Clinical Study Protocol
Sponsor:
GlaxoSmithKline Biologicals
Rue de l'Institut 89
1330 Rixensart, Belgium

Primary Study vaccine and number	*Porcine circovirus* (PCV)-free liquid formulation of GlaxoSmithKline (GSK) Biologicals' oral live attenuated human rotavirus (HRV) vaccine (444563)
Other Study vaccine	Lyophilised formulation of GSK Biologicals' oral live attenuated HRV vaccine (444563)
eTrack study number and Abbreviated Title	115461 (ROTA-081)
Investigational New Drug (IND) number	BB-IND-16992
EudraCT number	2016-000598-19
Date of protocol	Final Version 1: 03 June 2016
Date of protocol amendment/administrative change	Administrative change 1 Final: 22 June 2016 Administrative change 2 Final: 06 September 2016 Amendment 1 Final: 09 March 2017
Title	Immunogenicity and safety study of two formulations of GlaxoSmithKline (GSK) Biologicals' human rotavirus (HRV) vaccine (444563), in healthy infants starting at age 6-12 weeks.
Detailed Title	A phase IIIA, randomised, observer-blind, multi-centre study to evaluate the clinical consistency of three production lots of the *Porcine circovirus* (PCV)-free liquid formulation of GlaxoSmithKline (GSK) Biologicals' oral live attenuated human rotavirus (HRV) vaccine and to evaluate the PCV-free liquid formulation of GSK Biologicals' HRV vaccine as compared to the currently licensed lyophilised formulation of the HRV vaccine in terms of immunogenicity, reactogenicity and safety when administered as a two-dose vaccination in healthy infants starting at age 6-12 weeks.
Co-ordinating author	PPD
Contributing authors (Amended: 09 March 2017)	• PPD, Clinical & Epidemiology Project Lead • PPD Clinical Research and Epidemiology Lead • PPD, Statistician • PPD, Lead Statistician

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Contributing authors (Amended: 09 March 2017)	• PPD, Study Delivery Lead • PPD, Project Delivery Lead • PPD, Clinical Read-Out Team Leader • PPD, Laboratory Study Manager • PPD, Clinical Safety representative • PPD, ***Oversight*** Data Manager • PPD, Global Regulatory Affairs representative • PPD, Global Patents representative • PPD, Clinical Trial Supply Manager

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Protocol Amendment 1 Sponsor Signatory Approval

eTrack study number and Abbreviated Title	115461 (ROTA-081)
IND number	BB-IND-16992
EudraCT number	2016-000598-19
Date of protocol amendment	Amendment 1 Final: 09 March 2017
Detailed Title	A phase IIIA, randomised, observer-blind, multi-centre study to evaluate the clinical consistency of three production lots of the Porcine circovirus (PCV)-free liquid formulation of GlaxoSmithKline (GSK) Biologicals' oral live attenuated human rotavirus (HRV) vaccine and to evaluate the PCV-free liquid formulation of GSK Biologicals' HRV vaccine as compared to the currently licensed lyophilised formulation of the HRV vaccine in terms of immunogenicity, reactogenicity and safety when administered as a two-dose vaccination in healthy infants starting at age 6-12 weeks.
Sponsor signatory	Paul Gillard, Clinical & Epidemiology Project Lead (CEPL), GlaxoSmithKline Biologicals, SA.
Signature	_____
Date	_____

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Protocol Amendment 1 Rationale

Amendment number:	Amendment 1
Rationale/background for changes: The protocol is being amended to include the text related to the unapproved medical devices and incidents associated with it as per Japan specific requirements.	

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

Hence I:

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

eTrack study number and Abbreviated Title	115461 (ROTA-081)
IND number	BB-IND-16992
EudraCT number	2016-000598-19
Date of protocol amendment	Amendment 1 Final: 09 March 2017
Detailed Title	A phase IIIA, randomised, observer-blind, multi-centre study to evaluate the clinical consistency of three production lots of the Porcine circovirus (PCV)-free liquid formulation of GlaxoSmithKline (GSK) Biologicals' oral live attenuated human rotavirus (HRV) vaccine and to evaluate the PCV-free liquid formulation of GSK Biologicals' HRV vaccine as compared to the currently licensed lyophilised formulation of the HRV vaccine in terms of immunogenicity, reactogenicity and safety when administered as a two-dose vaccination in healthy infants starting at age 6-12 weeks.

Investigator name _____

Signature _____

Date _____

PPD _____

Signature _____

Date _____

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Sponsor Information

1. Sponsor

GlaxoSmithKline Biologicals
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 Biologicals Central Back-up Study Contact for Reporting SAEs: refer to protocol Section 8.4.2.

5. GSK Biologicals' Central Safety Physician On-Call Contact information for Emergency Unblinding.

GSK Biologicals Central Safety Physician and Back-up Phone contact: refer to protocol Section 8.8.

SYNOPSIS

Detailed Title	A phase IIIA, randomised, observer-blind, multi-centre study to evaluate the clinical consistency of three production lots of the *Porcine circovirus* (PCV)-free liquid formulation of GlaxoSmithKline (GSK) Biologicals' oral live attenuated human rotavirus (HRV) vaccine and to evaluate the PCV-free liquid formulation of GSK Biologicals' HRV vaccine as compared to the currently licensed lyophilised formulation of the HRV vaccine in terms of immunogenicity, reactogenicity and safety when administered as a two-dose vaccination in healthy infants starting at age 6-12 weeks.
Indication	Active immunisation of infants against gastroenteritis (GE) due to rotavirus (RV).
Rationale for the study and study design	• Rationale for the study Using advanced technology in 2010, researchers from the University of California, San Francisco identified Deoxyribonucleic acid (DNA) fragments of *Porcine circovirus* type 1 (PCV-1) in *Rotarix*. Further investigations conducted by GlaxoSmithKline (GSK) and the United States (US) Food and Drug Administration (FDA) confirmed the presence of PCV-1 DNA fragments in *Rotarix* and its starting materials as well as low levels of PCV-1 viral particles during production process and in the final container. The evidence from retrospective laboratory investigations conducted by GSK on 40 HRV vaccine recipients showed that none of the subjects who received the HRV vaccine demonstrated seroconversion to PCV-1 while the PCV-1 from the vaccine was identified in the stool samples of 4 infants from the HRV group (at Day 3 and Day 7 post Dose 1). The detection of PCV-1 DNA only at the earliest time points post-vaccination was consistent with transient passage of DNA through the infants' digestive tracts without replication. Lack of PCV-1 infection is further supported by the absence of anti-PCV-1 antibody in the HRV vaccine recipients, including the infants who had PCV-1 DNA detected in their stool samples. Therefore, currently available data do not suggest occurrence of PCV-1 infection in infants who received *Rotarix* in clinical trials [Dubin, 2013]. These results are consistent with published literature which indicates that PCV-1 is not capable of causing infection in humans [Hattermann, 2004a; Hattermann, 2004b]. GSK is in the process of replacing the cell bank and virus seeds used as base production material for its HRV vaccine. In the meantime, and in accordance with the regulators, the

company continues to manufacture *Rotarix* to the existing approved production and quality standards to meet public health needs worldwide.

- Rationale for the study design

In order to support licensure of the PCV-free liquid HRV vaccine, GSK Biologicals proposes to conduct a clinical study to demonstrate the lot-to-lot consistency of the PCV-free liquid HRV vaccine in terms of anti-RV Immunoglobulin A (IgA) antibody geometric mean antibody concentrations (GMCs), 1-2 months after Dose 2 and the non-inferiority of the PCV-free liquid HRV vaccine to GSK Biologicals' currently licensed lyophilised HRV vaccine in terms of anti-rotavirus IgA seroconversion rates and GMCs 1-2 months after Dose 2.

This study is planned to be conducted in 1600 children aged 6-12 weeks, randomised (1:1:1:1) between groups receiving GSK Biologicals' currently licensed lyophilised HRV vaccine and three different lots of PCV-free liquid HRV vaccine.

The current lyophilised PCV-containing vaccine will be used as control, since the study is planned to be conducted in US and non-US sites and the liquid formulation of *Rotarix* is not licensed in the US.

Two oral doses of the study vaccines will be administered at an approximate 1-month or 2-months interval to subjects, according to the immunisation schedule for RV vaccine administration in participating countries. Blood samples for immunogenicity assessment will be collected from all subjects before the first dose and at 1-2 months post Dose 2.

An Independent Data Monitoring Committee (IDMC) will review the safety data of the first 5%, 10% and 50% of the subjects enrolled to evaluate if there is any safety concern with the PCV-free liquid HRV vaccine. Enrolment will be paused when first 10% of study sets are enrolled, for the purpose of the IDMC review of the safety data up to 8 days post dose 2 (Day 0-Day 7) and will only resume if the outcome of the IDMC review is positive.

Objectives

Co-Primary

- To demonstrate the lot-to-lot consistency of the PCV-free liquid HRV vaccine in terms of immunogenicity as measured by serum anti-RV IgA antibody concentrations 1-2 months after Dose 2.

Consistency will be demonstrated if, for all pairs of lots, the two-sided 95% confidence intervals (CIs) for the ratio of anti-RV IgA antibody GMCs 1-2 months after Dose 2 are within the [0.5; 2] clinical limit interval.

- To demonstrate the immunological non-inferiority of PCV-free liquid HRV vaccine as compared to the currently licensed lyophilised HRV vaccine in terms of seroconversion rates 1-2 months after 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 PCV-free liquid HRV vaccine (pooled HRV liquid groups) and licensed lyophilised HRV vaccine is greater than or equal to -10%.

- To demonstrate the non-inferiority of the PCV-free liquid HRV vaccine to that of the currently licensed lyophilised HRV vaccine in terms of serum anti-RV IgA antibody concentrations 1-2 months after Dose 2.

Non-inferiority will be demonstrated if the lower limit of the two-sided 95% CI for the ratio of anti-RV IgA antibody GMCs 1-2 months after Dose 2 between the PCV-free liquid HRV vaccine (pooled HRV liquid groups) and the lyophilised HRV vaccine is greater than or equal to 0.67.

