Clinical Study Protocol

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

Primary study intervention and number	*Porcine circovirus* (PCV)-free liquid formulation of GlaxoSmithKline Biologicals SA (GSK) oral live attenuated human rotavirus (HRV) vaccine (444563)
Other study intervention	GSK's liquid oral live attenuated HRV vaccine (*Rotarix*)
eTrack study number and abbreviated title	212692 (ROTA-097)
EudraCT number	2020-000972-38
Date of protocol	Final: 13 May 2022
Date of protocol amendment	Amendment 1 Final: 18 Dec 2023
Title	A Phase III, observer-blind, randomized, multicenter study to evaluate immunogenicity, reactogenicity and safety of GlaxoSmithKline (GSK) Biologicals' *Rotarix Porcine circovirus* (PCV)-free liquid as compared to GSK's *Rotarix* liquid, given in 2-doses in healthy Chinese infants starting at age 6-16 weeks.
Brief title	Immunogenicity, reactogenicity and safety of GlaxoSmithKline (GSK) Biologicals' *Rotarix Porcine circovirus* (PCV)-free liquid compared to *Rotarix* liquid given in 2-doses in healthy Chinese infants starting at age 6-16 weeks.

Based on GSK Biologicals' Protocol WS v17.0

Protocol Amendment 1 Sponsor Signatory Approval

eTrack study number and Abbreviated Title	212692 (ROTA-097)
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Sponsor signatory	Md Ahsan Habib, Clinical and Epidemiology Project Lead, Live viral vaccines
Signature	_____
Date	_____

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

Protocol Amendment 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 Biologicals SA.
- To assume responsibility for the proper conduct of the study at this site.
- That I am aware of, and will comply with, 'Good Clinical Practice' (GCP) and all applicable regulatory requirements.
- That I will comply with the terms of the site agreement.
- To comply with local bio-safety legislation.
- To ensure that all persons assisting me with the study are adequately informed about the GSK study interventions and other study-related duties and functions as described in the protocol.
- To supervise any individual or party to whom I have delegated trial-related duties and functions conducted at the trial site.
- To ensure that any individual or party to whom I have delegated trial-related duties and functions conducted at the trial site are qualified to perform those trial-related duties and functions.
- To acquire the reference ranges for laboratory tests performed locally and, if required by local regulations, obtain the laboratory's current certification or Quality Assurance procedure manual.
- To ensure that no clinical samples (including serum samples) are retained onsite or elsewhere without the approval of GSK and the express written informed consent of the participant and/or the participant's legally acceptable representative (LAR).
- To perform no biological assays on the clinical samples other than those described in the protocol or its amendment(s).
- To co-operate with representatives of GSK in the monitoring process of the study and in resolution of queries about the data.
- To have control of all essential documents and records generated under my responsibility before, during, and after the trial.
- That I have been informed that certain regulatory authorities require the sponsor to obtain and supply, as necessary, details about the investigator's ownership interest in the sponsor or the investigational interventions, and more generally about their financial ties with the sponsor. GSK will use and disclose the information solely for the purpose of complying with regulatory requirements.

Hence, I:

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

eTrack study number and Abbreviated Title	212692 (ROTA-097)
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Investigator name	_____
Signature	_____
Date	_____

SPONSOR INFORMATION

1. Sponsor

GlaxoSmithKline Biologicals SA
Rue de l'Institut, 89
1330 Rixensart
Belgium

2. Sponsor Medical Expert for the Study

Refer to the local study contact information document.

3. Sponsor Study Monitor

Refer to the local study contact information document.

4. Sponsor Study Contact for Reporting of a Serious Adverse Event

GSK Central Back-up Study Contact for Reporting SAEs: refer to the protocol section 8.3.3.1.

Study Contact for Reporting SAEs: refer to the local study contact information document.

5. GSK Biologicals' Helpdesk for Emergency Unblinding

Refer to the protocol section 6.3.4.1.

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date of Issue**
Amendment 1	18 Dec 2023
Original Protocol	13 May 2022

Amendment 1 (18 Dec 2023)

Overall rationale for the current Amendment: The protocol is being amended in order to align with the requirements of the corresponding CDMS version 21 R2 being used. The original protocol became effective on 13 May 2022, while the new protocol template came into effect on 26 October 2022. The CDMS has no "reviewed" box to tick, in line with the new protocol template. Therefore, the following statement is not required in this protocol: "The investigator will be required to confirm the review of the SAE causality by ticking the 'reviewed' box in the electronic Expedited Adverse Events Report within 72 hours of submission of the SAE".

List of main changes in the protocol and their rationale:

Section # and title	Description of change	Brief rationale
Section 10.3.8.1: Events requiring expedited reporting to GSK	Deletion of the text "The investigator will be required to confirm the review of the SAE causality by ticking the 'reviewed' box in the electronic Expedited Adverse Events Report within 72 hours of submission of the SAE."	To align with the requirements of the corresponding CDMS version 21 R2 being used. This CDMS version is based on the current protocol template (effective 26 Oct 2022) and therefore, it does not have a "reviewed" box to tick.

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1. PROTOCOL SUMMARY

1.1. Synopsis

Rationale:

Study ROTA-097 is designed to support licensure of the *Rotarix Porcine circovirus* (PCV)-free (no detection of PCV-1 and PCV-2 according to the limit of detection of the tests used) liquid vaccine in China. The objective of study ROTA-097 is to evaluate, in the Chinese population, the immunogenicity, reactogenicity and safety of GSK's *Rotarix* PCV-free liquid, compared to *Rotarix* liquid, for which vaccine efficacy was demonstrated in the ROTA-075 study conducted in China.

Objectives and Endpoints: See Table 3 Study objectives and endpoints from Section 3.

1.2. Schema

See Figure 1 from Section 4.1.

1.3. Schedule of Activities (SoA)

Table 1 Schedule of Activities

Age at enrolment	6-16 weeks				Notes
Type of contact	Visit 1	Visit 2	Visit 3	Extended Safety Follow-up	
Time points	Day 1	Month 1	Month 2	Month 7	
Informed consent by parent(s)/LAR(s)	●				See Section 10.1.3 for details
Check inclusion/exclusion criteria	●				Recheck clinical status before randomization and/or 1st dose of study intervention. See Sections 5.1 and 5.2 for Inclusion and Exclusion criteria
Collect demographic data including gestational age	●				See Section 8.2.1 for more information
Medical and vaccination history	●				See Section 8.2.1.2 for more information
Physical examination	●				See Section 8.2.1.3 for more information
Measure/record height and weight	●				See Section 8.2.1.3 for more information
Study intervention					
Check contraindications to study intervention administration	●	●			See Section 7.1.2 for more information
Randomization	●				See Section 6.3 for more information
Allocation of treatment number for subsequent dose		●			See Section 6.3.3 for more information
Check criteria for temporary delay for enrolment and study intervention administration	○	○			See Section 7.1.1 for more information
Study group and intervention number allocation	○				See Sections 6.3.2 and 6.3.3 for more information
Body temperature before study intervention administration	●	●			See Section 8.2.1.3 for more information. The preferred route for measuring temperature will be axillary. Fever is defined as temperature ≥ 37.5°C
Administration of study intervention	●	●			See Section 6.1 for more information
Recording of administered intervention number	●	●			
Recording of regurgitation/vomiting	●	●			

Age at enrolment	6-16 weeks				Notes
Type of contact	**Visit 1**	**Visit 2**	**Visit 3**	**Extended Safety Follow-up**	
Time points	**Day 1**	**Month 1**	**Month 2**	**Month 7**	
Replacement of study intervention administration in case of regurgitation/vomiting	●	●			If regurgitation or vomiting, which may impair the study intervention take, occurs within 30 minutes after study intervention administration, a single replacement dose may be given at the same study intervention administration visit at the discretion of the investigator. This information should be recorded in the eCRF. The participant should continue to participate in the study.
Distribution of diary cards	○	○			
Laboratory Assessment					
Blood sampling for antibody determination (~2 mL)	●		●		Blood sampling to be done before study intervention (Rotarix and Rotarix PCV-free) administration. See Section 8.1.1 for more information
Safety assessments					
Recording of any concomitant medications/vaccinations	●	●	●		See Section 6.5 for more information
Recording of solicited events after each dose of study intervention (Days 1-14*)	●	●			See Sections 10.3.3 and 10.3.6 for more information
Recording of unsolicited AEs after each dose of study intervention (Days 1-31)	●	●			See Sections 10.3.4 and 10.3.6 for more information
Recording of AEs/SAEs leading to withdrawal from study	●	●	●	●	See Section 10.3.6 for more information
Recording of SAEs	●	●	●	●	See Section 10.3.6 for more information
Return of diary cards		○	○		
Diary card transcription by investigator or designee		●	●		
Recording of SAEs related to study participation, or to a concurrent GSK medication/vaccine	●	●	●	●	See Section 10.3.6 for more information
Contact for safety follow-up				●	A safety follow-up contact will be done by a telephone call or any other convenient procedure to collect information on SAEs and medication taken for treatment of SAEs

Age at enrolment	6-16 weeks				Notes
Type of contact	Visit 1	Visit 2	Visit 3	Extended Safety Follow-up	
Time points	Day 1	Month 1	Month 2	Month 7	
Analysis on data collected up to Visit 3			○		See Section 9.5.1 for more information
Study Conclusion				●	See Section 4.4 for more information

LAR = Legally Acceptable Representative; AE = Adverse Event; SAE = Serious Adverse Event; mL= milliliter.
● is used to indicate a study procedure that requires documentation in the individual eCRF
○ is used to indicate a study procedure that does not require documentation in the individual eCRF.
Notes: All participants are allowed to receive routine childhood vaccinations according to the local immunization practice.
The double-line border following Visit 3 indicates the analyses which will be performed on all data (i.e., data that are as clean as possible) obtained up to Visit 3.
*Number of days for recording of solicited events after each dose of study intervention is defined by Chinese authorities [NMPA, 2019a].

Table 2 Intervals between study visits

Interval	Optimal length of interval[1]	Allowed interval
Visit 1→Visit 2	30-48 days	28-48† days after Dose 1
Visit 2→Visit 3	30-48 days	28-48† days after Dose 2
Visit 2→ESFU contact‡	6 months	180-210 days after Dose 2

[1] Whenever possible the investigator should arrange study visits within this interval.
† Participants will not be eligible for inclusion in the Per-Protocol Set for immunogenicity if they make the study visit outside this interval.
‡An extended safety follow-up (ESFU) contact (by telephone call or any other convenient procedure) to collect information on serious adverse events and medication taken for treatment of the same.

