query. All corrections and clarifications will be entered into the EDC system and will be identified by the person entering the information, the reason for the change, as well as the time of the changes made. If changes are made to a previously and electronically signed CRF, the investigator must confirm and endorse the changes.

10.3 Data Protection

The Sponsor respect the subjects' rights to privacy and will ensure the confidentiality of their medical information in accordance with all applicable laws and regulations.

The Sponsor as Data Controller according to the European Directive on the protection of individuals with regard to the processing of personal data and on the free movement of such data (95/46/EC) confirms herewith compliance to Directive 95/46/EC in all stages of Data Management.

11. RECORD RETENTION

Following closure of the study, the investigator must maintain all site study records (except for those required by local regulations to be maintained elsewhere) in a safe and secure location. The records must be easily accessible, when needed (e.g. audit or inspection), and must be available for review in conjunction with assessment of the facility, supporting systems, and staff. Where permitted by applicable laws/regulations or institutional policy, some or all of these records can be maintained in a validated format other than hard copy (e.g. microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken. The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure that an acceptable back-up of the reproductions exists and that there is an acceptable quality control procedure in place for making these reproductions.

The Sponsor will inform the investigator/institution of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to a particular site, as dictated by ICH GCP, any institutional requirements, applicable laws or regulations, or GSK standards/procedures, otherwise, the minimum retention period will default to 25 years after completion of the study report.

The investigator/institution must notify the Sponsor of any changes in the archival arrangements, including, but not limited to archival at an off-site facility, transfer of ownership of the records in the event the investigator leaves the site. The principles for the storage of laboratory samples are provided below:

Collected samples will be stored for a maximum of 20 years (counting from when the last subject performed the last study visit), unless local rules, regulations or guidelines require different timeframes or different procedures, which will then be in line with the subject consent. These extra requirements need to be communicated formally to and discussed and agreed with the Sponsor.

12. USE OF INFORMATION AND PUBLICATION

GSK assures that key results of this clinical study will be posted in a publicly accessible database within the required time-frame from the end of study as defined in [section 3.9, End of Study](#).

In accordance with standard editorial, ethical practices and current guidelines of Good Publication Practice ([Graf 2009](#)), GSK will generally support publication of multicenter studies only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement prior to the start of the study. The coordinating investigator will also sign the clinical study report on behalf of the principal investigators ([CPMP/EWP/2747/00](#)). Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship

requirements. Any formal publication of the study in which contribution of GSK personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate GSK personnel.

The Sponsor must be notified of any intent to publish data collected from the study and prior approval from the Sponsor must be obtained prior to submission for publication.

13. ETHICAL CONSIDERATIONS

13.1 Regulatory and Ethical Compliance

The study will be conducted in compliance with the protocol, GCP and applicable regulatory requirement(s).

This clinical study was designed and shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations including [European Directive 2001/20/EC](#), GSK codes on protection of human rights, and with the ethical principles laid down in the Declaration of Helsinki ([European Council 2001](#), [US Code of Federal Regulations](#), [ICH 1997](#)).

The Sponsor will have an account for the trial in the French national database (VRB – Volontaires pour la Recherche Biomédicale) where investigator will register each volunteer at the day of enrollment.

After the end of the study, each subject will receive a monetary compensation for a total of 530 euros to cover for the time spent and any inconvenience due to the study participation. This indemnification will be proportional to the number of visits completed as follows:

- 50 euros: screening visit
- 120 euros: vaccination visit
- 90 euros: follow up visit

13.2 Informed Consent Procedures

Eligible subjects may only be included in the study after providing written informed consent, as described in [section 5.1.1, Informed Consent/Assent](#). Before the start of the study, the investigator will have the informed consent and any other materials that will be provided to the subjects reviewed and approved by the IRB/EC. This review and approval will be documented and stored with other study documents. The investigator or designee must fully inform the subject of all pertinent aspects of the study. A copy of the written informed consent will be given to the subject. The subject must be allowed ample time to ask about the details of the study and to make a decision as to whether or not to participate in the study. The subject **must** sign the consent form indicating their agreement to participate in the study before any study-related procedures are conducted. The informed consent process may be conducted up to 21 days prior to vaccination on day 1. If the subject is unable to read and write, a witness must be present during the informed consent discussion and at the time of informed consent signature.