Secondary

Reactogenicity and safety

- To evaluate the reactogenicity of the liquid HRV vaccine and currently licensed lyophilised HRV vaccine in terms of solicited AEs during the 8 days (Day 0-Day 7) follow-up period after each vaccination.
- To assess the safety of the study vaccines in terms of unsolicited AEs during the 31 days (Day 0-Day 30) follow-up period after each vaccination and Serious Adverse Events (SAEs) during the entire study period.

Immunogenicity

- To assess the immunogenicity of the PCV-free liquid HRV vaccine and the currently licensed lyophilised HRV vaccine, in terms of percentage of subjects with anti-RV IgA antibody concentrations ≥ 90 U/mL 1-2 months after Dose 2.

Study design

- Experimental design: Phase IIIA, observer-blind, randomised (1:1:1:1), controlled, multi-centric, with four parallel groups and a staggered enrolment (Part A and Part B).
- Duration of the study: The intended duration of the study, per subject, will be approximately 7-8 months including the 6 months of extended safety follow-up period after the last dose of HRV vaccine.
  - Epoch 001: Primary starting at Visit 1 (Day 0) and ending at the safety follow-up contact (Month 7-8).
- Primary completion Date (PCD): Visit 3 (Month 2-4).
- End of Study (EoS): Last testing results released of samples collected at Visit 3 or Last Subject Last Visit (LSLV) (Follow up contact at month 7-8).
- Study groups: The study groups and epoch foreseen in the study are provided in Synopsis Table 1.

The study groups and treatments foreseen in the study are provided in Synopsis Table 2.

Synopsis Table 1 Study groups and epoch foreseen in the study

Study Groups	Number of subjects	Age at Dose 1 (Min-Max)	Epoch
			Epoch 001
Liq_A	400	6 weeks-12 weeks	●
Liq_B	400	6 weeks-12 weeks	●
Liq_C	400	6 weeks-12 weeks	●
Lyo	400	6 weeks-12 weeks	●

Synopsis Table 2 Study groups and treatments foreseen in the study

Treatment name	Vaccine name	Study Groups			
		Liq_A	Liq_B	Liq_C	Lyo
HRV Liquid	HRV PCV-free ‡	x	x	x	
HRV Lyophilised	HRV *				x

‡ PCV-free HRV liquid vaccine
* Licensed formulation of HRV lyophilised vaccine

- PCV-free HRV liquid formulation lot A (also referred to as Liq_A group)
- PCV-free HRV liquid formulation lot B (also referred to as Liq_B group)
- PCV-free HRV liquid formulation lot C (also referred to as Liq_C group)
- GSK Biologicals' currently licensed lyophilised HRV formulation (also referred to as Lyo group)

- Control: active control-GSK Biologicals' currently licensed lyophilised HRV vaccine.
- Vaccination schedule: Two doses of HRV vaccine to be administered according to a 0, 1-2 month schedule according to the immunisation schedule for RV vaccine.
  - Concomitant administration of routine childhood vaccines will be allowed according to local immunisation practices in each participating country.
- Treatment allocation: Randomised 1:1:1:1 using GSK Biologicals' central randomisation system on Internet (SBIR).
- Blinding: observer-blind

The blinding of study epoch is provided in Synopsis Table 3.

Synopsis Table 3 Blinding of study epoch

Study Epoch	Blinding*
Epoch 001	Double-blind
Epoch 001	Observer-blind

*Double blind for the three lots of PCV-free HRV liquid vaccine and observer-blind for the liquid formulation versus the lyophilised formulation.

- Sampling schedule: Blood samples will be collected from all subjects at Visit 1 and Visit 3 to measure serum anti-RV IgA antibody concentrations using Enzyme Linked Immunosorbent Assay (ELISA).
- Recording of GE episodes: Any GE episodes occurring from Dose 1 of HRV vaccine up to Visit 3 will be recorded for all subjects in the diary card. Parents/Legally Acceptable Representative(s) (LARs) will be instructed to collect stool sample(s) if the subject develops GE during the period from Dose 1 of HRV vaccine up to Visit 3. A stool sample should be collected as soon as possible after illness begins and preferably not later than 7 days after the start of GE symptoms. Two occurrences of diarrhoea will be classified as separate episodes if there will be five or more diarrhoea-free days between the episodes. Refer to the glossary of terms for definitions of GE and diarrhoea.
- Recording of Solicited AEs: Solicited AEs (fever, fussiness/irritability, loss of appetite, cough/runny nose, diarrhoea and vomiting) occurring between the day of each HRV vaccine dose and the following 7 days (Day 0-Day 7) will be recorded daily using diary cards for all subjects.
- Recording of Unsolicited AEs: Unsolicited AEs occurring within 31 days (Day 0-Day 30) after each dose of HRV vaccine will be recorded using diary cards for all subjects.

- Recording of SAEs: SAEs will be recorded from Visit 1 (Day 0) up to 6 months after Dose 2 of HRV vaccine.
- Type of study: e.g., self-contained
- Data collection: Electronic Case Report Form (eCRF)
- Safety monitoring: An IDMC comprising of clinical experts and a biostatistician, will review the safety data accrued during the study and the details of the review will be described in an IDMC charter. The IDMC review will happen after enrolment of 5%, 10% and 50% of subjects. The IDMC review will happen at the following stages:

  Review of all safety data for the first 80 enrolled subjects (5% of total enrolment) as soon as data until 8 days post Dose 2 (Day 0-Day 7) are available for 80 subjects.

  – any available data beyond 8 days post Dose 2 will also be reviewed.

  – during this IDMC review, enrolment of subjects will continue.

  Review of all safety data for the first 160 enrolled subjects (10% of total enrolment) as soon as data until 8 days post Dose 2 (Day 0-Day 7) are available for160 subjects.

  – any available data beyond 8 days post Dose 2 will also be reviewed.

  – until this IDMC review, enrolment of subjects will pause. Enrolment will resume only if no safety concerns are raised by IDMC.

  Review of all safety data for the first 800 enrolled subjects (50% of total enrolment) as soon as data until 8 days post Dose 2 (Day 0-Day 7) are available for 800 subjects.

  – any available data beyond 8 days post Dose 2 will also be reviewed.

  – during this IDMC review, enrolment of subjects will continue.

Number of subjects The target enrolment will be 1600 subjects (400 subjects in each of the PCV-free liquid vaccine groups and 400 subjects in the lyophilised vaccine group) to obtain at least 1280 evaluable subjects (320 subjects in each of the PCV-free liquid vaccine groups and 320 subjects in the lyophilised vaccine group).

Endpoints

Primary

- Evaluation of immunogenicity in terms of anti-RV antibody concentrations
  - Serum anti-RV IgA antibody concentrations expressed as GMCs 1-2 months after Dose 2 in each of the HRV liquid formulation groups (Liq_A, Liq_B and Liq_C).
  - Anti-RV IgA antibody seroconversion rate* 1-2 months after Dose 2 in the lyophilised and pooled liquid groups.
  - Serum anti-RV IgA antibody concentrations expressed as GMCs 1-2 months after Dose 2 in the lyophilised and pooled liquid groups.

*Seroconversion rate is defined as the percentage of subjects who were initially seronegative (i.e., with anti-RV IgA antibody concentration < 20 U/mL prior the first dose of HRV vaccine) and developed anti-RV IgA antibody concentration ≥ 20 U/mL at Visit 3.

Secondary

- Solicited adverse events
  - Occurrence of each general solicited symptom within the 8 days (Day 0-Day 7) follow-up period after each dose of the lyophilised and PCV-free HRV liquid vaccine
- Unsolicited adverse events.
  - Occurrence of unsolicited AEs within 31 days (Day 0-Day 30) after any dose of HRV vaccine, according to the Medical Dictionary for Regulatory Activities (MedDRA) classification.
- Serious adverse events
  - Occurrence of serious adverse events from Dose 1 up to study end.
- Evaluation of immunogenicity in terms of anti-RV antibody concentrations.
  - Serum anti-RV IgA antibody concentrations ≥ 90 U/mL 1-2 months after Dose 2 in the lyophilised and pooled liquid groups.

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LIST OF ABBREVIATIONS

AE:	Adverse event
ATP:	According-To-Protocol
CCID50:	Median Cell Culture Infective Dose (quantity of virus causing infection in 50% of exposed cells)
CDISC:	Clinical Data Interchange Standards Consortium
CI:	Confidence Interval
CLS:	Clinical Laboratory Sciences
CSR:	Clinical Study Report
DNA:	Deoxyribonucleic acid
eCRF:	electronic Case Report Form
ELISA:	Enzyme Linked Immunosorbent Assay
EoS:	End of Study
ES:	Exposed Set
eTDF:	Electronic Temperature excursion Decision Form
EU:	European Union
FDA:	Food and Drug Administration
GCP:	Good Clinical Practice
GE:	Gastroenteritis
GMC:	Geometric Mean antibody Concentration
GSK:	GlaxoSmithKline
HRV:	Human Rotavirus
ICF:	Informed Consent Form
ICH:	International Conference on Harmonisation
IDMC:	Independent Data Monitoring Committee
IEC:	Independent Ethics Committee

IgA:	Immunoglobulin A
IMP:	Investigational Medicinal Products
IND:	Investigational New Drug
IRB:	Institutional Review Board
IS:	Intussusception
Kg:	Kilograms
LAR:	Legally Acceptable Representative
Liq_A:	Group receiving PCV-free HRV liquid formulation lot A
Liq_B:	Group receiving PCV-free HRV liquid formulation lot B
Liq_C:	Group receiving PCV-free HRV liquid formulation lot C
LSLV:	Last Subject Last Visit
Lyo:	Group receiving GSK Biologicals' currently licensed lyophilised HRV formulation
MATEX:	MATerial Excellence
MedDRA:	Medical Dictionary for Regulatory Activities
Mg:	Milligrams
mL:	Millilitre
PASS:	Power Analysis and Sample Size
PCD:	Primary Completion Date
RT-PCR:	Reverse Transcription Polymerase Chain reaction
PCV:	Porcine Circovirus
PPS:	Per-Protocol Set
RCC:	Reverse Cumulative Curve
RV:	Rotavirus
RVGE:	Rotavirus Gastroenteritis
SAS:	Statistical Analysis System