2. INTRODUCTION

2.1. Study rationale

Study ROTA-097 is designed to support licensure of the *Rotarix* PCV-free (no detection of PCV-1 and PCV-2 according to the limit of detection of the tests used) liquid vaccine (hereafter referred as *Rotarix* PCV-free) in China. The objective of the study is to evaluate, in the Chinese population the immunogenicity, reactogenicity and safety of GSK's *Rotarix* PCV-free, compared to *Rotarix* liquid (hereafter referred as *Rotarix*), for which vaccine efficacy was demonstrated in the ROTA-075 study conducted in China.

In 2010, PCV-1 deoxyribonucleic acid fragments were identified in *Rotarix* and in its starting materials, as well as low levels of PCV-1 viral particles during production process and in the final container [Dubin, 2013]. PCV-1 is not known to cause disease in either animals or humans [Hattermann, 2004a; Hattermann, 2004b] and there is no evidence that the presence of PCV-1 in *Rotarix* poses a safety risk to vaccinated participants. The presence of PCV-1 in *Rotarix* is, therefore, a manufacturing quality issue [Dubin, 2013; Han, 2017]. GSK has replaced the cell bank and virus seeds used as the base production material for *Rotarix*.

To support worldwide licensure of *Rotarix* PCV-free, GSK conducted the global clinical study ROTA-081. The study demonstrated lot-to-lot consistency of 3 production lots of the *Rotarix* PCV-free and its non-inferiority compared to *Rotarix* lyophilized in terms of immunogenicity. No safety concerns were raised, and the study showed that *Rotarix* PCV-free and *Rotarix* lyophilized have a similar reactogenicity and safety profile. The European Medicines Agency (EMA) approved the use of new cell banks and virus seeds to render *Rotarix* PCV-free based on a comparability package that included the results of study ROTA-081 on 13 February 2020.

Rotarix showed high vaccine efficacy against severe rotavirus gastroenteritis (RVGE) and an acceptable safety profile in several global efficacy studies and in the efficacy study ROTA-075 conducted in China [Li, 2013; Li, 2014; Li, 2016]. The current study is conducted to evaluate, in the Chinese population, the immunogenicity, reactogenicity and safety of GSK's *Rotarix* PCV-free compared to *Rotarix*.

Though no recognized immunological correlate of protection (CoP) has been established for human rotavirus (HRV) vaccines, anti-rotavirus (RV) serum immunoglobulin A (IgA)

antibody (Ab) concentration is considered as the best correlate of efficacy [Velazquez, 2000; Franco, 2006; Patel, 2013; Cheuvart, 2014; Baker, 2020]. Analyses on GSK sponsored efficacy studies conducted by GSK [Cheuvart, 2014] and by independent research groups [Baker, 2020] showed that a post-vaccination anti-RV IgA antibody concentration of ≥ 20 U/mL measured by the GSK anti-RV IgA Enzyme linked Immunosorbent Assay (ELISA) is a correlate of efficacy against RVGE for *Rotarix* clinical trials. The analysis conducted by Baker et al, 2020 included the Phase III efficacy study ROTA-075 conducted in China [Baker, 2020].

2.2. Background

RV infects almost every child before they reach the age of 3 to 5 years and is the leading cause of acute gastroenteritis (GE) and diarrhea, which can lead to severe dehydration [Atherly, 2009]. Prior to the introduction of RV vaccines in 2006, RV was accountable for an estimated 528 000 deaths worldwide annually, with the largest number of deaths occurring in the Sub-Saharan Africa region [WHO position paper, 2013; Tate, 2016; Bányai, 2018]. In 2013, several years after the launch of RV vaccines, it has been estimated that approximately 215 000 deaths (95% confidence interval [CI]: 197 000, 233 000) were caused by RV infection. India, Nigeria, Pakistan, and Democratic Republic of Congo accounted for approximately half (49%) of all the estimated RV deaths in 2013 [Dennehy, 2008; Tate, 2016]. In China, 42.6% of all the hospitalizations for severe GE, 32.5% of outpatient visits for diarrhea and 9.3% of all diarrhea episodes in community settings are caused by RV [Fu, 2018].

The World Health Organization (WHO) recognizes RV vaccination as an effective measure to prevent RV infection and to reduce disease burden, and recommends its inclusion into all national infant immunization programs, particularly in countries where RVGE-associated fatality rates are high among children aged <5 years (e.g., south and south-eastern Asia and sub Saharan Africa) [WHO position paper, 2013].

GSK HRV vaccine (Rotarix) is registered in around 130 countries worldwide and the Rotarix liquid formulation is pre-qualified by WHO. More than 716 million doses of the vaccine (lyophilized and liquid formulations) are estimated to have been distributed worldwide from its launch until July 2021.

Please refer to the current investigator's brochure (IB) for information regarding the pre-clinical and clinical studies and the epidemiological information of *Rotarix* and *Rotarix* PCV-free vaccines.

2.3. Benefit/Risk assessment

Detailed information about the known and expected benefits and risks and expected adverse events (AEs) of *Rotarix* and *Rotarix* PCV-free can be found in the current IB.

2.3.1. Risk Assessment

Participants will be observed for at least 30 minutes after study intervention administration, with medical attention available in case of anaphylaxis.

In addition to risks related to the study intervention, there may be risks related to the blood sampling planned in the study:

- Pain and bruising may occur at the site where blood is drawn; as a mitigation strategy, a topical analgesic may be applied to the site where blood will be taken.

For details of study procedures, refer to Section 1.3.

2.3.2. Benefit Assessment

By receiving the HRV vaccines the participants may have the benefit of being protected against RV disease. In addition, the participants will undergo a physical examination at the first study visit. In case the study doctor discovers any medical condition, the participant will be referred to the local healthcare system.

2.3.3. Overall Benefit/Risk Conclusion

Taking into account the measures taken to minimize the risk for participants taking part in this study, the potential or identified risks in association with live attenuated human (RIX4414 strain) RV vaccine are justified by the potential benefits (prevention/treatment) that may be afforded to participants receiving the study intervention for the prevention of GE due to RV infection.

3. OBJECTIVES AND ENDPOINTS

Table 3 Study objectives and endpoints

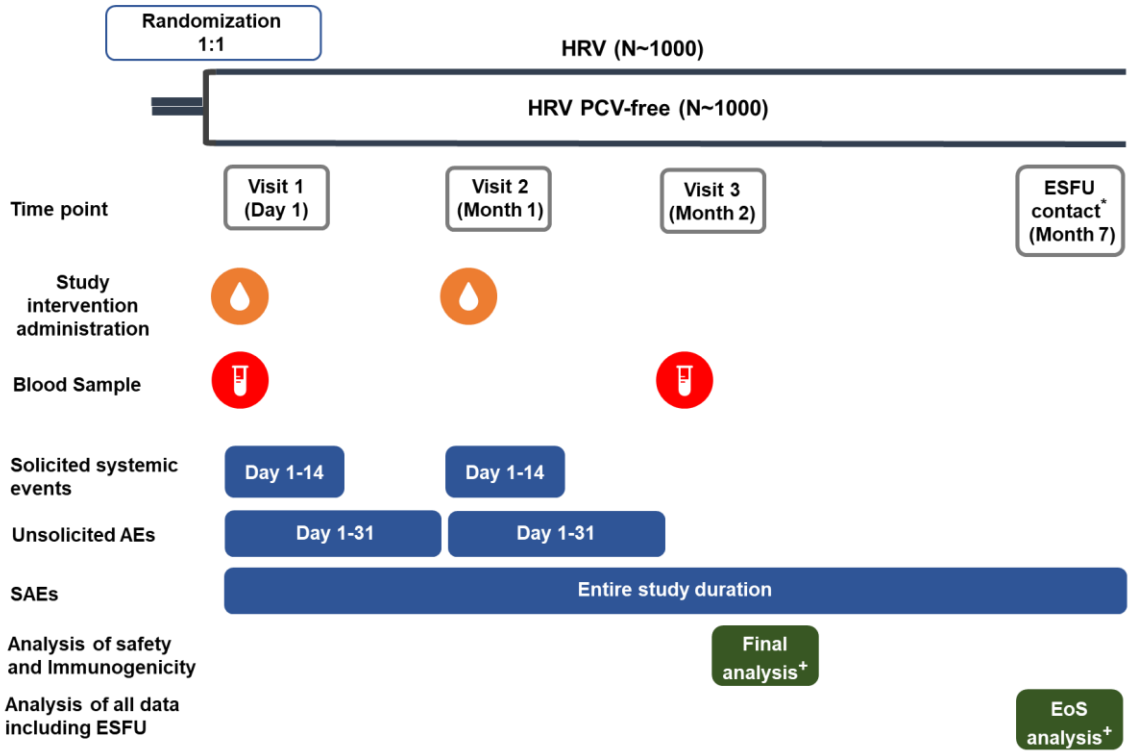
Objectives	Endpoints
Primary	
• To demonstrate the immunological non-inferiority of *Rotarix* PCV-free as compared to *Rotarix* in terms of seroconversion rates 1 month post Dose 2. - Non-inferiority will be demonstrated if the lower limit of the two-sided asymptotic standardized 95% CI for the difference in seroconversion rate between the *Rotarix* PCV-free and *Rotarix* is greater than or equal to -10%. • To demonstrate the non-inferiority of the *Rotarix* PCV-free as compared to *Rotarix* in terms of serum anti-RV IgA Ab concentrations 1 month post Dose 2. - Non-inferiority will be demonstrated if the lower limit of the two-sided 95% CI for the ratio of anti-RV IgA Ab geometric mean concentration (GMC) 1 month post Dose 2 between the *Rotarix* PCV-free and *Rotarix* is greater than or equal to 0.67.	Evaluation of immunogenicity in terms of anti-RV antibody concentrations. • Anti-RV IgA Ab seroconversion rate* 1 month post Dose 2 in the *Rotarix* PCV-free and *Rotarix* groups. • Serum anti-RV IgA Ab concentrations expressed as GMCs 1 month post Dose 2 in the *Rotarix* PCV-free and *Rotarix* groups. **Seroconversion rate is defined as the percentage of participants who were initially seronegative (i.e., with anti-RV IgA Ab concentration < 20 U/mL prior the first dose of Rotarix) and developed anti-RV IgA Ab concentration ≥ 20 U/mL at Visit 3* (1 month post Dose 2).
Secondary	
• To assess the immunological non-inferiority of *Rotarix* PCV-free as compared to *Rotarix* in terms of percentage of participants with anti-RV IgA antibody concentrations ≥ 90 U/mL 1 month post Dose 2. – Non-inferiority will be demonstrated if the lower limit of the two-sided asymptotic standardized 95% CI for the difference in the percentage between the *Rotarix* PCV-free and *Rotarix* is greater than or equal to -10%.	Evaluation of immunogenicity in terms of anti-RV antibody concentrations. • Percentage of participants with serum anti-RV IgA antibody concentrations ≥ 90 U/mL 1 month post Dose 2 in *Rotarix* PCV-free and *Rotarix* groups.
• To evaluate the reactogenicity of *Rotarix* PCV-free and *Rotarix* in terms of solicited systemic events. • To assess the safety of *Rotarix* PCV-free and *Rotarix* in terms of unsolicited AEs and serious adverse events (SAEs).	• Solicited AEs – For each solicited systemic event, percentage of participants reporting the occurrence of the event within 14 days (Day 1- Day 14) after each study intervention administration. • Unsolicited AEs – Percentage of participants reporting the occurrence of unsolicited AEs within 31 days (Day 1- Day 31) after each study intervention administration, according to the Medical Dictionary for Regulatory Activities (MedDRA) classification. • SAEs – Percentage of participants reporting the occurrence of SAEs from Dose 1 of the study intervention up to study end.