Prior to the start of the study, the Sponsor will provide to investigators a proposed informed consent form that complies with the ICH GCP guideline and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form

suggested by the investigator must be agreed to by the Sponsor before submission to the IRB/EC and a copy of the approved version must be provided to the Sponsor monitor after IRB/EC approval.

Women of childbearing potential should be informed that taking the study medication may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirements indicated in the protocol for the duration of the study. If case of doubts on the ability of a subject to adhere to these requirements, that subject should not be allowed in the study

13.3 Responsibilities of the Investigator and IRB/EC

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted IRB/EC before study start. Properly constituted IRB/EC is defined in ICH Guideline for Good Clinical Practice E6 (R1), Section 3 ([ICH 1997](#)). A signed and dated statement that the protocol and informed consent have been approved by the IRB/EC must be given to GSK before study initiation. Prior to study start and at any time the protocol is amended during study conduct, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to GSK monitors, auditors, GSK Clinical Quality Assurance representatives, designated agents of GSK, IRBs/ECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform GSK immediately that this request has been made. The investigator also responsible for the following:

- Maintaining a list of appropriately qualified persons to whom the investigator has delegated significant study-related duties
- Demonstrating the capability of recruiting the required number of suitable subjects within the recruitment period
- Demonstrating sufficient time and staffing to properly conduct and complete the study within the agreed study period
- Ensuring that all persons assisting with the study are adequately informed about the protocol, the investigational product(s), and their study-related duties and functions
- Ensuring that appropriately trained health care professionals are responsible for all study-related medical decisions and for ensuring appropriate medical care of subjects experiencing any adverse event related to the study
- If permission to do so is given by the subject, ensuring that the subject's primary healthcare provider is informed of the subject's participation in the study.

The investigator should not implement any deviation from, or changes of the protocol without agreement by the Sponsor and prior review and documented approval/favourable

opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to study subjects, or when the change(s) involves only logistical or administrative aspects of the study (e.g., change in monitor(s), change of telephone number(s)). In addition, the investigator, or person designated by the investigator, should document and explain any deviation from the approved protocol.

The investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to study subjects without prior IRB/IEC approval/favourable opinion. As soon as possible, the implemented deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendment(s) should be submitted:

- (a) To the IRB/IEC for review and approval/favourable opinion,
- (b) To GSK for agreement and, if required,
- (c) To the regulatory authority(ies).

13.4 Protocol Amendments

An amendment is a written description of change(s) to or formal clarification of a study protocol which may impact on the conduct of the clinical study, potential benefit of the clinical study, or may affect subject safety, including changes of study objectives, study design, subject population, sample sizes, study procedures, or significant administrative aspects. An administrative change of a study protocol is a minor correction or clarification that has no significant impact on the way the clinical study is to be conducted and no effect on subject safety (e.g., change of telephone number(s), logistical changes). Protocol amendments must be approved by the Sponsor, health authorities where required, and the IRB/EC. In cases when the amendment is required in order to protect the subject safety, the amendment can be implemented prior to IRB/EC approval. Notwithstanding, the need for formal approval of a protocol amendment, the investigator is expected to take any immediate action required for the safety of any subject included in this study, even if this action represents a deviation from the protocol. In such cases, the Sponsor should be notified of this action, the IRB/EC at the study site, and, if required by local regulations, the relevant health authority) should be informed within 10 working days.