SAE:	Serious Adverse Event
SBIR:	Randomisation System on Internet
SCID:	Severe Combined Immunodeficiency
SDV:	Source Document Verification
SPM:	Study Procedures Manual
TVC:	Total Vaccinated Cohort
U:	Unit
US:	United States
WHO:	World Health Organisation

GLOSSARY OF TERMS

Adverse event:	Any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. An Adverse Event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e., lack of efficacy), abuse or misuse.
Blinding:	A procedure in which one or more parties to the trial are kept unaware of the treatment 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 subject and the site and sponsor personnel involved in the clinical evaluation of the subjects are blinded while other study personnel may be aware of the treatment assignment (see Section 5.3 for details on observer-blinded studies). In a double blind study, the subject, the investigator and sponsor staff who are involved in the treatment or clinical evaluation of the subjects and the review or analysis of data are all unaware of the treatment assignment.
Child in care:	A child who has been placed under the control or protection of an agency, organisation, 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.
Diarrhoea:	Passage of three or more looser than normal stools within a day.
Eligible:	Qualified for enrolment into the study based upon strict adherence to inclusion/exclusion criteria.

End of Study **(Synonym of End of Trial):**	For studies without collection of human biologicals samples or imaging data EoS is the Last Subject Last Visit (LSLV). For studies with collection of Human Biologicals Samples or imaging data, EoS is defined as the date of the last testing/reading released of the Human Biological Samples or imaging data, related to primary and secondary endpoints. EoS must be achieved no later than 8 months after LSLV.
Epoch:	An epoch is a self-contained set of consecutive time points or a single time point from a single protocol. Self-contained means that data collected for all subjects at all time points within that epoch allows to draw a complete conclusion to define or precise the targeted label of the product. Typical examples of epochs are primary vaccinations, boosters, yearly immunogenicity follow-ups, and surveillance periods for efficacy or safety.
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 Set (PPS) analysis (see Sections 6.7.2 and 10.4 for details on criteria for evaluability).
Gastroenteritis:	Diarrhoea with or without vomiting.
Immunological correlate of protection:	The defined immune response above which there is a high likelihood of protection in the absence of any host factors that might increase susceptibility to the infectious agent.
Investigational vaccine: **(Synonym of Investigational Medicinal Product)**	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorisation when used in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.

Legally acceptable representative: **(The terms legal representative or legally authorized representative are used in some settings.)**	An individual or juridical or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical trial.
Primary completion date:	The date that the final subject was examined or received an intervention for the purpose of final collection of data for the primary outcomes, whether the clinical trial concluded according to the pre-specified protocol or was terminated.
Randomisation:	Process of random attribution of treatment to subjects in order to reduce bias of selection.
Site Monitor:	An individual assigned by the sponsor who is responsible for assuring proper conduct of clinical studies at one or more investigational sites.
Solicited adverse event:	AEs to be recorded as endpoints in the clinical study. The presence/occurrence/intensity of these events is actively solicited from the subject or an observer during a specified post-vaccination follow-up period.
Subject:	Term used throughout the protocol to denote an individual who has been contacted in order to participate or participates in the clinical study, either as a recipient of the vaccines or as a control.
Subject number:	A unique number identifying a subject, assigned to each subject consenting to participate in the study.
Treatment:	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 subject, identified by a unique number, according to the study randomisation or treatment allocation.
Treatment number:	A number identifying a treatment to a subject, according to the study randomisation or treatment allocation.

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.
Vomiting:	One or more episodes of forceful emptying of partially digested stomach contents ≥ 1 hour after feeding within a day.

TRADEMARK

The following trademark is used in the present protocol.

Note: In the body of the protocol (including the synopsis), the names of the vaccine will be written without the superscript symbol ™ or ® and in *italics*.

Trademarks of the GlaxoSmithKline group of companies	Generic description
Rotarix®/™	Human rotavirus vaccine

1. INTRODUCTION

1.1. Background

Rotavirus (RV) infection is the leading cause of acute gastroenteritis (GE) and severe diarrhoea in infants and young children <5 years of age [Atherly, 2009]. It has been estimated that in 2008, approximately 453,000 (420,000-494,000) deaths were caused due to RV. Approximately 85% of this burden was in low-income countries globally [WHO position paper, 2013].

Although RV disease only rarely causes death in Europe, North America and Australia, it has severe effects in countries of southeast Asia (India, Pakistan) and sub-Saharan Africa (DR Congo, Ethiopia, Nigeria) [Desselberger, 2012]. In developed countries, RV infection remains the most common cause of hospitalisation for GE in children and leads to major medical and societal costs. During the past years, vaccines have been developed that could prevent the enormous morbidity and mortality from RV. Two live oral RV vaccines have been licensed in many countries; one is derived from an attenuated human strain of RV and the other combines five bovine-human reassortant strains [Glass, 2006]. Each of these vaccines has proven highly effective in preventing severe RV diarrhoea by substantially reducing number and associated costs of child hospitalisations and clinical visits for acute diarrhoea in children. Moreover, these vaccines could reduce deaths from diarrhoea and improve child survival through programmes such as childhood immunisations and diarrhoeal disease control in developing countries. The World Health Organisation (WHO) recognises RV vaccination as an effective measure to prevent RV infection and to reduce disease burden, and recommends its inclusion into all national infant immunisation programs [WHO position paper, 2013].

GlaxoSmithKline (GSK) Biologicals' RV vaccine (Rotarix™) is a vaccine for oral use, containing the live attenuated human rotavirus (HRV) RIX4414 strain. Infants aged younger than 3 months who received the vaccine did not develop diarrhoea, vomiting or fever [Vesikari, 2004(a)]. The initial trials that GSK conducted in Finland showed safety, immunogenicity and efficacy of the *Rotarix* vaccine [Vesikari, 2004(b)]. In Latin American and European studies, vaccine efficacy of oral live attenuated HRV vaccine *Rotarix* (RIX4414) was high, ranging from 80.5% to 90.4% against severe Rotavirus Gastroenteritis (RVGE), and 83.0% to 96.0% against hospitalisation due to RVGE during the first two years of life [Vesikari, 2007; Linhares, 2008]. Furthermore, results from a phase III clinical study undertaken in Singapore, Hong Kong, and Taiwan showed that during the first two years of life, two doses of RIX4414 vaccine provided a high level of protection against severe RVGE (vaccine efficacy: 96.1%), and had a safety profile similar to placebo [Phua, 2012]. Such safety and efficacy studies in Europe, Latin America and Asia have confirmed that the vaccine is safe, well-tolerated and efficacious (range: 80-96%) in preventing severe RVGE in the first two years of life [Cunliffe, 2014].

Rotarix is registered in at least 130 countries and about 280 million doses of the vaccine (lyophilised and liquid formulations) are estimated to have been distributed worldwide since its launch until July 2015.

Please refer to the current Investigator Brochure for information regarding the pre-clinical and clinical studies and the epidemiological information of *Rotarix* vaccine.

1.2. Rationale for the study and study design

1.2.1. Rationale for the study

Using advanced technology in 2010, researchers from the University of California, San Francisco identified Deoxyribonucleic acid (DNA) fragments of *Porcine circovirus* type 1 (PCV-1) in *Rotarix*. Further investigations conducted by GSK and the United States (US) Food and Drug Administration (FDA) confirmed the presence of PCV-1 DNA fragments in *Rotarix* and its starting materials as well as low levels of PCV-1 viral particles during production process and in the final container. The evidence from retrospective laboratory investigations conducted by GSK on 40 HRV vaccine recipients showed that none of the subjects who received the HRV vaccine demonstrated seroconversion to PCV-1 while the PCV-1 from the vaccine was identified in the stool samples of 4 infants from the HRV group (at Day 3 and Day 7 post Dose 1). The detection of PCV-1 DNA only at the earliest time points post-vaccination was consistent with transient passage of DNA through the infants' digestive tracts without replication. Lack of PCV-1 infection is further supported by the absence of anti-PCV-1 antibody in the HRV vaccine recipients, including the infants who had PCV-1 DNA detected in their stool samples. Therefore, currently available data do not suggest occurrence of PCV-1 infection in infants who received *Rotarix* in clinical trials [Dubin, 2013]. These results are consistent with published literature which indicates that PCV-1 is not capable of causing infection in humans [Hattermann, 2004a; Hattermann, 2004b].

GSK is in the process of replacing the cell bank and virus seeds used as base production material for its HRV vaccine. In the meantime, and in accordance with the regulators, the company continues to manufacture *Rotarix* to the existing approved production and quality standards to meet public health needs worldwide.

1.2.2. Rationale for the study design

In order to support licensure of the PCV-free liquid HRV vaccine, GSK Biologicals proposes to conduct a clinical study to demonstrate the lot-to-lot consistency of the PCV-free liquid HRV vaccine in terms of anti-RV Immunoglobulin A (IgA) antibody geometric mean antibody concentrations (GMCs), 1-2 months after Dose 2 and the non-inferiority of the PCV-free liquid HRV vaccine to GSK Biologicals' currently licensed lyophilised HRV vaccine in terms of anti-rotavirus IgA seroconversion rates and GMCs 1-2 months after Dose 2.

This study is planned to be conducted in 1600 children aged 6-12 weeks, randomised (1:1:1:1) between groups receiving GSK Biologicals' currently licensed lyophilised HRV vaccine and three different lots of PCV-free liquid HRV vaccine.

The current lyophilised PCV-containing vaccine will be used as control, since the study is planned to be conducted in US and non-US sites and the liquid formulation of *Rotarix* is not licensed in the US.