Ab = Antibody; AE = Adverse event; CI = Confidence Interval; IgA = Immunoglobulin A; GMC = Geometric mean Ab concentration; MedDRA = Medical Dictionary for Regulatory Activities; PCV = Porcine circovirus; SAE = Serious adverse event; RV = Rotavirus; U = Unit; mL = milliliter

4. STUDY DESIGN

4.1. Overall design

Figure 1 Study design overview



N = number of participants; AE = adverse event; SAE = serious adverse event; EoS: end of study; ESFU: extended safety follow-up; HRV: Human Rotavirus; PCV-free = No detection of PCV-1 and PCV-2 according to the limit of detection of the tests used.
* An ESFU contact (by telephone call or any convenient procedure) 6 months post Dose 2.
+ Refer to Section 9.5.1 for detailed information about sequence of analysis.

- **Experimental design**: Phase III, self-contained, observer-blind, randomized, multicenter study with 2 parallel groups (see Figure 1).
- **Duration of the study**: The total duration of the study, per participant, will be approximately 7 months including the 6 months of extended safety follow-up (ESFU) period after the last dose of study intervention.
- **Primary completion date**: Visit 3 (Month 2).
- **Control:** Active control, GSK's HRV liquid vaccine (*Rotarix*).
- **Blinding**: Observer-blind. Refer to Section 6.3.4 for details.
- **Data collection**: Standardized electronic Case Report Form (eCRF). Solicited systemic events will be collected using a diary card.
- **Study groups**: Refer to Figure 1 and Table 4 for an overview of the study groups.

Table 4 Study groups, intervention and blinding foreseen in the study

Study Groups	Number of participants	Age (Min-Max)	Study intervention(s)	Blinding		
				Visit 1→Visit 2 (Observer-blind)	**Visit 2→Visit 3** (Observer-blind)	**Visit 3→ ESFU contact** (Observer-blind)*
HRV	1000	6 – 16 weeks	HRV RIX4414 live attenuated $\geq 10^{6.0} CCID_{50}$	X	X	X
HRV PCV-free	1000	6 – 16 weeks	HRV PCV-free RIX4414 live attenuated $\geq 10^{6.0} CCID_{50}$	X	X	X

*Observer-blind except for a limited number of GSK personnel. For unblinding after Visit 3, refer to Section 4.2.1.
ESFU: extended safety follow-up

4.2. Scientific rationale for study design

The study is designed as a Phase III study in healthy Chinese infants aged 6-16 weeks at the time of the first dose.

Refer to Section 4.3 for information about justification for dose.

4.2.1. Rationale for study blinding

The study will be conducted in an observer-blind manner because of the different presentations of the study interventions. For more details regarding the blinding of study refer to Section 6.3.4.

The final analysis (Visit 3) will be performed by GSK. Access to the individual treatment codes during the final analysis will be limited to the statistician and the database administrator. The study personnel involved in the clinical evaluation of the participants and the participants' parents/LARs will remain blinded during the ESFU. This will allow unbiased evaluation of the study interventions.

4.3. Justification for dose

Two oral doses of the study interventions will be administered at approximately 1 month interval to participants, according to the immunization schedule of *Rotarix* licensed outside of China.

4.4. End of Study (EoS) definition

A participant is considered to have completed the study if he/she is available for contact (Month 7) as described in the protocol.

EoS is defined as last subject last contact (Month 7).

5. STUDY POPULATION

5.1. Inclusion criteria for enrolment

Adherence to these criteria as specified in the protocol is essential. Inclusion criteria deviations are not allowed because they can jeopardize the scientific integrity or regulatory acceptability of the study or participant safety.

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

- Participants' parent(s)/ LAR(s), who, in the opinion of the investigator, can and will comply with the requirements of the protocol (e.g., completion of the diary cards, return for follow-up visits).
- Written or witnessed/thumb printed informed consent obtained from the parent(s)/LAR(s) of the participant prior to performance of any study specific procedure.
- A male or female with Chinese origin, between, and including, 6 and 16 weeks (42-112 days) of age at the time of the first study intervention administration.
- Healthy participants as established by medical history and clinical examination before entering into the study.
- Born after a gestation period of 36 to 42 weeks inclusive.

5.2. Exclusion criteria for enrolment

Adherence to criteria specified in the protocol is essential. Exclusion criteria deviations are not allowed because they can potentially jeopardize the scientific integrity or regulatory acceptability of the study or safety of the participant.

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

5.2.1. Medical conditions

- Any confirmed or suspected immunosuppressive or immunodeficient condition, based on medical history and physical examination (no laboratory testing required).
- History of severe combined immunodeficiency.
- History of any reaction or hypersensitivity likely to be exacerbated by any component of the study intervention.
- History of seizures or progressive neurological disease.
- Family history of congenital or hereditary immunodeficiency.
- Uncorrected congenital malformation (such as Meckel's diverticulum) of the gastrointestinal tract that would predispose for intussusception (IS).
- History of IS.

- Major congenital defects, or serious chronic illness as assessed by the investigator.
- Previous confirmed occurrence of RVGE.
- Participants with confirmed or suspected Coronavirus Disease 2019 (COVID-19).

5.2.2. Prior/Concomitant therapy

- Use of any investigational or non-registered product (drug, vaccine, or invasive medical device) other than the study interventions during the period beginning 30 days before the first dose of study interventions (Day -29 to Day 1), or planned use during the study period.
- Planned administration/administration of a vaccine not foreseen by the study protocol in the period starting 30 days before the first dose and ending 30 days after the second dose of study intervention administration*, with the exception of the inactivated influenza vaccine, which is allowed at any time during the study and other licensed routine childhood vaccinations.

  *In case emergency mass vaccination for an unforeseen public health threat (e.g., a pandemic) is organized by public health authorities outside the routine immunization programme, the time period described above can be reduced if, necessary for that mass vaccination vaccine, provided it is licensed and used according to its Product Information.
- Administration of immunoglobulins and/or any blood products or plasma derivatives from birth or planned administration during the study period.
- Administration of long-acting immune-modifying drugs from birth or planned administration at any time during the study period (e.g., infliximab).
- Chronic administration (defined as more than 14 days in total) of immunosuppressants or other immune-modifying drugs since birth. For corticosteroids, this will mean prednisone ≥0.5 milligram/kilogram (kg)/day, or equivalent. Inhaled and topical steroids are allowed.
- Previous vaccination against RV.

5.2.3. Prior/Concurrent clinical study experience

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

5.2.4. Other exclusions

- Child in care

Please refer to the glossary of terms for the definition of child in care.

5.3. Lifestyle considerations

This section is not applicable.

5.4. Screening failures

A screening failure is an individual who consents to participate in this study but is not entered in the study/randomized to a study intervention.

Limited data for screening failures (including reason for screening failure) will be collected and reported in the eCRF.

6. STUDY INTERVENTION

A 'study intervention' is defined as a set of investigational or marketed product(s) or placebo intended to be administered to a participant during the study.

Refer to the Study Procedures Manual (SPM) for additional details.

6.1. Study interventions administered

Table 5 Study interventions administered

Study intervention name	HRV (*Rotarix*)	HRV PCV-free (*Rotarix* PCV-free)
Presentation	CCI	
Study interventions formulation	Human Rotavirus, Live Attenuated, RIX4414 strain (≥ $10^{6.0}$ $CCID_{50}$); Sucrose (1.073 g); Di-sodium adipate; DMEM; Sterile water q.s. 1.5 mL	Human Rotavirus, Live Attenuated, RIX4414 strain (≥ $10^{6.0}$ $CCID_{50}$); Sucrose (1.073 g); Di-sodium adipate; DMEM; Sterile water q.s. 1.5 mL
Type	Control	Study
Product category	Combination Product*	Combination Product*
Route of administration	Oral use	Oral use
Number of doses to be administered	2	2
Volume to be administered	1.5 mL	1.5 mL
Packaging, labelling and TM	Refer to SPM for more details	Refer to SPM for more details
Manufacturer	GSK	GSK

Refer to Section 4.1 for schedule of study intervention administration; mL: milliliter; qs: quantum satis
*Combining a biological product and device

The participants must be observed closely for at least 30 minutes after the administration of the study interventions. Appropriate medical treatment must be readily available during the observation period in case of anaphylaxis and/or syncope.

6.2. Preparation/Handling/Storage/Accountability

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

Only authorized study personnel should be allowed access to the study interventions. Storage conditions will be assessed by a sponsor study contact during pre-study activities. Refer to the section on Study Supplies in the SPM for more details on storage and handling of the study interventions.