14. REFERENCE LIST

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Appendix 1: Investigator Agreement

I agree:

- To conduct the study in compliance with this protocol, any future protocol amendments or protocol administrative changes, with the terms of the clinical trial agreement and with any other study conduct procedures and/or study conduct documents provided by GSK.
- To assume responsibility for the proper conduct of the study at this site.
- That I am aware of, and will comply with, 'Good Clinical Practice' (GCP) and all applicable regulatory requirements.
- To ensure that all persons assisting me with the study are adequately informed about the GSK study vaccine(s)/product(s) and other study-related duties and functions as described in the protocol.
- To acquire the reference ranges for laboratory tests performed locally and, if required by local regulations, obtain the laboratory's current certification or Quality Assurance procedure manual.
- To ensure that no clinical samples (including serum samples) are retained onsite or elsewhere without the approval of GSK and the express written informed consent of the subject and/or the subject's legally acceptable representative.
- To perform no other biological assays on the clinical samples except those described in the protocol or its amendment(s).
- To co-operate with a representative of GSK in the monitoring process of the study and in resolution of queries about the data.
- That I have been informed that certain regulatory authorities require the sponsor to obtain and supply, as necessary, details about the investigator's ownership interest in the sponsor or the investigational vaccine(s)/product(s), and more generally about his/her financial ties with the sponsor. GSK Biologicals 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 course of the study and for one year following completion of the study.
- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.

- Agree to provide GSK with an updated Curriculum Vitae and other documents required by regulatory agencies for this study.

eTrack study number and Abbreviated Title 205905 (S SONNEI MONO GMMA SBVGH-005
EXT: 001 SUPP (H03_01E1TP))

EudraCT number 2016-004178-16

Date of protocol Version 2: 08 February 2017

Detailed Title A Phase 1, open label, non-randomized, single center study to evaluate the safety and immunogenicity of 1 booster vaccination with GVGH *Shigella sonnei* 1790GAHB vaccine administered intramuscularly in healthy adults previously primed with three doses of the same vaccine in study H03_01TP compared to 1 vaccination with 1790GAHB administered intramuscularly either to subjects who received placebo in the H03_01TP study or naïve subjects who were not part of H03_01TP study.

Investigator name

PPD

Signature

PPD

Date

16 FEB 20

PPD



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Protocol Amendment Summary Form

#:	H03_01E1TP
Protocol Version # and date:	Version 1 of 12 October 2016
Protocol Title:	A Phase 1, open label, non-randomized, single center study to evaluate the safety and immunogenicity of 1 booster vaccination with GVGH <i>Shigella sonnei</i> 1790GAHB vaccine administered intramuscularly in healthy adults previously primed with three doses of the same vaccine in study H03_01TP compared to 1 vaccination with 1790GAHB administered intramuscularly either to subjects who received placebo in the H03_01TP study or naïve subjects who were not part of H03_01TP study
Amendment # and date:	Amendment #1 of 06 February 2017
Amended Protocol # and date:	Protocol v2.0 of 08 February 2017
Protocol Amendment Summary Form	Pietro Ferruzzi
Author:	[REDACTED]
Type of amendment:	<input checked="" type="checkbox"/> Non-substantial <input type="checkbox"/> Substantial
Regulatory Affairs signature:	[REDACTED]

Revisions required?

Report Form	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No	<input type="checkbox"/> Not Applicable
Informed Consent Form	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No	<input type="checkbox"/> Not Applicable
Statistical Analysis Plan	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No	<input type="checkbox"/> Not Applicable
Investigator Manual	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No	<input type="checkbox"/> Not Applicable
Other (specify):	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No	<input type="checkbox"/> Not Applicable

Amendment Rationale:

February 2017 we received the Authorization for study H03_01E1TP from the Ethical Committee (CPP EST 1) and from the Regulatory Authority (ANSM). However, we received few comments/requests for clarification from the ANSM on study protocol as follows:



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Request to specify that the study volunteer should contact the study doctor in case of fever in the study protocol, paragraph 5.2.1.

Purpose of H03_01E1TP protocol amendment #1 of 06FEB2017 is to correct the inconsistency found between exclusion criteria #10 and to add the sentence "The site staff/doctor should instruct the subject to contact the study doctor immediately in case of fever" as requested by ANSM.