Two oral doses of the study vaccines will be administered at an approximate 1-month or 2-months interval to subjects, according to the immunisation schedule for RV vaccine administration in participating countries. Blood samples for immunogenicity assessment will be collected from all subjects before the first dose and at 1-2 months post Dose 2.

An Independent Data Monitoring Committee (IDMC) will review the safety data of the first 5%, 10% and 50% of the subjects enrolled to evaluate if there is any safety concern with the PCV-free liquid HRV vaccine. Enrolment will be paused when first 10% of study sets are enrolled, for the purpose of the IDMC review of the safety data up to 8 days post Dose 2 (Day 0-Day 7) and will only resume if the outcome of the IDMC review is positive.

1.3. Benefit: Risk Assessment

Please refer to the current Investigator Brochure for the summary of potential risks and benefits of *Rotarix* vaccine.

The following section outlines the risk assessment and mitigation strategy for this study protocol:

1.3.1. Risk Assessment

Important Potential/Identified Risk	Data/Rationale for Risk	Mitigation Strategy
Investigational study vaccine *(Rotarix)*		
Intussusception	Spontaneous data	• Subjects will be followed up to 6 months after receipt of the vaccine to check for any safety signal. • Subjects should report any untoward symptoms experienced after receiving the vaccine immediately to the investigator. • All SAEs should be reported immediately to GSK. • An IDMC will review the safety data of the first 160 subjects enrolled in the study to provide recommendation on recruitment of the remaining study subjects. Please refer to Section 3 for more details.
Hematochezia	Spontaneous data	
Gastroenteritis with vaccine viral shedding in infants with severe combined immunodeficiency (SCID)	Spontaneous data	
Kawasaki disease	Based on signal observed for *Rota Teq* vaccine	
Study Procedures		
Allergic reaction to the vaccine.	Spontaneous data	Subjects will be observed for at least 30 minutes after vaccine administration, with medical attention available in case of anaphylaxis reactions.

1.3.2. Benefit Assessment

By receiving the HRV vaccine the subject may have the benefit of being protected against RV disease. In addition the subject's participation will benefit other children in the future since information collected during this study will help in evaluation of the HRV vaccine against RV GE.

In addition, the subjects will undergo a history directed physical examination at the first study visit. In case the study doctor discovers any medical condition, the subject will be referred to the local healthcare system.

The vaccine and study tests will be provided free of cost to the subjects.

1.3.3. Overall Benefit: Risk Conclusion

Taking into account the measures taken to minimize risk to subjects participating in this study, the potential or identified risks identified in association with [444563/Rotavirus vaccine] are justified by the potential benefits (prevention/treatment) that may be afforded to subjects receiving the vaccine for immunisation against RV.

2. OBJECTIVES

2.1. Co-Primary objectives

- To demonstrate the lot-to-lot consistency of the PCV-free liquid HRV vaccine in terms of immunogenicity as measured by serum anti-RV IgA antibody concentrations 1-2 months after Dose 2.

Consistency will be demonstrated if, for all pairs of lots, the two-sided 95% confidence intervals (CIs) for the ratio of anti-RV IgA antibody GMCs 1-2 months after Dose 2 are within the [0.5; 2] clinical limit interval.

- To demonstrate the immunological non-inferiority of PCV-free liquid HRV vaccine as compared to the currently licensed lyophilised HRV vaccine in terms of seroconversion rates 1-2 months after 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 PCV-free liquid HRV vaccine (pooled HRV liquid groups) and licensed lyophilised HRV vaccine is greater than or equal to -10%.

- To demonstrate the non-inferiority of the PCV-free liquid HRV vaccine to that of the currently licensed lyophilised HRV vaccine in terms of serum anti-RV IgA antibody concentrations 1-2 months after Dose 2.

Non-inferiority will be demonstrated if the lower limit of the two-sided 95% CI for the ratio of anti-RV IgA antibody GMCs 1-2 months after Dose 2 between the PCV-free liquid HRV vaccine (pooled HRV liquid groups) and the lyophilised HRV vaccine is greater than or equal to 0.67.

Refer to Section 10.1 for the definition of the primary endpoints.

2.2. Secondary objectives

Reactogenicity and safety

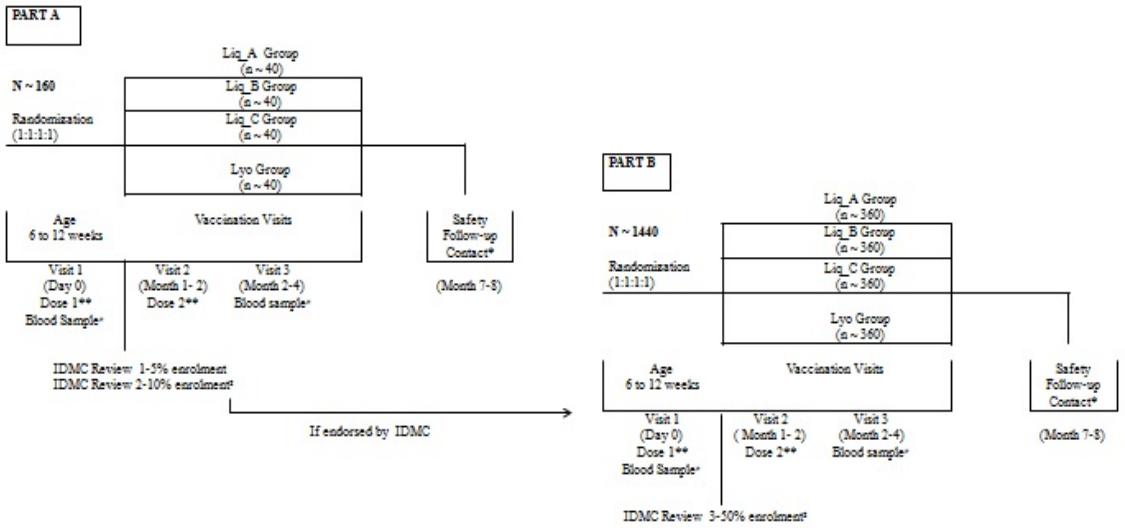
- To evaluate the reactogenicity of the liquid HRV vaccine and currently licensed lyophilised HRV vaccine in terms of solicited AEs during the 8 days (Day 0-Day 7) follow-up period after each vaccination.
- To assess the safety of the study vaccines in terms of unsolicited AEs during the 31 days (Day 0-Day 30) follow-up period after each vaccination and Serious Adverse Events (SAEs) during the entire study period.

Immunogenicity

- To assess the immunogenicity of the PCV-free liquid HRV vaccine and the currently licensed lyophilised HRV vaccine, in terms of percentage of subjects with anti-RV IgA antibody concentrations ≥ 90 U/mL 1-2 months after Dose 2.

Refer to Section 10.2 for the definition of the secondary endpoints.

3. STUDY DESIGN OVERVIEW



N: Number of subjects planned to be enrolled, n = number of subjects in each group
* Contact (by telephone call or any other convenient procedure) for the safety follow-up will take place 6 months after the last dose of HRV vaccine.
** Two oral doses of the study vaccines will be administered at an approximate 1-month or 2-months interval to subjects, according to the immunisation schedule for RV vaccine administration in participating countries.
#Blood samples will be taken before the first dose and 1 to 2 months after the second dose.
$ An IDMC will review the safety data for the first 80 enrolled subjects (5% of total enrolment) and first 160 enrolled subjects (10% of total enrolment) as soon as data until 8 days post Dose 2 (Day 0-Day 7) are available. Enrolment will be paused when first 10% of the subjects are enrolled for the purpose of the IDMC review of the safety data and will only resume if the outcome of the IDMC review is positive.
Review of the safety data for the first 800 enrolled subjects (50% of total enrolment) will be conducted as soon as data until 8 days post Dose 2 (Day 0-Day 7) are available for 800 subjects.

Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the outline of study procedures (Section 5.5), are essential and required for study conduct.

- Experimental design: Phase IIIA, observer-blind, randomised (1:1:1:1), controlled, multi-centric, with four parallel groups and a staggered enrolment (Part A and Part B).
- Duration of the study: The intended duration of the study, per subject, will be approximately 7-8 months including the 6 months of extended safety follow-up period after the last dose of HRV vaccine.
  - Epoch 001: Primary starting at Visit 1 (Day 0) and ending at the safety follow-up contact (Month 7-8).
- Primary completion Date (PCD): Visit 3 (Month 2-4).

Refer to glossary of terms for the definition of PCD.

- End of Study (EoS): Last testing results released of samples collected at Visit 3 or Last Subject Last Visit (LSLV) (Follow up contact at month 7-8).

Refer to glossary of terms for the definition of EoS.

- Study groups: The study groups and epoch foreseen in the study are provided in Table 1.

Table 1 Study groups and epoch foreseen in the study

Study Groups	Number of subjects	Age at Dose 1 (Min-Max)	Epoch
			Epoch 001
Liq_A	400	6 weeks-12 weeks	●
Liq_B	400	6 weeks-12 weeks	●
Liq_C	400	6 weeks-12 weeks	●
Lyo	400	6 weeks-12 weeks	●

The study groups and treatments foreseen in the study are given in Table 2.

Table 2 Study groups and treatments foreseen in the study

Treatment name	Vaccine name		Study Groups		
		Liq_A	Liq_B	Liq_C	Lyo
HRV Liquid	HRV PCV-free ‡	x	x	x	
HRV Lyophilised	HRV *				x

‡ PCV-free HRV liquid vaccine
* Licensed formulation of HRV lyophilised vaccine

  - PCV-free HRV liquid formulation lot A (also referred to as Liq_A group)
  - PCV-free HRV liquid formulation lot B (also referred to as Liq_B group)
  - PCV-free HRV liquid formulation lot C (also referred to as Liq_C group)
  - GSK Biologicals' currently licensed lyophilised HRV formulation (also referred to as Lyo group)

- Control: active control-GSK Biologicals' currently licensed lyophilised HRV vaccine.