6.3. Measures to minimize bias: randomization and blinding

6.3.1. Participant identification

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

6.3.2. Randomization to study intervention

Approximately 2000 eligible participants will be randomly assigned (1:1) to the 2 study groups (HRV and HRV PCV-free).

The numbering of HRV vaccine supplies will be performed at GSK, using a block scheme randomization in MATerial EXcellence, a program developed by GSK. Entire blocks will be shipped to the study centers/warehouse(s).

To allow GSK to take advantage of greater rates of recruitment than anticipated at individual centers in this multi-center study and to thus reduce the overall study recruitment period, an over-randomization of supplies will be prepared.

6.3.3. Intervention allocation to the participant

The system's randomization algorithm will use a minimization procedure accounting for center and the study as a whole as minimization factors**.**

Upon providing the participant identification number, the randomization system will determine the study group and will provide the intervention number to be used for the first study intervention administration. The intervention number(s) to be used for subsequent dose administration(s) will be provided by the same automated Internet-based system.

When source data base for internet randomization (SBIR) is not available, please refer to the SBIR user guide or SPM for specific instructions.

Refer to the SPM for additional information relative to the intervention number allocation.

6.3.4. Blinding and unblinding

The study will be conducted in an observer-blind manner with respect to *Rotarix* PCV-free and *Rotarix*. To do so, study interventions will be prepared and administered by qualified study personnel who will not participate in data collection, evaluation, review, or the entry of any study endpoint.

The parents/LARs of the participants will be unaware of the study intervention administered throughout the study. The site and sponsor personnel involved in the clinical evaluation of the participants will also be unaware of the study intervention, while other study personnel may be aware of the treatment assignment.

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

The study will be unblinded for a limited number of people at GSK at the final analysis (Visit 3). The study personnel involved in the clinical evaluation of the participants and parents/LARs of the participants will be kept blinded throughout the conduct of the study.

6.3.4.1. Emergency unblinding

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

The emergency unblinding process enables the investigator to have unrestricted, immediate, and direct access to the participant's individual study intervention via an automated internet-based system (SBIR).

As back up process, the investigator has the option of contacting a GSK Biologicals' Helpdesk (refer to the Table 6) if he/she needs help performing the unblinding (i.e., he/she cannot access the SBIR).

A non-investigator physician (e.g., physician from emergency room) or participant/care giver/family member may also request emergency unblinding either via the investigator (preferred option) or via the GSK Biologicals' Helpdesk (back up process). The patient/participant card lists contact information for both the investigator and GSK Biologicals' Helpdesk.

Table 6 Contact information for emergency unblinding

GSK Helpdesk Available 24/24 hours and 7/7 days
The Helpdesk is available by phone, fax and email Phone: +32 2 656 68 04, 4008423236 Fax: +32 2 401 25 75 Email: rix.ugrdehelpdesk@gsk.com

6.3.4.2. Emergency unblinding prior to regulatory reporting of SAEs

GSK policy (which incorporates International Council on Harmonization [ICH] E2A guidance, the European Union Clinical Trial Directive and United States Federal Regulations) is to unblind the report of any unexpected SAE and which is attributable/suspected to be attributable to the study interventions, prior to regulatory reporting. Vaccines Clinical Safety and Pharmacovigilance (VCSP) is responsible for unblinding the intervention assignment in accordance with the specified timeframes for expedited reporting of SAEs (refer to the Section 10.3.8.1).

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

6.4. Study intervention compliance

Study intervention administration will be performed under medical supervision on Day 1 and Month 1 (refer to the Section 4.1). The date of each dose administered in the study center will be recorded in the source documents and in the eCRF.

6.5. Concomitant therapy

At each study visit/contact, the investigator or delegate should question the participant's parent(s)/LAR(s) about any medications/products taken and vaccinations received by the participant.

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

- All concomitant medications/products, except vitamins and dietary supplements, administered following each dose of study intervention (Day 1 to Day 31).
- All concomitant vaccinations from Visit 1 up to the Visit 3 (blood sample visit).
- Any concomitant medications/products/vaccines leading to the withdrawal or non-eligibility of the participant from the study (Please refer to the Section 5.2.2 for further details).
- Prophylactic medication (i.e., medication administered in the absence of ANY symptom and in anticipation of a reaction to the study intervention administration) e.g., an anti-pyretic is considered to be prophylactic when it is given in the absence of fever and any other symptom, to prevent fever from occurring [fever is defined as temperature ≥ 37.5°C. The preferred location for measuring temperature in this study will be the axilla].

- Any concomitant medications/products/vaccines relevant to an SAE to be reported as per protocol or administered at any time during the study period for the treatment of an SAE. Concomitant medications relevant to SAEs must be recorded on the Expedited Adverse Event report.

The Local Medical Lead should be contacted if there are any questions regarding concomitant or prior therapy.

6.6. Dose modification

This section is not applicable.

6.7. Intervention after the end of the study

The immunological assay results will be shared with investigators after the end of the study.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of study intervention

'Discontinuation' of study interventions means any participant who has not received all planned doses of study interventions. A participant who discontinued study interventions may, if deemed appropriate by the investigator, continue other study procedures (e.g., safety or immunogenicity) if planned in the study protocol.

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

- Adverse event requiring expedited reporting to GSK
- Unsolicited non-serious adverse event
- Solicited adverse event
- Protocol deviation
- Not willing to be vaccinated
- Migrated/moved from study area
- Other (specify).

7.1.1. Criteria for temporary delay for enrolment and/or study intervention administration

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

- Non-rotavirus GE within 7 days preceding the study intervention administration.
- Acute disease and/or fever at the time of enrolment and/or study intervention administration. Refer to the SoA for fever definition and preferred location for measuring temperature in this study.
- Participants with a minor illness (such as mild diarrhea, mild upper respiratory infection) without fever may be enrolled and/or vaccinated at the discretion of the investigator.
- Participants with known COVID-19 positive contacts within the past 14 days.

7.1.2. Contraindications to subsequent study intervention(s) administration

Participants must be evaluated to confirm they are eligible for subsequent study intervention administration before administering each additional study dose.

Participants who meet any of the criteria listed below or criteria listed in Sections 5.2.1, 5.2.2, 5.2.3 and 5.2.4 should not receive additional study intervention administrations. However, these participants should be encouraged to continue other study procedures at the discretion of the investigator (Section 10.3.6.2). The relevant criteria for discontinuing study intervention administration must be recorded in the eCRF.

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

7.2. Participant discontinuation/withdrawal from the study

A participant is considered a ‘withdrawal’ from the study when no study procedure has occurred, no follow-up has been performed and no further information has been collected for this participant from the date of withdrawal/last contact.

From an analysis perspective, a ‘withdrawal’ from the study refers to any participant who was not available for the concluding contact foreseen in the protocol.

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

All data and samples collected until the date of withdrawal/last contact of the participant will be used for the analysis.

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

- AEs requiring expedited reporting to GSK (please refer to Section 10.3.8.1 for the details).
- Unsolicited non-serious AE.
- Solicited AE.
- Protocol deviation.
- Withdrawal by participant, not due to an AE*.
- Migrated/Moved from the study area.
- Lost to follow-up.
- Sponsor study termination.
- Other (specify).

*If a participant is withdrawn from the study because the participant's parent(s)/LAR(s) has withdrawn consent and provided the reason for its withdrawal, the investigator must document this reason in the eCRF.

Participants who are withdrawn from the study because of SAEs/AEs must be clearly distinguished from participants who are withdrawn for other reasons. Investigators will follow participants who are withdrawn from the study as result of an SAE/AE until the event is resolved (see Section 10.3.6.2).

7.3. Lost to follow-up

A participant will be considered 'lost to follow-up' if participant's parent(s)/LAR(s) fails to return for scheduled visits and is unable to be contacted by the study site.

Please refer to the SPM for a description of the actions to be taken before considering the participant as lost to follow-up.

8. STUDY ASSESSMENTS AND PROCEDURES

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

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

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

Adherence to the protocol is required for study conduct.

The investigator is not allowed to do testing on samples outside of what has been agreed upon by the Institutional Review Board/ Independent Ethics Committee (IRB/IEC).

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

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

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

- ESFU may be made by a telephone call, other means of virtual contact or home visit, if appropriate.
- Diary cards may be transmitted from and to the site by electronic means and or conventional mail.
- Biological samples may be collected at a different location* other than the study site or at participant's home. Biological samples should not be collected if they cannot be processed in a timely manner or appropriately stored until the intended use.
- If despite best efforts it is not possible to collect the biological samples within the interval predefined in the protocol (see Table 2), then the interval may be extended up to a maximum length of 60 days.
- If despite best efforts it is not possible to administer the 2nd dose of study intervention as defined in the protocol (see Table 2), a maximum age of 24 weeks may be used.

* It is the investigator's responsibility to identify an alternate location. The investigator should ensure that this alternate location meets ICH Good Clinical Practice (GCP) requirements, such as adequate facilities to perform study procedures, appropriate training of the staff and documented delegation of responsibilities in this location. This alternate location should be covered by proper insurance for the conduct of study on participants by investigator and staff at a site other than the designated study site. Refer to EMA Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) pandemic (version 2, 27 March, 2020) for more details.

8.1. Immunogenicity assessments

Collected biological 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.

Sample testing will be done in accordance with the recorded consent of the individual participant's parent(s)/LAR(s).

Collected samples will be stored for a maximum of 20 years. This storage period begins when the last participant performed the last study visit, unless local rules, regulations or guidelines require different timeframes or procedures, which would then be in line with participant consent. These extra requirements need to be communicated formally to and discussed and agreed with GSK.

8.1.1. Biological samples

An overall volume of approximately 4 mL will be collected during the entire study period. Refer to Table 7 and SoA for details of volumes collected for different assessments.

Table 7 Biological samples

Sample type	Quantity	Unit	Time point
Blood	~2	mL	Visit 1 (Day 1 [pre-study intervention administration])
	~2	mL	Visit 3 (Month 2)

mL = milliliter

8.1.2. Laboratory assays

The serological assay (anti-RV IgA ELISA) will be transferred to and performed at laboratories in China designated by GSK and using validated GSK's procedures.