Minor corrections have been implemented in protocol amendment #1 (see section proposed changes).

Proposed Changes:

SECTION Page and numbers changed	CURRENT Language currently in use in protocol	PROPOSED CHANGE Language proposed	JUSTIFICATION State specific reason for the change or refer to rationale
	12 OCT 16 Version 1	08 FEB 17 Version 2	Date and Version number aligned to the document
Page, page 1	Version 1	Amendment 1 of 06 February 2017 Version 2	Added Amendment 1 and date in the cover page and updated the version number
Protocol synopsis,	PROTOCOL SYNOPSIS [H03_01E1TP, Version 1]	PROTOCOL SYNOPSIS [H03_01E1TP, Version 2]	Version Number aligned to the document
Protocol synopsis, "procedure section of Adverse Events"	will be collected and recorded at V2, V3 and V4 by clinical study staff in the in the subject's source document.	will be collected and recorded at V2, V3 and V4 by clinical study staff in the subject's source document.	"in the" repeated twice in error
Page 17, 18 Header.	0 to -1	0 to +1	Clinic Visit 2 has to be performed 7-8 days



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Abbreviations, page	N/A	EoS End of Study	Added in the List of Abbreviations
3.1, Page 28	refer to Section 3.8 Procedures Related to Neutropenia	refer to Section 5.4 Unscheduled Visits	Inserted reference to the correct section
“Blood for biological samples”, page 31, visit 4” column /Sub-cohort	TBD	N/A	“TBD” has been deleted because all subjects giving their consent accept to donate additional serum for the standard creation
“Blood for biological samples”, page 31, visit 4” column subjects”	TBD	50	All the subjects giving their consent accept to donate additional serum for the standard creation.
3.6, page 32	There are no predetermined stopping rules in this study. Subjects may be withdrawn from the study according to investigator discretion as described in section 3.8, Premature Withdrawal from Study.	N/A	Sentence deleted as repeated twice in error
3.8, Premature withdrawal from the study, Protocol Amendment, page 34	GVGH	GSK	GSK is the study sponsor
4.2, page 37	15. Individuals who have received blood, blood products, and/or plasma derivatives	15. Individuals who have received blood, blood products, and/or plasma derivatives including	Exclusion criteria #15 has been modified



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			Exclusion criterion #10.
5.2.1, "Post ation ures", page	The collection of unsolicited adverse events and medications will continue after the 7 days on the Diary Card.	Unsolicited adverse events and medications will be collected by the site staff on the source document at the next planned visit based on subject's interview or when reported by the subject to the site staff by phone/unplanned visits.	Unsolicited AEs are not recorded by the subject in the diary card but they are collected by the study staff only in the source documents based on subject's interview.
5.2.1, "Post ation ures", page ore last ph	N/A	The site staff/doctor should instruct the subject to contact the study doctor immediately in case of fever.	Added as requested by ANSM
5.2.2, ct Diary der Calls / page 43	the subject should be reminded to write the information down in the diary card.	the subject should be reminded to write the information down in the diary card, as applicable.	Only solicited local and systemic AE should be recorded in the Subject Diary.
6.1 "Study e(s); page 47	GAHB-Diluent	GAHB-Placebo	The name of the diluent is GAHB-Placebo.
8.4.2.1.4 is of Safety tory Values, 8	Clinically significant modifications in blood chemistry, hematology, and urinalysis test values will be assessed by medical judgment based on interpretation of deviations from the institution's normal values.	Clinically significant modifications in hematology test values will be assessed by medical judgment based on interpretation of deviations from the institution's normal values.	Blood chemistry analysis and urinalysis not performed in this study
13.3, nsibilities of	GVGH	GSK	Sponsor is GSK



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ent, page 83			twice.
lix 1, gator ent, page 83	Version 1: 12 October 2016	Version 2: 08 February 2017	Version number and date aligned to the document