- Vaccination schedule: Two doses of HRV vaccine to be administered according to a 0, 1-2 month schedule according to the immunisation schedule for RV vaccine administration in participating countries.
  - Concomitant administration of routine childhood vaccines will be allowed according to local immunisation practices in each participating country.
- Treatment allocation: Randomised 1:1:1:1 using GSK Biologicals' central randomisation system on Internet (SBIR).

- Blinding: observer-blind

The blinding in the study is given in Table 3.

Table 3 Blinding of study epoch

Study Epoch	Blinding*
Epoch 001	Double-blind
Epoch 001	Observer-blind

*Double blind for the three lots of PCV-free HRV liquid vaccine and observer-blind for the liquid formulation versus the lyophilised formulation.

- Sampling schedule: Blood samples will be collected from all subjects at Visit 1 and Visit 3 to measure serum anti-RV IgA antibody concentrations using Enzyme Linked Immunosorbent Assay (ELISA).
- Recording of GE episodes: Any GE episodes occurring from Dose 1 of HRV vaccine up to Visit 3 will be recorded for all subjects in the diary card. Parents/Legally Acceptable Representative(s) (LARs) will be instructed to collect stool sample(s) if the subject develops GE during the period from Dose 1 of HRV vaccine up to Visit 3. A stool sample should be collected as soon as possible after illness begins and preferably not later than 7 days after the start of GE symptoms. Two occurrences of diarrhoea will be classified as separate episodes if there will be five or more diarrhoea-free days between the episodes. Refer to the glossary of terms for definitions of GE and diarrhoea.
- Recording of Solicited AEs: Solicited AEs (fever, fussiness/irritability, loss of appetite, cough/runny nose, diarrhoea and vomiting) occurring between the day of each HRV vaccine dose and the following 7 days (Day 0-Day 7) will be recorded daily using diary cards for all subjects.
- Recording of Unsolicited AEs: Unsolicited AEs occurring within 31 days (Day 0-Day 30) after each dose of HRV vaccine will be recorded using diary cards for all subjects.
- Recording of SAEs: SAEs will be recorded from Visit 1 (Day 0) up to 6 months after Dose 2 of HRV vaccine.
- Type of study: self-contained
- Data collection: Electronic Case Report Form (eCRF)
- Safety monitoring: An IDMC comprising of clinical experts and a biostatistician, will review the safety data accrued during the study and the details of the review will be described in an IDMC charter. The IDMC review will happen after enrolment of 5%, 10% and 50% of subjects. The IDMC review will happen at the following stages:

  Review of all safety data for the first 80 enrolled subjects (5% of total enrolment) as soon as data until 8 days post Dose 2 (Day 0-Day 7) are available for 80 subjects.

  – any available data beyond 8 days post Dose 2 will also be reviewed.

  – during this IDMC review, enrolment of subjects will continue.

  Review of all safety data for the first 160 enrolled subjects (10% of total enrolment) as soon as data until 8 days post Dose 2 (Day 0-Day 7) are available for160 subjects.

  – any available data beyond 8 days post Dose 2 will also be reviewed.

– until this IDMC review, enrolment of subjects will pause. Enrolment will resume only if no safety concerns are raised by IDMC.

Review of all safety data for the first 800 enrolled subjects (50% of total enrolment) as soon as data until 8 days post Dose 2 (Day 0-Day 7) are available for 800 subjects.

– any available data beyond 8 days post Dose 2 will also be reviewed.

– during this IDMC review, enrolment of subjects will continue.

4. STUDY SET

4.1. Number of subjects/centres

The target enrolment will be 1600 subjects (400 subjects in each of the PCV-free liquid vaccine groups and 400 subjects in the lyophilised vaccine group) to obtain at least 1280 evaluable subjects (320 subjects in each of the PCV-free liquid vaccine groups and 320 subjects in the lyophilised vaccine group).

Refer to Section 10.3 for a detailed description of the criteria used in the estimation of sample size.

Overview of the recruitment plan

- Subjects will be enrolled at multiple sites in the US and other countries. Approximately 25% of subjects will be enrolled in the US.
- Enrolment will be terminated when 1600 subjects have been enrolled.
- The subjects will be enrolled in two parts: the first part (Part A enrolment) will include 160 subjects (approximately 40 subjects in each study group) for IDMC safety data evaluation and the second part (Part B enrolment) will include the remaining subjects.
- Recruitment and randomisation will be monitored by SBIR

4.2. Inclusion criteria for enrolment

Deviations from inclusion criteria are not allowed because they can potentially jeopardise the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

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

- Subjects' 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 informed consent obtained from the parent(s)/LAR(s) of the subject prior to performing any study specific procedure.

- A male or female infant between, and including, 6 and 12 weeks (42-90 days) of age at the time of the first study vaccination.
- Born full-term (i.e., between a gestation period of 37 weeks 0 days and 41 weeks 6 days).
- Healthy subjects as established by medical history and clinical examination before entering into the study.

4.3. Exclusion criteria for enrolment

Deviations from exclusion criteria are not allowed because they can potentially jeopardise the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

The following criteria should be checked at the time of study entry. If ANY exclusion criterion applies, the subject must not be included in the study:

- Child in care
  Please refer to the glossary of terms for the definition of child in care.
- Use of any investigational or non-registered product (drug or vaccine) other than the study vaccines during the period starting 30 days before the first dose of study vaccines (Day-29 to Day 0), or planned use during the study period.
- 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 mg/kg/day, or equivalent). Inhaled and topical steroids are allowed.
- Administration of immunoglobulins and/or any blood products since birth or planned administration during the study period.
- Administration of long-acting immune-modifying drugs at any time during the study period (e.g., infliximab).
- Planned administration/administration of a vaccine not foreseen by the study protocol in the period starting 30 days before the first dose of vaccine administration and ending at Visit 3, with the exception of the inactivated influenza vaccine, which is allowed at any time during the study and other licensed routine childhood vaccinations.
- Concurrently participating in another clinical study, at any time during the study period, in which the subject has been or will be exposed to an investigational or a non-investigational vaccine/product (pharmaceutical product or device).
- Uncorrected congenital malformation (such as Meckel's diverticulum) of the gastrointestinal tract that would predispose for Intussusception (IS).
- History of IS.
- Family history of congenital or hereditary immunodeficiency.

- Any confirmed or suspected immunosuppressive or immunodeficient condition, based on medical history and physical examination (no laboratory testing required).
- Major congenital defects or serious chronic illness.
- Previous vaccination against RV.
- Previous confirmed occurrence of RVGE.
- GE within 7 days preceding the study vaccine administration (warrants deferral of the vaccination).
- History of any reaction or hypersensitivity likely to be exacerbated by any component of the vaccines.
- Hypersensitivity to latex.
- Acute disease and/or fever at the time of enrolment.
  - Fever is defined as temperature ≥ 38.0°C/100.4°F. The preferred location for measuring temperature in this study will be the oral cavity, the axilla and the rectum.
  - Subjects with a minor illness (such as mild diarrhoea, mild upper respiratory infection) without fever may be enrolled at the discretion of the investigator.

5. CONDUCT OF THE STUDY

5.1. Regulatory and ethical considerations, including the informed consent process

The study will be conducted in accordance with all applicable regulatory requirements.

The study will be conducted in accordance with the International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (GCP), all applicable subject privacy requirements and the guiding principles of the Declaration of Helsinki.

The study has been designed and will be conducted in accordance with the ICH Harmonised Tripartite Guideline for clinical investigation of medicinal products in the paediatric population (ICH E11) and all other applicable ethical guidelines.

GSK will obtain favourable opinion/approval to conduct the study from the appropriate regulatory agency, in accordance with applicable regulatory requirements, prior to a site initiating the study in that country.

Conduct of the study includes, but is not limited to, the following:

- Institutional Review Board (IRB)/Independent Ethics Committee (IEC) review and favourable opinion/approval of study protocol and any subsequent amendments.
- Subject's parent(s)/LAR(s) informed consent as appropriate.
- Investigator reporting requirements as stated in the protocol.

GSK will provide full details of the above procedures to the investigator, either verbally, in writing, or both.

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

GSK Biologicals will prepare a model Informed Consent Form (ICF) which will embody the ICH GCP and GSK Biologicals required elements. While it is strongly recommended that this model ICF is to be followed as closely as possible, the informed consent requirements given in this document are not intended to pre-empt any local regulations which require additional information to be disclosed for informed consent to be legally effective. Clinical judgement, local regulations and requirements should guide the final structure and content of the local version of the ICF.

5.2. Subject identification and randomisation of treatment

5.2.1. Subject identification

Subject identification numbers will be assigned sequentially to the subjects whose parent(s)/LAR(s) have consented to their participation in the study, according to the range of subject identification numbers allocated to each study centre.

5.2.2. Randomisation of treatment

5.2.2.1. Randomisation of supplies

The numbering of supplies will be performed at GSK Biologicals, using a block scheme randomisation in MATerial EXcellence (MATEX), a program developed for use in Statistical Analysis System (SAS®) (Cary, NC, USA) by GSK Biologicals. Entire blocks will be shipped to the study centres/warehouse(s).

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

5.2.2.2. Treatment allocation to the subject

The treatment numbers will be allocated by dose.

5.2.2.2.1. Study group and treatment number allocation

The target will be to enrol 1600 eligible subjects who will be randomly assigned to four study groups in a 1: 1: 1: 1 ratio (approximately 400 subjects in each group).

Allocation of the subject to a study group at the investigator site will be performed using SBIR. The randomisation algorithm will use a minimisation procedure accounting for

centre and country. Minimisation factors will have equal weight in the minimisation algorithm.

After obtaining the signed and dated ICF from the subject's parent(s)/LAR(s) and having checked the eligibility of the subject, the site staff in charge of the vaccine administration will access SBIR. Upon providing the subject identification number, the randomisation system will determine the study group and will provide the treatment number to be used for the first dose.