Table 8 Laboratory assays

Assay type	System	Component	Method	Laboratory*
Humoral Immunity (Ab determination)	SERUM	Rotavirus Ab, IgA	ELISA	GSK designated lab in China

*Refer to the list of clinical laboratories for details.
Ab = Antibody; IgA = Immunoglobulin A; ELISA = Enzyme Linked Immunosorbent Assay

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

The addresses of clinical laboratory (ies) used for sample analysis are provided in a separate document accompanying this study protocol.

8.1.3. Immunological read-outs

Table 9 Immunological read-outs

Blood sampling timepoint		No. participants	Component	Components priority rank
Type of contact and timepoint	Sampling timepoint			
Visit 1 (Day 1)	Pre-Dose 1	2000	Rotavirus Ab.IgA	Not applicable
Visit 3 (Month 2)	Post-Dose 2	2000	Rotavirus Ab.IgA	Not applicable

Ab = Antibody; IgA = Immunoglobulin A; Dose = study intervention administration

8.1.4. Immunological correlates of protection

No recognized immunological CoP has been established for the antigen used as part of the HRV vaccines. However, an analysis by Cheuvart et al. in 2014 showed that post-vaccination anti-RV IgA seropositivity (Ab concentration ≥ 20 U/mL) is a correlate of vaccine efficacy in clinical trials of *Rotarix* [Cheuvart, 2014]. This was confirmed by an independent research group in 2020 [Baker, 2020].

The immunological assay results will be communicated to the investigator after the end of the study.

8.2. Safety Assessments

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE. The investigator and any designees remain responsible for following up AEs that are serious, considered related to the study intervention or the study, or that caused the participant to discontinue the study intervention or the study**.**

8.2.1. Procedures prior to study intervention administration

8.2.1.1. Collection of demographic data

Record demographic data such as date of birth including gestational age, sex, and race in the participants' eCRF.

8.2.1.2. Medical and vaccination history

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

8.2.1.3. Physical examination

- Axillary body temperature[*] of each participant needs to be measured prior to any study intervention administration and recorded in the eCRF. If the participant has fever (defined as temperature ≥ 37.5°C) on the day of administration of the study intervention, the administration of study intervention visit will be rescheduled within the allowed interval for this visit (see Table 2).

  [*]Axilla is the preferred route to measure temperature in China. If temperature is taken by other routes, conversion can be made as per local guidelines:

  – Axillary temperature = oral temperature - 0.2°C;
  – Axillary temperature = rectal temperature - 0.3°C.

- Weight and height must be collected at Visit 1 and recorded in the eCRF.
- Physical examination at each study visit subsequent to the first study intervention administration visit will be performed only if the participant's parent(s)/LAR(s) indicates during questioning that there might be some underlying pathology(ies) or if deemed necessary by the investigator or delegate.
- If the investigator determines that the participant's health on the day of study intervention administration temporarily precludes dosing, the visit will be rescheduled.
- Treatment of any abnormality observed during this examination has to be performed according to local medical practice outside this study or by referral to an appropriate health care provider.

8.3. AEs, SAEs and other events of interest

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

An overview of the protocol-required reporting periods for AEs and SAEs is given in Table 10 and Table 11.

Table 10 Timeframes for collecting and reporting of safety information

Event	V1[+] Dose 1 D1	D14	D31	V2[+] Dose 2 M1	M1+13 days	M1+30 days	V3 M2	ESFU contact M 7
Systemic solicited events								
Unsolicited AEs								
AEs/SAEs leading to withdrawal from the study								
SAEs								
SAEs related to study participation or concurrent GSK medication/vaccine								

Pre-V1: pre -visit 1; V: Visit; D: Day; M: Month; AE: adverse event; SAE: serious adverse event; ESFU: extended safety follow-up; [+]Refer to Section 1.3 for information about optimal interval.

The investigator or designee will record and immediately report all SAEs to the sponsor or designee via the Expedited AE Reporting Form. This reporting should, under no circumstances, occur later than 24 hours after the investigator becomes aware of an SAE, as indicated in Section 10.3.8. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

A post-study AE/SAE is defined as any event that occurs outside of the AE/SAE reporting periods defined in Table 10. Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study interventions, the investigator will promptly notify the Study Contact for Reporting SAEs mentioned in the Table 12.

8.3.2. Method of detecting AEs and SAEs

Methods of detecting and recording AE/SAE are detailed in the Section 10.3.6. The assessment of AE/SAE intensity, causality and outcome are provided in the Section 10.3.7.

Open-ended and non-leading verbal questioning of the participants' parent(s)/LAR(s) is the preferred method of acquiring information related to an AE/SAE.

8.3.3. Regulatory reporting requirements for SAEs, and other events

Once an investigator (or designee) becomes aware that a study participant has experienced an SAE, he/she must report it to GSK using the required documentation, and within the timeframes, mentioned in the Table 11. This is essential for meeting legal obligations and ethical responsibilities for participant safety and the safety of a study intervention under clinical investigation.

For SAEs, the investigator will always provide an assessment of causality at the time of the initial report, as defined in the Section 10.3.7.2.

Local regulatory requirements and sponsor policy for the preparation of an investigator safety report for SUSAR must be followed. These reports will be forwarded to investigators as necessary.

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

Please refer to Section 10.3.8 for further details regarding the reporting of SAEs.

Table 11 Timeframes for submitting SAE and other events reports to GSK

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

* Timeframe allowed after receipt or awareness of the information by the investigator/site staff.
‡ Paper Expedited Adverse Events Report will be dated and signed by the investigator (or designee)
‡‡ For each SAE, the investigator(s) must document in the medical notes that they have reviewed the SAE and have provided an assessment of causality.

8.3.3.1. Contact information for reporting of SAEs

Table 12 Contact information for reporting of SAEs

Study contact for questions regarding SAEs Refer to the local study contact information document
Back-up study contact for reporting SAEs Available 24/24 hours and 7/7 days: **GSK Clinical Safety & Pharmacovigilance** Outside US & Canada sites: Fax: +32 2 656 51 16 or +32 2 656 80 09 Email address: ogm28723@gsk.com

8.3.4. Treatment of adverse events

Any medication administered for the treatment of an SAE should be recorded in the Expedited Adverse Event Report of the participant's eCRF screen (refer to the Section 10.3.8.1).

8.3.5. Participant card

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

8.3.6. Medical device deficiencies

Both study groups have study interventions that are a combination product constituted of a device (e.g., CCI [redacted]) and biologic product. Refer to the Glossary of terms for the definition of combination product and medical device deficiency.

8.3.6.1. Detection, follow-up, and prompt reporting of medical device deficiency

The investigator is responsible for the detection, documentation and prompt reporting of any medical device deficiency occurring during the study to GSK. This applies to any medical device provided for the conduct of the study.

Device deficiencies will be reported to GSK within 24 hours after the investigator determines that the event meets the protocol definition of a device deficiency. Refer to Section 10.4 for definitions and details on recording and reporting of these events.

The investigator will ensure that follow-up includes any additional investigations to elucidate the nature and/or relatedness of the device deficiency to the incident.

New or updated information will be recorded on the originally completed form with all changes signed and dated by the investigator and reported to GSK within 24 hours.

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

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

8.3.6.2. Regulatory reporting of medical device deficiency when used as combination product

The investigator will promptly report all device deficiencies occurring with any medical device provided for use in the study to GSK. GSK has a legal responsibility to notify appropriate regulatory authorities and other entities about safety information linked to medical devices being used in clinical studies. Refer to Section 10.4.3 for details of reporting.

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

8.4. Treatment of overdose

This section is not applicable.

8.5. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Genetics

This section is not applicable.

8.8. Biomarkers

This section is not applicable.

8.9. Health outcomes

This section is not applicable.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical hypotheses

This section is not applicable

9.2. Sample size determination

A maximum of 2000 participants (1000 per arm) will be randomized such that approximately 1500 evaluable participants complete the study, considering that 25% of the participants will not be evaluable for the analysis of the primary endpoint leading to 750 evaluable participants per arm.

To control the type 1 error for the primary objectives and first secondary objective a hierarchical procedure will be used. Namely the primary objective on ratio of anti-RV IgA Ab GMCs will be conclusive if the success criterion is reached and the first primary objective is met. The first secondary objective will be conclusive if the success criterion is reached and the 2 primary objectives are met.

The sample size provides at least 90% power to reach the first primary endpoint (see Table 13) and at least 80.7% power to reach the second primary endpoint. 80.7% is a very conservative power estimate and is obtained as 100% minus the sum of type II errors for the 2 primary objectives, see Table 13 and Table 14. Using the same approach, the power to meet the first secondary objectives will be at least 67% power.

9.2.1. Power for non-inferiority in seroconversion

The power presented in Table 13 is based on PASS 2019 (one-sided Non-Inferiority Tests for the Difference Between Two Proportions), under the alternative of a 70% and 67.8% seroconversion rate for *Rotarix* and *Rotarix* PCV-free, respectively, Miettinen and Nurminen's Likelihood Score Test of the Difference).

Table 13 Probability that the lower limit of the 95% CI around group difference in seroconversion rate (*Rotarix* PCV-free minus *Rotarix*), 1 month after Dose 2 of *Rotarix*, is greater or equal to -10%

Expected Seroconversion rate (*Rotarix* / *Rotarix* PCV-free)	N evaluable (each *Rotarix* group)	Power	Alpha
70%* / 67.8%	750	90%	0.025

* = Reference from Rota-075

9.2.2. Power for non-inferiority in GMC

The power presented in Table 14 is based on PASS 2019 (one-sided non-inferiority test for 2 independent means, under the alternative of equal variance & alpha=2.5%).

Table 14 Probability that the lower limit of the 95% CI around the anti-RV IgA Ab GMC ratio (*Rotarix* PCV-free / *Rotarix*), 1 month after Dose 2 of *Rotarix*, is greater or equal to 0.67

Endpoint	True group GMC ratio	Standard deviation [Log_{10} (titer)]	N evaluable (each *Rotarix* group)	Power	Alpha
Anti-RV IgA Ab concentration	1	0.797*	750	99.0%	0.025
Anti-RV IgA Ab concentration	0.91	0.797*	750	90.7%	0.025

* = Reference from Rota-075

9.2.3. Power for non-inferiority in the percentage of participants with serum anti-RV IgA antibody concentrations greater or equal to 90 U/mL 1 month post Dose 2

The power presented in Table 15 is based on PASS 2019 (one-sided Non-Inferiority Tests for the Difference Between Two Proportions), under the alternative of a 45.7% and 43.5% percentage for *Rotarix* and *Rotarix* PCV-free, respectively, Miettinen and Nurminen's Likelihood Score Test of the Difference).

Table 15 Probability that the lower limit of the 95% CI around group difference in the percentage of participants with serum anti-RV IgA antibody concentrations greater or equal to 90 U/mL (*Rotarix* PCV-free minus *Rotarix*), 1 month after Dose 2 of *Rotarix*, is greater or equal to -10%

Expected rate (*Rotarix* / *Rotarix* PCV-free)	N evaluable (each *Rotarix* group)	Power	Alpha
45.7%* / 43.5%	750	86.2%	0.025

* = Reference from Rota-075

9.3. Populations for analyses

Table 16 Populations for analyses

Analysis set	Description
Screened	All participants who were screened for eligibility
Enrolled Set	All participants who entered the study (who were randomized or received study intervention or underwent a post-screening study procedure). Note: screening failures (who never passed screening even if rescreened) and participants screened but never enrolled into the study (met eligibility but not needed) are excluded from the Enrolled Analysis set as they did not enter the study.
Exposed Set (ES)	All participants with at least 1 dose of the study intervention documented. The allocation in a group is done in function of the administered intervention. The ES analysis will be performed per treatment actually administered at Dose 1.
Per Protocol Set (PPS)	All eligible participants from the ES who meet all the following requirements: • who received the study interventions according to their random assignment and the expected study intervention administration schedule (see Table 2). Note that in case regurgitation or vomiting occurs within 30 minutes after study intervention administration and impairs up-take of the intervention, a single replacement dose should be used for the participant to be part of the PPS, • who were not unblinded, • who did not receive a vaccine not specified or forbidden in the protocol up to Visit 3 blood sampling, • who did not receive medication forbidden by the protocol up to Visit 3 blood sampling, • who had anti-RV concentration below 20 U/mL before study intervention administration and who had anti-RV results from the Visit 3 blood sampling, • who complied with the blood sampling schedule for Visit 3 (see Table 2), • who had no concomitant infection up to Visit 3 blood sample, which may influence the immune system.

9.4. Statistical analyses

9.4.1. General considerations

9.4.1.1. Immunogenicity

Ab concentrations below the assay cut-off will be given an arbitrary value of half the assay cut-off for the purpose of GMC calculation.

- The GMC calculations will be performed by taking the anti-log of the mean of the log concentration transformations. Ab concentrations below the cut-off of the assay will be given an arbitrary value of half the cut-off for the purpose of GMC calculation.
- For a given participant and a given immunogenicity measurement time point, missing or non-evaluable measurements will not be replaced.

9.4.1.2. Reactogenicity/Safety

Participants who missed reporting events (solicited/unsolicited AEs or concomitant medications) will be treated as participants without the events (solicited/unsolicited AEs or concomitant medications, respectively).

9.4.2. Participant disposition

Number of enrolled, vaccinated participants and reason for withdrawal will be described.

The distribution of participants enrolled in each site will be tabulated across and per study group.

Number of participants excluded from PPS analyses will be tabulated for the total population and for each group based on the reason for exclusion.

9.4.3. Analysis of immunogenicity

The immunogenicity analysis will be based on the PPS for analysis of immunogenicity. If, in any study intervention group, the percentage of vaccinated participants with serological results excluded from the PPS for analysis of immunogenicity is 5% or more, a second analysis based on the ES will be performed to complement the PPS analysis.

9.4.3.1. Within groups assessment

The following calculations will be performed.

- For each group, at Visit 1 and Visit 3 time point,
  - Seropositivity/seroconversion rates and their exact 95% CI will be computed,
  - Percentage of participants with anti-RV IgA antibody concentrations ≥ 90 U/mL and their exact 95% CI will be computed.
  - GMCs and their exact 95% CIs will be computed,
  - The distribution of anti-RV IgA Ab concentrations at Visit 3 will be displayed using reverse cumulative curves.

9.4.3.2. Between groups assessment

- The asymptotic standardized 95% CI for the difference in seroconversion rate at Visit 3 between *Rotarix* PCV-free minus *Rotarix* will be computed.
- The 95% CI for the ratio of anti-RV IgA Ab GMCs at Visit 3 between *Rotarix* PCV-free over *Rotarix* will be computed.
- The asymptotic standardized 95% CI for the difference in the percentage of participants with anti-RV IgA antibody concentrations ≥ 90 U/mL at Visit 3 between *Rotarix* PCV-free minus *Rotarix* will be computed.

9.4.4. Analysis of safety

Safety analysis will be performed on the ES.

9.4.4.1. Within groups assessment

The following calculations will be performed for each group:

- The percentage of doses and participants reporting at least 1 AE (solicited or unsolicited) during the 14-day (Day 1 to Day 14) solicited follow-up period will be computed, along with exact 95% CI. The same calculations will be done for AEs (solicited or unsolicited) rated as grade 3 in intensity and for AEs leading to a medically attended visit.
- The percentage of doses and participants reporting each individual solicited systemic event will be computed, over the 14-day (Day 1 to Day 14) solicited follow-up period, following study intervention administration, along with exact 95% CI. The same calculations will be done for each individual solicited systemic event rated as grade 3 in intensity and events leading to a medically attended visit. Temperature above specific thresholds will also be summarized with threshold defined by half degree increment.

Note: Intensity of fever will be assessed by considering the grading scales recommended by the Chinese authorities [NMPA, 2019b].

- The verbatim reports of unsolicited AEs will be reviewed by a physician and will be coded according to MedDRA. Every verbatim term will be matched with the appropriate Preferred Term. The percentage of participants with unsolicited AEs occurring within 31-day (Day 1 to Day 31) follow-up period after any dose with its exact 95% CI will be tabulated by preferred term. The same calculations will be done for each AE rated as grade 3 in intensity, for AEs leading to a medically attended visit and for AEs causally related to HRV as per the investigator assessment.
- The percentages of participants who started taking at least 1 concomitant medication, by type (any, antipyretic), from Day 1 to Day 14 after study intervention administrations will be tabulated with exact 95% CI. The percentages of participants who started taking at least 1 concomitant medication, by type (any, antipyretic), within 1 month after each dose will also be tabulated with exact 95% CI.
- SAEs and drop outs due to AEs will be described in detail.

9.4.5. Other analyses

9.4.5.1. Demography and baseline characteristics analyses

The median, mean, range and standard deviation of age (in weeks) for each dose of *Rotarix* and for gestational age (in weeks) will be computed by group. Median, mean and standard deviation of height in centimeter and weight in kg at Visit 1 will be computed by group. The geographical ancestry and sex composition will be presented.

Summary of co-administered vaccinations (i.e., vaccinations given on the day of each *Rotarix* dose) and intercurrent vaccinations (i.e., vaccinations other than *Rotarix* administered from birth up to Visit 3, excluding vaccination given on the day of *Rotarix* administration) will be summarized by group for the ES.

9.5. Interim analyses

9.5.1. Sequence of analyses

Final analysis will be conducted once anti-RV IgA ELISA testing at Visit 3 (1 month after Dose 2) is completed and all the immunogenicity data are available. This final analysis will include immunogenicity and safety data up to Visit 3 and a clinical study report (CSR) will be written.

An EoS analysis with all data including the data obtained during ESFU period will be performed and an integrated CSR will be written and made available to the investigators and submitted to regulatory authorities as appropriate.

Note: If there is a delay in availability of the immunogenicity data, leading to a window between the 2 analyses shorter than what is planned at the time of protocol writing, only 1 statistical analysis including all immunogenicity and safety data will be performed and 1 study report will be developed.

9.6. Data Monitoring Committee

This section is not applicable.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and ethical considerations

- This study will be conducted in accordance with the protocol and with:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
  - Applicable ICH GCP Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g., advertisements) must be submitted, to an IRB/IEC by the investigator for review and approval. These documents will be signed and dated by the investigator before the study is initiated.
- Any protocol amendments will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- GSK will provide full details of the above procedures to the investigator, either verbally, in writing, or both.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC.
  - Notifying the IRB/IEC of SAE(s) or other significant safety findings as required by IRB/IEC procedures.
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

10.1.2. Financial disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing financial interest information prior initiation of the center and at the end of the study. Investigators are responsible for providing a

Financial Disclosure update if their financial interests change at any point during their participation in a study and for 1 year after completion of the study.

10.1.3. Informed consent process

The investigator or his/her representative will explain the nature of the study to the participants' parent(s) or his/her LAR(s) and answer all questions regarding the study.

Participants' parent(s)/LAR(s) must be informed that the participant's involvement is voluntary.

Freely given and written/ witnessed/thumb printed informed consent must be obtained from each participant's parent(s)/LAR(s)/witness as appropriate, prior to participation in the study.

The content of informed consent form must meet the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study center.

The medical record must include a statement that written, or witnessed/thumb printed informed consent was obtained before the participant was enrolled in the study and the date the consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Participants must be re-consented to the most current version of the ICF(s) or an ICF addendum during their participation in the study.

A copy of the ICF(s) must be provided to the participants' parent(s)/LAR(s).

If follow-up information from a treating physician or other licensed medical practitioner is required for a medical device incident with an AE/SAE involving an associated person(s), the Associated Person Safety Reporting Information and Authorization Letter must be signed by the associated person to obtain consent.

10.1.4. Data protection

Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participants' parent(s)/LAR(s) must be informed that his/her child's/ward's personal study-related data will be used by the sponsor in accordance with local data protection law.

The participants' parent(s)/LAR(s) must be informed of his/her child's/ward's rights regarding the use of their personal data in accordance with the data privacy Section of the ICF.

The participants' parent(s)/LAR(s) must be informed that his/her child's/ward's medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

GSK will also ensure protection of the personal data of the investigator and site staff which will be collected within the framework and for the purpose of the study in accordance with the Data Privacy Notice that will be sent to the site staff.

10.1.5. Dissemination of clinical study data

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

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

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

GSK will provide the investigator with the randomization codes for their site only after completion of the full statistical analysis.

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

10.1.6. Data quality assurance

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

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

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

The investigator must maintain adequate and accurate source documents and trial records that include all pertinent observations on each of the site's trial participants that supports information entered in the eCRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source documents or certified copies.