The number of each administered treatment must be recorded in the eCRF on the Vaccine Administration screen.

When SBIR is not available, please refer to the SBIR user guide or the Study Procedures Manual (SPM) for specific instructions.

5.2.2.2.2. Treatment number allocation for subsequent doses

For each dose subsequent to the first dose, the study staff in charge of the vaccine administration will access SBIR, provide the subject identification number, and the system will provide a treatment number consistent with the allocated study group.

The number of each administered treatment must be recorded in the eCRF on the Vaccine Administration screen.

5.3. Method of blinding

This study is observer-blind (double blind for the three lots of PCV-free HRV liquid vaccine and observer-blind for the liquid formulation versus the lyophilised formulation).

Data will be collected in an observer-blind manner. By observer-blind, it is meant that during the course of the study, the vaccines recipient and those responsible for the evaluation of any study endpoint (e.g., safety and reactogenicity) will all be unaware of which vaccine was administered. To do so, vaccine preparation and administration will be done by authorised medical personnel who will not participate in any of the study clinical evaluation assays.

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

5.4. General study aspects

Supplementary study conduct information not mandated to be present in this protocol is provided in the accompanying SPM. The SPM provides the investigator and the site personnel with administrative and detailed technical information that does not impact the safety of the subjects.

The burden of the study for the subject will be minimised as much as possible. For taking blood samples, three attempts at most should be performed. If the physician is not successful after the third attempt, he/she will make no further attempts. A local numbing cream or patch will also be offered at the discretion of the investigator prior to blood sampling, in order to minimise pain when blood samples are drawn.

5.5. Outline of study procedures

The outline of study procedures is detailed in Table 4.

Table 4 List of study procedures

Age	6-12 weeks	3-5 months	4-7 months	9-11 months
Epoch	Epoch 001			
Type of contact	Visit 1	Visit 2	Visit 3	Extended Safety Follow-up Contact
Time points	Day 0	Month 1-2	Month 2-4	Month 7-8
Sampling time points	Pre-Vacc		Post-Vacc 2	
Informed consent	●			
Check inclusion/exclusion criteria	●			
Check contraindications	●	●		
Check warnings and precautions	●	●		
Medical history	●			
Recording of gestational age	●			
Recording of demography	●			
History directed physical examination	●			
History of previous vaccination from birth	●			
Pre-vaccination body temperature	●	●		
Measure/record height and weight	●			
Randomisation	●			
Recording of Treatment number	●	●		
Blood sampling for anti-RV antibody determination (approximately 2 ml)	●		●	
Vaccination *	●	●		
Record regurgitation	●	●		
Distribution of diary cards	O	O		
Daily post-vaccination recording of solicited adverse events within 8 days (Day 0–Day 7) after each vaccination by subjects' parent(s)/LAR(s) in diary card.	●	●		
Recording of non-serious adverse events within 31 days (Day 0–Day 30) after each vaccination, by investigator	●	●	●	
Recording of GE episodes for all subjects	●	●	●	
Collection of stool samples if the child develops GE	●	●	●	
Return of diary cards		O	O	
Diary card transcription by investigator or designee		●	●	
Record any concomitant medication/vaccination in the diary card	●	●	●	
Record any intercurrent medical conditions	●	●	●	●
Recording of Serious Adverse Events (SAEs) and AEs leading to withdrawal	●	●	●	●
Phone Contact				●
Analysis on data collected up to Visit 3			O	
Study Conclusion				●

Note: The double-line border indicates the analyses which will be performed on all data obtained up to that visit or contact.

● is used to indicate a study procedure that requires documentation in the individual eCRF.

O is used to indicate a study procedure that does not require documentation in the individual eCRF.

* Two oral doses of the study vaccines will be administered at an approximate 1-month or 2-months interval to subjects, according to the immunisation schedule for RV vaccine administration in participating countries. Any regurgitation or vomiting by the subjects after study vaccine administration should be recorded in the eCRF. Concomitant administration of routine pediatric vaccines will be allowed according to local immunisation practices in each participating country.

LAR = Legally Acceptable Representative

The intervals between study visits are presented in Table 5.

Table 5 Intervals between study visits

Interval	Optimal length of interval [1]	Allowed interval
Visit 1→Visit 2	1-2 months	28-83 days† after Dose 1
Visit 2→Visit 3	1-2 months	28-83 days† after Dose 2
Visit 2→Contact‡	6 months	180-210 days after Dose 2 of HRV vaccine

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

5.6. Detailed description of study procedures

5.6.1. Informed consent

The signed/witnessed/thumb printed informed consent of the subject's parent(s)/LAR(s) must be obtained before study participation. Refer to Section 5.1 for the requirements on how to obtain informed consent, as appropriate.

5.6.2. Check inclusion and exclusion criteria

Check all inclusion and exclusion criteria as described in Sections 4.2 and 4.3 before enrolment.

5.6.3. Check contraindications, warnings and precautions to vaccination

Contraindications, warnings and precautions to vaccination must be checked at the beginning of each vaccination visit. Refer to Sections 6.5 and 6.6 for more details.

5.6.4. Medical and vaccination history

Obtain the subject's medical and vaccination history by interview and/or review of the subject's medical records and record any pre-existing conditions or signs and/or symptoms present in a subject prior to the first study vaccination in the eCRF. Also record any medication and vaccine administration prior to the study vaccination in the eCRF.

5.6.5. Collect demographic data

Record demographic data such as gestational age, gender and geographic ancestry at Visit 1 in the subject's eCRF.

5.6.6. History directed physical examination

Perform a history directed physical examination. If the investigator determines that the subject's health on the day of vaccination temporarily precludes vaccination, the visit will be rescheduled. Collected information needs to be recorded in the eCRF.

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.

5.6.7. Physical examination

Perform a physical examination of the subject, including assessment of oral/axillary/rectal, body temperature, height and weight. Collected information needs to be recorded in the eCRF.

Physical examination at each study visit subsequent to the first vaccination visit, will be performed only if the subjects' parent(s)/LAR(s) indicates during questioning that there might be some underlying pathology(ies) or if deemed necessary by the Investigator or delegate.

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

5.6.8. Assess pre-vaccination body temperature

The oral/axillary/rectal body temperature of each subject needs to be measured prior to any study vaccine administration. If the subject has fever [fever is defined as temperature ≥38.0°C/100.4°F regardless the location of measurement on the day of vaccination, the vaccination visit will be rescheduled within the allowed interval for this visit (see Table 5).

5.6.9. Study group and treatment number allocation

Study group and treatment number allocation will be performed as described in Section 5.2.2. The number of each administered treatment must be recorded in the eCRF.

5.6.10. Sampling

Refer to the Module on Biospecimen Management in the SPM for detailed instructions for the collection, handling and processing of the samples.

5.6.10.1. Blood sampling for safety and immune response assessments

Blood samples will be taken during certain study visits as specified in Section 5.5-Outline of Study Procedures.

- A volume of approximately 2 mL of whole blood (to provide approximately 0.7 mL of serum) should be drawn from all subjects for anti-RV antibody determination at Visit 1 (Pre-Vacc) and Visit 3 (Post-Vacc 2). After centrifugation, serum samples should be kept at –20°C/–4°F or below until shipment. Refer to the SPM for more details on sample storage conditions.

5.6.10.2. Other biological samples

GE Stool analysis

All GE stool samples collected between Visit 1 and Visit 3 will be tested for the purpose of identifying wild type RV exposure during vaccination and to eliminate such cases from Per-Protocol Set (PPS) immunogenicity analysis at GSK Biologicals' laboratory or in a validated laboratory designated by GSK Biologicals using standardized and validated procedures.

5.6.11. Study Vaccines administration

- After completing all prerequisite procedures prior to vaccination, two oral doses of the study vaccines will be administered at an approximate 1-month or 2-months interval to subjects, according to the immunisation schedule for RV vaccine administration in participating countries (refer to Section 6.3 for detailed description of the vaccines administration procedure). If the investigator or delegate determines that the subject's health on the day of administration temporarily precludes vaccines administration, the visit will be rescheduled within the allowed interval for this visit (refer to Table 5).
- The subjects will be observed closely for at least 30 minutes following the administration of the vaccines, with appropriate medical treatment readily available in case of anaphylaxis.

5.6.12. Record regurgitation

If regurgitation or vomiting occurs after vaccination, no new study vaccine dose should be administered. This information should be recorded in the eCRF. The subject may continue to participate in the study but will be excluded from the planned statistical analyses on the PPS.

5.6.13. Check and record concomitant medication/vaccination and intercurrent medical conditions

Concomitant medication/vaccination must be checked and recorded in the eCRF as described in Section 6.7.

Intercurrent medical conditions must be checked and recorded in the eCRF as described in Section 6.8.

5.6.14. Recording of AEs and SAEs

- Refer to Section 8.3 for procedures for the investigator to record AEs and SAEs. Refer to Section 8.4 for guidelines and how to report SAE reports to GSK Biologicals.
- The subjects' parent(s)/LAR(s) will be instructed to contact the investigator immediately should the subjects manifest any signs or symptoms they perceive as serious.

At each vaccination visit, diary cards will be provided to the subject's parent(s)/LAR(s):

- Recording of GE episodes: Any GE episodes occurring from Dose 1 of HRV vaccine up to Visit 3 will be recorded for all subjects in the diary card. Parent(s)/LAR(s) will be instructed to collect stool sample(s) if the subject develops GE during the period from Dose 1 of HRV vaccine up to Visit 3. A stool sample should be collected as soon as possible after illness begins and preferably not later than 7 days after the start of GE symptoms. Two occurrences of diarrhoea will be classified as separate episodes if there will be five or more diarrhoea-free days between the episodes. Refer to the glossary of terms for definitions of GE and diarrhoea.
- Recording of Solicited AEs: Solicited AEs (fever, fussiness/irritability, loss of appetite, cough/runny nose, diarrhoea and vomiting) occurring between the day of each HRV vaccine dose and the following 7 days (Day 0-Day 7) will be recorded daily using diary cards for all subjects.
- Recording of Unsolicited AEs: Unsolicited AEs occurring within 31 days (Day 0-Day 30) after each dose of HRV vaccine will be recorded using diary cards for all subjects.
- Recording of SAEs: SAEs will be recorded from Visit 1 (Day 0) up to 6 months after Dose 2 of HRV vaccine.
- Collect and verify completed diary cards during discussion with the subject's parent(s)/LAR(s) on Visit 2 and Visit 3.
- Any unreturned diary cards will be sought from the subject's parent(s)/LAR(s) through telephone call(s) or any other convenient procedure.
- The investigator will transcribe the collected information into the eCRF in English.