The sponsor or designee is responsible for the data management of this study including quality checking of the source data.

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

Trial records and source documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 15 years from the Report Complete date entered in eTrack. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.7. Source documents

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

Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

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

10.1.8. Study and site start and closure

First act of recruitment

The start of study is defined as FSFV.

Study/Site termination

GSK or its designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of GSK, provided there is sufficient notice given to account for patient's safe exit from study participation. Study sites regular closure will occur upon study completion. A study site is considered closed when all required data/documents and study supplies have been collected and a study-site closure visit has been performed.

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

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

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

10.1.9. Publication policy

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

10.2. Appendix 2: Tests

Anti-RV IgA Ab Determination

The anti-RV Ab concentrations are determined by a validated anti-RV IgA ELISA. Microtiter plates (96-well) are coated with an anti-RV monoclonal Ab. The wells are washed and incubated with (positive wells) or without (negative wells) RV. Following incubation, the plates are washed and serum, standard and control dilutions are incubated in both types of wells (positive and negative). Bound anti-RV IgA in the wells are detected by incubation with peroxidase conjugated anti-human IgA polyclonal Abs. Color development proportional to the quantity of bound anti-RV IgA occurs in the presence of a chromogen, TetraMethylBenzidine, and measured spectrophotometrically. Specific optical densities are calculated for each sample/control/standard dilution by measuring the difference between positive and negative wells, the use of negative wells allowing to assess non-specific IgA binding. The concentrations of the samples expressed in units per milliliter are calculated relative to the four-parameter logistic function generated from the standard curve.

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

10.3.1. Definition of an Adverse Event (AE)

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

10.3.1.1. Events Meeting the AE Definition

- Significant or unexpected worsening or exacerbation of the condition/indication under study.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention(s) administration even though they may have been present prior to the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention(s) or a concurrent medication (overdose per se should not be reported as an AE/SAE).
- Signs or symptoms temporally associated with study intervention(s) administration.
- Signs, symptoms that require medical attention (e.g., hospital stays, physician visits and emergency room visits)
- Significant failure of an expected pharmacologic or biological action.
- Pre- or post- intervention events that occur as a result of protocol-mandated procedures (i.e., invasive procedures, modification of participant's previous therapeutic regimen).
- Clinically significant abnormal laboratory findings or other abnormal assessments that are present at baseline and significantly worsen following the start of the study will also be reported as AEs or SAEs.
- AEs to be recorded as solicited AEs are described in the Section 10.3.3. All other AEs will be recorded as UNSOLICITED AEs.
- The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE.

10.3.1.2. Events NOT Meeting the AE Definition
• Situations where an untoward medical occurrence did not occur (e.g., social and/or convenience admission to a hospital, admission for routine examination). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen. • Pre-existing conditions or signs and/or symptoms present in a participant prior to the first dose of study intervention. These events will be recorded in the medical history Section of the eCRF. • Hospitalization for elective treatment of a pre-existing condition (known or diagnosed prior to informed consent signature) that did not worsen from baseline. • Clinically significant abnormal laboratory findings or other abnormal assessments that are associated with the disease being studied, unless judged by the investigator as more severe than expected for the participant's condition, or that are present or detected at the start of the study and do not worsen.

10.3.2. Definition of a Serious Adverse Event (SAE)

An SAE is any untoward medical occurrence that:	
a.	Results in death
b.	Is life-threatening Note: The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, had it been more severe.
c.	Requires hospitalization or prolongation of existing hospitalization Note: In general, hospitalization signifies that the participant has been admitted at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or in an out-patient setting. Complications that occur during hospitalization are also considered as AEs. If a complication prolongs hospitalization or fulfils any other serious criteria, the event will also be considered serious. When in doubt as to whether 'hospitalization' occurred, or was necessary, the AE should be considered serious.
d.	Results in disability/incapacity Note: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza like illness, and accidental trauma (e.g., sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

e. Other situations

Medical or scientific judgement should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization.

10.3.3. Solicited events

The following systemic events will be solicited:

Table 17 Solicited systemic events

Fever
Diarrhea
Vomiting
Irritability/Fussiness
Loss of appetite
Cough/runny nose

Note: participants' parent(s)/LAR(s) will be instructed to measure and record the body temperature in the evening. Should additional temperature measurements be performed at other times of day, participants' parent(s)/LAR(s) will be instructed to record the highest temperature in the diary card.

10.3.4. Unsolicited adverse events

An unsolicited adverse event is an adverse event that was not solicited using a Participant Diary and that was spontaneously communicated by a participant's parent(s)/LAR(s) who has signed the informed consent. Unsolicited AEs include serious and non-serious AEs.

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

Unsolicited AEs that are not medically attended nor perceived as a concern by participant's parent(s)/LAR(s) will be collected during interview with the participant's parent(s)/LAR(s) and by review of available medical records at the next visit.

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

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

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

10.3.6. Recording and follow-up of AEs, SAEs

The participants' parent(s)/LAR(s) will be instructed to contact the investigator immediately should the participants manifest any signs or symptoms they perceive as serious.

When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) relative to the event. The investigator will then record all relevant information regarding an AE/SAE in the eCRF. The investigator is not allowed to send photocopies of the participant's medical records to GSK instead of appropriately completing the eCRF. However, there may be instances when copies of medical records for certain cases are requested by GSK. In this instance, all participant identifiers will be blinded on the copies of the medical records prior to submission to GSK.

The investigator will attempt to establish a diagnosis pertaining to the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE/SAE and not the individual signs/symptoms.

A Paper Diary, hereafter referred to as Participant Diary will be used in this study to capture solicited systemic events. The participant should be trained on how and when to complete each field of the Participant Diary.

Any individual(s) who performs the measurements of systemic events and who will enter the information into the Participant Diary should be trained on the use of the Diary. This training must be documented in the participant's source record. If any individual other than the participant's parent(s)/LAR(s) is making entries in the Participant Diary, their identity should be documented in the Participant Diary/participant's source record.

- Collect and verify completed diary cards during discussion with the participant's parent(s)/LAR(s) on Visit 2 and Visit 3.
- Any unreturned diary cards will be sought from the participant's parent(s)/LAR(s) through telephone call(s) or any other convenient procedure.

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

10.3.6.1. Time period for collecting and recording AEs, and SAEs

All AEs that occur during 30 days following administration of each dose of study intervention(s) (Day 1 to Day 31) must be recorded into the appropriate section of the eCRF, irrespective of intensity or whether or not they are considered related to the study intervention.

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

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

Other non-serious AEs must be followed until 30 days after the last study intervention administration or until the participant is lost to follow-up.

10.3.6.2.1. Follow-up during the study

AEs documented at a previous visit/contact and defined as not recovered/not resolved or recovering/resolving will be reviewed at subsequent visits/contacts until 30 days after the last study intervention administration.

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

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

The investigator will provide any new or updated relevant information on previously reported SAE to GSK using a paper/electronic Expedited Adverse Events Report as applicable. The investigator is obliged to perform or arrange for the conduct of supplemental clinical examinations/tests and/or evaluations to elucidate the nature and/or causality of the AE or SAE as fully as possible.

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

When additional SAE information is received after removal of write access to the participant's eCRF, new or updated information should be recorded on the appropriate paper report, with all changes signed and dated by the investigator. The updated report should be faxed or emailed to the Study Contact for Reporting SAEs (refer to the Section 8.3.3.1 or to GSK Clinical Safety and Pharmacovigilance department within the defined reporting time frames specified in the Table 11).

10.3.7. Assessment of intensity and toxicity

10.3.7.1. Assessment of intensity

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

Table 18 Intensity scales to be used by the parent(s)/LAR(s) for solicited symptoms during the solicited follow-up period

Infant		
Adverse Event	**Intensity grade**	**Parameter**
Fever*		Record temperature in °C
Diarrhea $		Record the number of looser than normal stools/day
Vomiting §		Record the number of episodes of vomiting/day
Loss of appetite	0	Appetite as usual
	1	Eating less than usual/no effect on normal activity
	2	Eating less than usual/interferes with normal activity
	3	Not eating at all
Irritability/Fussiness	0	Behavior as usual
	1	Crying more than usual/no effect on normal activity
	2	Crying more than usual/interferes with normal activity
	3	Crying that cannot be comforted/prevents normal activity
Cough/runny nose	0	Normal
	1	Cough/runny nose which is easily tolerated
	2	Cough/runny nose which interferes with daily activity
	3	Cough/runny nose which prevents daily activity

*Refer to the SoA for the definition of fever and the preferred location for temperature measurement.
$ Diarrhea is defined as passage of 3 or more looser than normal stools within a day.
§ Vomiting is defined as 1 or more episodes of forceful emptying of partially digested stomach contents ≥1 hour after feeding within a day.

Table 19 Intensity scales for diarrhea, vomiting and fever in infants

Infant		
Event	**Intensity grade**	**Parameter**
Diarrhea	0	Normal (0-2 looser than normal stools/day)
	1	3 looser than normal stools/day
	2	4-5 looser than normal stools/day
	3	≥ 6 looser than normal stools/day
Vomiting	0	Normal (no emesis)
	1	1 episode of vomiting/day
	2	2 episodes of vomiting/day
	3	≥3 episodes of vomiting/day
Fever+	0	Normal (< 37.5°C)
	1	37.5°C – < 38.0°C
	2	38.0°C – < 39.5°C
	3	≥ 39.5°C
	4	≥ 39.5°C, lasts more than 5 consecutive days

+ The intensity of fever using the grading scale as defined by Chinese authorities [NMPA, 2019b].

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

The intensity should be assigned to 1 of the following categories:

1 (mild)	=	An AE which is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
2 (moderate)	=	An AE which is sufficiently discomforting to interfere with normal everyday activities.
3 (severe)	=	An AE which prevents normal, everyday activities (in a young child, such an AE would, for example, prevent attendance at school/kindergarten/a day-care center and would cause the parent(s)/LAR(s) to seek medical advice).

An AE that is assessed as grade 3 (severe) should not be confused with an SAE. Grade 3 is a category used for rating the intensity of an event; and both AEs and SAEs can be assessed as grade 3. An event is defined as 'serious' when it meets 1 of the pre-defined outcomes as described in the Section 10.3.2.