5.6.15. Phone Contact

A safety follow-up contact will be done by a telephone call to collect information on SAEs and medication taken for treatment of the same.

5.6.16. Study conclusion

The investigator will:

- review data collected to ensure accuracy and completeness
- complete the Study Conclusion screen in the eCRF.

5.7. Biological sample handling and analysis

Please refer to the SPM for details on biospecimen management (handling, storage and shipment).

Samples will not be labelled with information that directly identifies the subject but will be coded with the identification number for the subject (subject number).

- Collected samples will be used for protocol mandated research and purposes related to the improvement, development and quality assurance of the laboratory tests described in this protocol. This may include the management of the quality of these tests, the maintenance or improvement of these tests, the development of new test methods, as well as making sure that new tests are comparable to previous methods and work reliably.
- It is also possible that future findings may make it desirable to use the samples acquired in this study for future research, not described in this protocol. Therefore, all subjects/subjects' parent(s)/LAR(s) in countries where this is allowed will be asked to give specific consent to allow GSK or a contracted partner to use the samples for future research. Future research will be subject to the laws and regulations in the respective countries and will only be performed once an independent Ethics Committee or Review Board has approved this research.

Information on further investigations and their rationale can be obtained from GSK Biologicals.

Any sample testing will be done in line with the consent of the individual subject/subject's parent(s)/LAR(s).

Refer also to the Investigator Agreement, where it is noted that the investigator cannot perform any other biological assays except those described in the protocol or its amendment(s).

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

5.7.1. Use of specified study materials

When materials are provided by GSK Biologicals, it is MANDATORY that all clinical samples (including serum samples) be collected and stored exclusively using those materials in the appropriate manner. The use of other materials could result in the exclusion of the subject from the PPS analysis (See Section 10.4 for the definition of sets to be analysed). The investigator must ensure that his/her personnel and the laboratory(ies) under his/her supervision comply with this requirement. However, when GSK Biologicals does not provide material for collecting and storing clinical samples, appropriate materials from the investigator's site must be used. Refer to the Module on Clinical Trial Supplies in the SPM.

5.7.2. Biological samples

The biological samples to be collected from subjects are described in Table 6.

Table 6 Biological samples

Sample Type	Quantity	Unit	Sampling time point	Subset/No. subjects
Blood	Approximately 2	ml	Pre-Vacc	All
	Approximately 2	ml	Post-Vacc 2	All
GE Stool †	NA	NA	From Visit 1 up to Visit 3	All subjects with GE

† Stool analysis performed for subjects who experience GE episodes.

5.7.3. Laboratory assays

Please refer to APPENDIX A for a detailed description of the assays performed in the study. Please refer to APPENDIX B for the address of the clinical laboratories used for sample analysis and/or sample management.

GE Stool analysis

All GE stool samples collected between Visit 1 and Visit 3 will be tested for the purpose of identifying wild type RV exposure during vaccination and to eliminate such cases from PPS immunogenicity analysis at GSK Biologicals' laboratory or in a validated laboratory designated by GSK Biologicals using standardized and validated procedures.

All GE stool samples will be analysed by ELISA for detection of RV antigen. If a stool sample tests positive for RV antigen, the sample will be tested by Reverse Transcription Polymerase Chain reaction (RT-PCR) followed by sequencing to determine the G and P genotype.

Serum analysis

All serological assays will be performed at GSK Biologicals' laboratory or in a validated laboratory designated by GSK Biologicals using standardized and validated procedures.

The laboratory assays to be performed are presented in Table 7.

Table 7 Humoral Immunity (Antibody determination)

System	Component	Method	Kit/Manufacturer	Unit	Cut-off†	Laboratory
SER	Rotavirus Ab.IgA	ELI	NA	U/ml	20	GSK Biologicals*

†The assay cut-off is subject to change
*GSK Biologicals laboratory refers to the Clinical Laboratory Sciences (CLS) in Rixensart, Belgium; Wavre, Belgium
*GSK Biologicals' laboratory or validated laboratory designated by GSK Biologicals.
SER = Serum
IgA = Immunoglobulin A
ELI =ELISA (Enzyme Linked Immunosorbent Assay)
U = Units; ml = millilitres
NA = Not Applicable

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

5.7.4. Biological samples evaluation

5.7.4.1. Immunological read-outs

The immunological read-outs are given in Table 8.

Table 8 Immunological read-outs

Blood sampling time point				
Type of contact and time point	**Sampling time point**	**No. subjects**	**Component**	**Components priority rank**
Visit 1 (Day 0)	Pre-Vacc	All	anti-HRV IgA	None
Visit 3 (Month 2-4)	Post-Vacc 2	All	anti-HRV IgA	None
GE stool analysis†				
Visit 1 (Day 0) to Visit 3 (Month 2-4)	From Visit 1 up to Visit 3	All subjects with GE	RV antigen	None

† Stool analysis performed for subjects who experience GE episodes.

In case of insufficient blood sample volume to perform assays for all antibodies, the samples will be analysed according to priority ranking provided in Table 8.

5.7.5. Immunological correlates of protection

No immunological correlate of protection has been demonstrated so far for the antigen used as part of the HRV vaccine. However, a study by Cheuvart et al., in 2014 indicated that post-vaccination anti-RV IgA seropositivity (antibody concentration ≥ 20 U/mL) may serve as a useful correlate of vaccine efficacy in clinical trials of *Rotarix* [Cheuvart, 2014].

The immunological assay results will be communicated to the investigator as soon as they become available.

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

For the subjects identified as non-responders, it remains the responsibility of the investigator in charge of the subject's clinical management to determine the medical need for re-vaccination and to re-vaccinate the subjects as per local/regional practices.

6. STUDY VACCINES

6.1. Description of study vaccines

All candidate vaccines to be used have been developed and manufactured by GSK Biologicals.

The Quality Control Standards and Requirements for each candidate vaccine are described in separate Quality Assurance documents (e.g., release protocols, certificate of analysis) and the required approvals have been obtained.

The vaccines are labelled and packed according to applicable regulatory requirements.

Commercial vaccines are assumed to comply with the specifications given in the manufacturer's Summary of Product Characteristics.

The study vaccines to be utilized in the study are detailed in Table 9.

Table 9 Study vaccines

Treatment name	Vaccine name	Formulation	Presentation	Volume to be administered	Number of doses
HRV Liquid	HRV PCV-free	PCV-free HRV RIX4144 live attenuated >=$10^{6.0}$$CCID_{50}$	Liquid vaccine in a pre-filled oral applicator.	1.5 ml	2
HRV Lyophilised	HRV	HRV RIX4144 live attenuated >=$10^{6.0}$$CCID_{50}$	Lyophilised vaccine in a monodose glass vial.	1 ml	2
	HRV Diluent	$CaCO_3$=60mg	Diluent for lyophilised vaccine (calcium carbonate liquid antacid) supplied separately in a prefilled oral applicator.		

$CCID_{50}$ = median Cell Culture Infective Dose (quantity of virus causing infection in 50% of exposed cells)
$CaCO_3$ = Calcium carbonate
HRV = Human Rotavirus
ml = millilitre; mg = milligrams

6.2. Storage and handling of study vaccines

The study vaccines must be stored at the respective label storage temperature conditions in a safe and locked place. Access to the storage space should be limited to authorized study personnel. The storage conditions will be assessed during pre-study activities under the responsibility of the sponsor study contact. The storage temperature should be continuously monitored with calibrated (if not validated) temperature monitoring

device(s) and recorded. Refer to the Module on Clinical Trial Supplies in the SPM for more details on storage of the study vaccines.

Temperature excursions must be reported in degree Celsius.

Any temperature excursion outside the range of 0.0 to +8.0°C (for +2 to +8°C/+36 to +46°F label storage condition) impacting Investigational Medicinal Products (IMPs) must be reported in the appropriate (electronic) temperature excursion decision form ([e]TDF). The impacted IMPs must not be used and must be stored in quarantine at label temperature conditions until usage approval has been obtained from the sponsor.

In case of temperature excursion below +2.0°C down to 0.0°C impacting IMP(s) there is no need to report in (e)TDF, but adequate actions must be taken to restore the +2 to +8°C/+36 to +46°F label storage temperature conditions. The impacted IMP(s) may still be administered, but the site should avoid re-occurrence of such temperature excursion. Refer to the Module on Clinical Trial Supplies in the SPM for more details on actions to take.

Refer to the Module on Clinical Trial Supplies in the SPM for details and instructions on the temperature excursion reporting and usage decision process, packaging and accountability of the study vaccines.

6.3. Dosage and administration of study vaccines

Liquid formulation of HRV vaccine

The pre-filled oral applicator is shaken well before use. The vaccine (approximately 1.5 mL) should then be administered orally as a single dose.

Lyophilised formulation of HRV vaccine

To prepare GSK Biologicals' HRV lyophilised vaccine for administration, the entire content of the supplied diluent (calcium carbonate buffer) should be transferred from the oral applicator into the vial of the lyophilised product via the intermediate device. The vial should be shaken well to re-suspend the vaccine. The entire volume of the re-suspended product (approximately 1 mL) should be withdrawn into the same oral applicator and the re-suspended product should then be administered promptly as a single oral dose.