10.3.7.2. Assessment of causality

All solicited systemic events will be considered causally related to study intervention administration. The complete list of these events is provided in the Table 17.

The investigator must assess the relationship between study intervention(s) and the occurrence of each unsolicited AE/SAE using clinical judgement. Where several different vaccines/products were administered, the investigator should specify, when possible, if the unsolicited AE/SAE could be causally related to a specific vaccine/product (i.e., investigational, control/placebo or co-administered vaccine). When causal relationship to a specific vaccine(s) cannot be determined, the investigator should indicate the unsolicited AE/SAE to be related to all products.

Alternative plausible causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study intervention(s) will be considered and investigated. The investigator will also consult the IB determine his/her assessment.

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

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

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

If an event meets the criteria to be determined as 'serious' (see Section 10.3.2), additional examinations/tests will be performed by the investigator to determine ALL possible contributing factors for each SAE.

Possible contributing factors include:

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

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

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

10.3.7.3. Medically attended visits

For each solicited and unsolicited symptom the participant experiences, the participant's parent(s)/LAR(s) will be asked if the participant received medical attention defined as hospitalization, or an otherwise unscheduled visit to or from medical personnel for any reason, including emergency room visits. This information will be recorded in the eCRF.

10.3.7.4. Assessment of outcomes

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

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

10.3.8. Reporting of SAEs and other events

10.3.8.1. Events requiring expedited reporting to GSK

Once an investigator becomes aware that an SAE has occurred in a study participant, the investigator (or designee) must complete information in the electronic Expedited Adverse Events Report WITHIN 24 HOURS. The report will always be completed as thoroughly as possible with all available details of the event.

Even if the investigator does not have all information regarding an SAE, the report should still be completed within 24 hours. Once additional relevant information is received, the report should be updated WITHIN 24 HOURS. The investigator will always provide an assessment of causality at the time of the initial report.

Refer to the Table 11 for the details on timeframes for reporting of SAEs.

Refer to the Section 10.3.8.2 for the back-up system in case the electronic reporting system does not work.

10.3.8.2. Back-up system in case facsimile or electronic reporting system does not work

In rare circumstances if the electronic reporting system does not work, the investigator (or designee) must fax or email the completed, dated and signed paper Expedited Adverse Events Report to the Study Contact for Reporting SAEs (refer to the Sponsor Information) or to GSK Clinical Safety and Pharmacovigilance department within 24 hours (refer to Section 8.3.3.1 for contact information).

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

10.4. Appendix 4: Definition of medical device AE, adverse device effect (ADE), serious adverse device effect (SADE) and unanticipated SADE (USADE)

10.4.1. Definition of medical device AE and adverse device effect (ADE)

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

10.4.2. Definition of medical device SAE, SADE and USADE

A medical device SAE is any serious adverse event that:
a. Led to death
b. Led to serious deterioration in the health of the participant, that either resulted in: – A life-threatening illness or injury. The term ‘life-threatening' in the definition of ‘serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe. – A permanent impairment of a body structure or a body function. – Inpatient or prolonged hospitalization. Planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered an SAE. – Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function
c. Is a suspected transmission of any infectious agent via a medicinal product

Serious Adverse Device Effect (SADE) definition
• A SADE is defined as an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event. • Any device deficiency that might have led to an SAE if appropriate action had not been taken or circumstances had been less fortunate.
Unanticipated SADE (USADE) definition
• An USADE (also identified as UADE in US Regulations 21 CFR 813.3), is a serious adverse device effect that by its nature, incidence, severity, or outcome has not been identified in the current version of the IB.

10.4.3. Recording and reporting of medical device AE, ADEs, SADEs and USADE

- Any device deficiency must be reported to GSK within 24 hours after the investigator determines that the event meets the definition of a device deficiency.
- Refer to paper 'Medical device or combination product with device deficiency/incident report form' for details on transmission of this information to the sponsor.
- GSK will review all device deficiencies, determine, and document in writing whether they could have led to an SAE. These device deficiencies will be reported to the regulatory authorities and IRBs/IECs as required by national regulations.
- If required or in case of any issues refer to the general safety contacts for SAE/AE reporting in Section 8.3.3.1.

10.4.4. Reporting of Medical Device Deficiencies for Associated Person)

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

10.5. Appendix 5: Abbreviations and glossary of terms

10.5.1. List of abbreviations

Ab	Antibody
ADE	Adverse Device Effect
AE	Adverse Event
CI	Confidence Interval
CoP	Correlate of Protection
COVID-19	Coronavirus Disease 2019
CSR	Clinical Study Report
eCRF	electronic Case Report Form
ELISA	Enzyme Linked Immunosorbent Assay
EMA	European Medicines Agency
EoS	End of Study
ES	Exposed Set
ESFU	Extended Safety Follow-Up
GCP	Good Clinical Practice
GE	Gastroenteritis
GMC	Geometric Mean Antibody Concentration
GSK	GlaxoSmithKline
HRV	Human Rotavirus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council on Harmonization
IgA	Immunoglobulin A
IRB/IEC	Institutional Review Board/ Independent Ethics Committee

IS	Intussusception
Kg	Kilogram
LAR	Legally Acceptable Representative
MedDRA	Medical Dictionary for Regulatory Activities
mL	Milliliter
PCV	Porcine Circovirus
PP	Per Protocol
PPS	Per Protocol Set
RV	Rotavirus
RVGE	Rotavirus Gastroenteritis
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SBIR	Source data Base for Internet Randomization
SmPC	Summary of Product Characteristics
SoA	Schedule of Activities
SPM	Study Procedures Manual
SUSAR	Suspected Unexpected Serious Adverse Reaction
U	Unit
USADE or UADE	Unanticipated Serious Adverse Device Effect
VCSP	Vaccines Clinical Safety and Pharmacovigilance
WHO	World Health Organization

10.5.2. Glossary of terms

Adverse event: Any untoward medical occurrence in a patient or clinical investigation participant, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e., lack of efficacy), abuse or misuse.

Blinding: A procedure in which 1 or more parties to the trial are kept unaware of the intervention assignment in order to reduce the risk of biased study outcomes. The level of blinding is maintained throughout the conduct of the trial, and only when the data are cleaned to an acceptable level of quality will appropriate personnel be unblinded or when required in case of a serious adverse event. In an observer-blind study, the participant, the site and sponsor personnel involved in the clinical evaluation of the participants are blinded while other study personnel may be aware of the treatment assignment.

Caregiver: A ‘caregiver’ is someone who

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

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

Child in care: A child who has been placed under the control or protection of an agency, organization, institution or entity by the courts, the government or a government body, acting in accordance with powers conferred on them by law or regulation. The definition of a child in care can include a child cared for by foster parents or living in a care home or institution, provided that the arrangement falls within the definition above. The

	definition of a child in care does not include a child who is adopted or has an appointed legal guardian.
Combination product:	Combination product comprises any combination of – drug – device – biological product Each drug, device, and biological product included in a combination product is a constituent part.
Eligible:	Qualified for enrolment into the study based upon strict adherence to inclusion/exclusion criteria.
Enrolled:	'Enrolled' means a participant's/parent's/LAR's agreement to participate in a clinical study following completion of the informed consent process. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol. Refer to the Section 9.3 for the definition of 'enrolled' applicable to the study.
Essential documents:	Documents which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced
eTrack:	GSK's tracking tool for clinical trials.
Evaluable:	Meeting all eligibility criteria, complying with the procedures defined in the protocol, and, therefore, included in the per-protocol analysis (see Section 9.3 for details on criteria for evaluability).
Immunological correlate of protection:	A correlate of risk that has been validated to predict a certain level of protection from the targeted endpoint.
Intervention:	Term used throughout the clinical study to denote a set of investigational product(s) or marketed product(s) or placebo intended to be administered to a participant.
Intervention number:	A number identifying an intervention to a participant, according to intervention allocation.
Invasive medical device:	EEC directive 93/42/EEC defines an invasive medical device as 'A device which, in whole or in part, penetrates inside the body, either through a body orifice or through the surface of the body'.
Investigational vaccine:	A pharmaceutical form of an active ingredient being tested in a clinical trial, including a product with a marketing authorization when used in a way different

	from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use. Synonym: Investigational Medicinal Product
Investigator:	A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator. The investigator can delegate trial-related duties and functions conducted at the trial site to qualified individual or party to perform those trial-related duties and functions
Legally acceptable representative:	An individual or juridical or other body authorized under applicable law to consent, on behalf of a prospective participant, to the participant's participation in the clinical trial. The terms legal representative or legally authorized representative are used in some settings.
Medical device deficiency:	A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Device deficiencies include malfunctions, use errors and information supplied by the manufacturer.
Participant:	Term used throughout the protocol to denote an individual who has been contacted to participate or participates in the clinical study, either as a recipient of the study intervention(s) or as a control. Synonym: subject
Participant number:	A unique identification number assigned to each participant who consents to participate in the study.
Primary completion date:	The date that the final participant was examined or received an intervention for the purpose of final collection of data for all primary outcomes, whether the clinical trial was concluded according to the pre-specified protocol or was terminated.
Protocol amendment:	The International Council on Harmonization (ICH) defines a protocol amendment as: ‘A written description of a change(s) to or formal clarification of a protocol.’ GSK Biologicals further details this to include a change to an approved protocol that affects the safety of participants, scope of the investigation, study design, or scientific integrity of the study.

Protocol administrative change:	A protocol administrative change addresses changes to only logistical or administrative aspects of the study.
Randomization:	Process of random attribution of intervention to participants to reduce selection bias.
Self-contained study:	Study with objectives not linked to the data of another study.
Solicited event:	Events to be recorded as endpoints in the clinical study. The presence/occurrence/intensity of these events is actively solicited from the participant or an observer during a specified follow-up period following study intervention administration.
Source data:	All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).
Source documents:	Original legible documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, participants' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, participant files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial).
Study intervention /product:	Any investigational intervention /product being tested and/or any authorized use of an intervention /product/placebo as a reference or administered concomitantly, in a clinical trial that evaluates the use of an investigational intervention /product.
Unsolicited adverse event:	Any AE reported in addition to those solicited during the clinical study. Also, any ‘solicited’ symptom with onset outside the specified period of follow-up for solicited symptoms will be reported as an unsolicited adverse event.

10.6. Appendix 6: Protocol Amendment change history

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

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