Administration of the vaccines

In order to allow the swallowing of the entire volume of the single oral dose (of liquid or lyophilised formulation), the administration should occur in a quiet environment. The child should be seated in a reclining position. Administer orally (i.e., into the child’s mouth towards the inner cheek) the entire content of oral applicator. Sufficient time should be allowed for the baby to swallow the vaccine solution, to avoid regurgitation or vomiting. Should however the subject regurgitate or vomit after study vaccine administration, no new study vaccine dose should be administered. This information should be recorded in the eCRF. The subject may continue to participate in the study.

The vaccinees will be observed closely for at least 30 minutes, with appropriate medical treatment readily available in case of a rare anaphylactic reaction following the administration of vaccines.

The vaccination regimen is summarized in Table 10.

Table 10 Dosage and administration

Type of contact and time point	volume to be administered	Study Group	Treatment name	Route [1]	Site	Side
Visit 1, Visit 2	1.5 ml	Liq_A Liq_B Liq_C	HRV Liquid	O	Not applicable	Not applicable
Visit 1, Visit 2	1 ml	Lyo	HRV Lyophilised	O	Not applicable	Not applicable

[1]Oral (O)

6.4. Replacement of unusable vaccine doses

In addition to the vaccine doses provided for the planned number of subjects (including over-randomisation when applicable), at least 30% additional vaccine doses will be supplied to replace those that are unusable.

The investigator will use SBIR to obtain the replacement treatment number. The replacement numbers will be allocated by dose. The system will ensure, in a blinded manner, that the replacement applicator matches the formulation the subject was assigned to by randomisation.

6.5. Contraindications to subsequent vaccination

The following events constitute absolute contraindications to further administration of *Rotarix* vaccine. If any of these events occur during the study, the subject must not receive additional doses of vaccines but may continue other study procedures at the discretion of the investigator (see Section 8.5).

- Anaphylaxis following the administration of vaccines
- Hypersensitivity reaction following the administration of the HRV vaccine.
- Any uncorrected congenital malformation of the gastrointestinal tract (such as Meckel's diverticulum) that would predispose for IS.
- Any history of IS.
- SCID.

The following events constitute contraindications to administration of *Rotarix* vaccine at that point in time; if any of these events occur at the time scheduled for vaccination, the subject may be vaccinated at a later date, within the time window specified in the protocol (see Section 5.5), or withdrawn at the discretion of the investigator (see Section 8.5).

- Acute disease and/or fever at the time of vaccination.
  - Fever is defined as temperature ≥ 38.0°C/100.4°F. The preferred location for measuring temperature in this study will be the oral cavity, the axilla and the rectum.
  - Subjects with a minor illness (such as mild diarrhoea, mild upper respiratory infection) without fever may be enrolled at the discretion of the investigator.
- GE within 7 days preceding the study vaccine administration.

6.6. Warnings and precautions

The HRV vaccine should under no circumstances be injected.

There are no data on the safety and efficacy of *Rotarix* in infants with gastrointestinal illnesses. Administration of *Rotarix* may be considered with caution in such infants when, in the opinion of the physician, withholding the vaccine entails a greater risk.

The risk of IS has been evaluated in a large safety trial (including 63,225 infants) conducted in Latin America and Finland. No increased risk of IS was observed in this clinical trial following administration of *Rotarix* when compared with placebo.

However, post-marketing safety data indicate a transient increased risk of IS after vaccination, mostly within 8 days following the administration of the first dose of *Rotarix* and, to a lesser extent, the second dose. The overall incidence of IS remains rare. Whether *Rotarix* affects the overall risk of IS has not been established.

Therefore, parent(s)/LAR(s) should be advised to promptly report any symptoms indicative of IS (severe abdominal pain, persistent vomiting, bloody stools, abdominal bloating and/or high fever).

Excretion of the vaccine virus in the stools is known to occur after vaccination and lasts for 10 days on average with peak excretion around the 7th day. In clinical trials, cases of transmission of excreted vaccine virus to seronegative contacts of vaccines have been observed without causing any clinical symptoms. *Rotarix* should be administered with caution to individuals with immunodeficient close contacts, such as individuals with malignancies, or who are otherwise immunocompromised or receiving immunosuppressive therapy. Contacts of recent vaccinees should be advised to observe careful hygiene (including washing their hands) when changing children's diapers.

The tip caps of the prefilled oral applicators of diluent may contain natural rubber latex which may cause allergic reactions in individuals who are sensitive to latex.

Refer to the approved product label/package insert for more details.

6.7. Concomitant medications/products and concomitant vaccinations

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

6.7.1. Recording of concomitant medications/products and concomitant vaccinations

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

- All concomitant medications/products, except vitamins and dietary supplements, administered during the period starting 30 days before and following each dose of study vaccine.
- Any concomitant vaccination administered in the period from first study vaccination (Visit 1) and ending at the last study visit (Visit 3).
- Prophylactic medication (i.e., medication administered in the absence of ANY symptom and in anticipation of a reaction to the vaccination).

  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 ≥ 38.0°C/100.4°F. The preferred location for measuring temperature in this study will be the oral cavity, the axilla and the rectum].
- Any concomitant medications/products/vaccines listed in Section 6.7.2.
- Any concomitant medications/products/vaccines relevant to a SAE to be reported as per protocol or administered at any time during the study period for the treatment of a SAE. In addition, concomitant medications relevant to SAEs need to be recorded on the expedited Adverse Event report.
- Any antipyretic administered in the period starting 6 hours before vaccination and ending 12 hours after vaccination need to be recorded on the specific page of the eCRF.

6.7.2. Concomitant medications/products/vaccines that may lead to the elimination of a subject from PPS analyses

The use of the following concomitant medications/products/vaccines will not require withdrawal of the subject from the study but may determine a subject's evaluability in the PPS analysis. See Section 10.4 for sets to be analysed.

- Any investigational or non-registered product (drug or vaccine) other than the study vaccines used between Visit 1 and Visit 3 during the study period.
- Immunosuppressants or other immune-modifying drugs administered chronically (i.e., more than 14 days) during the study period between Visit 1 to Visit 3. For

corticosteroids, this will mean prednisone (0.5 mg/kg/day, or equivalent). Inhaled and topical steroids are allowed.

- Immunoglobulins and/or any blood products administered during the study period between Visit 1 to Visit 3.
- Long-acting immune-modifying drugs administered at any time during the study period (e.g., infliximab).
- A vaccine not foreseen by the study protocol administered during the period starting from 30 days before the first vaccination and ending at Visit 3*, 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 an emergency mass vaccination for an unforeseen public health threat (e.g.: a pandemic) is organised by the public health authorities, outside the routine immunisation program, the time period described above can be reduced if necessary for that vaccine provided it is licensed and used according to its SPC or PI and according to the local governmental recommendations and provided a written approval of the Sponsor is obtained. A detailed, comprehensive list of reasons for elimination from PPS analyses will be established at the time of data cleaning.

6.8. Intercurrent medical conditions that may lead to elimination of a subject from PPS analyses

At each study visit subsequent to the first vaccination, it must be verified if the subject has experienced or is experiencing any intercurrent medical condition. If it is the case, the condition(s) must be recorded in the eCRF.

Subjects may be eliminated from the PPS for immunogenicity if, during the study, they incur a condition that has the capability of altering their immune response or are confirmed to have an alteration of their initial immune status.

7. HEALTH ECONOMICS

Not applicable.

8. SAFETY

The investigator or site staff is/are responsible for the detection, documentation and reporting of events meeting the criteria and definition of an Adverse Event (AE) or SAE as provided in this protocol.

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

8.1. Safety definitions

8.1.1. Definition of an adverse event

An AE is any untoward medical occurrence in a clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

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

Examples of an AE include:

- 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 vaccines 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 vaccines or a concurrent medication (overdose per se should not be reported as an AE/SAE).
- Signs, symptoms temporally associated with study vaccines administration.
- Significant failure of expected pharmacological or biological action.
- Pre-or post-treatment events that occur as a result of protocol-mandated procedures (i.e., invasive procedures, modification of subject's previous therapeutic regimen).

AEs to be recorded as endpoints (solicited AEs) are described in Section 8.1.3. All other AEs will be recorded as UNSOLICITED AEs.

Examples of an AE DO NOT include:

- Medical or surgical procedures (e.g., endoscopy, appendectomy); the condition that leads to the procedure is an AE/SAE.
- 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 subject prior to the study vaccination. These events will be recorded in the medical history section of the eCRF.

8.1.2. Definition of a serious adverse event

A 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 subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, had it been more severe.

c. Requires hospitalisation or prolongation of existing hospitalisation,

   Note: In general, hospitalisation signifies that the subject has been admitted at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or in an out-patient setting. Complications that occur during hospitalisation are also considered AEs. If a complication prolongs hospitalisation or fulfils any other serious criteria, the event will also be considered serious. When in doubt as to whether 'hospitalisation' occurred or was necessary, the AE should be considered serious.

   Hospitalisation for elective treatment of a pre-existing condition (known or diagnosed prior to informed consent signature) that did not worsen from baseline is NOT considered an AE.

d. Results in disability/incapacity, OR

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

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 hospitalisation but may jeopardise the subject 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 hospitalisation.

8.1.3. Solicited adverse events

8.1.3.1. Solicited general adverse events

The following general AEs will be solicited (Table 11):

Table 11 Solicited general adverse events

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

Note: Temperature will be recorded in the evening. Should additional temperature measurements be performed at other times of day, the highest temperature will be recorded in the eCRF. The temperature can be recorded by any age-appropriate route. The preferred route for recording temperature in this study will be oral, axillary or rectal.

8.1.4. Clinical laboratory parameters and other abnormal assessments qualifying as adverse events or serious adverse events

In absence of diagnosis, abnormal laboratory findings (e.g., clinical chemistry, haematology, urinalysis) or other abnormal assessments (e.g., vital signs etc) that are judged by the investigator to be clinically significant will be recorded as AE or SAE if they meet the definition of an AE or SAE (refer to Sections 8.1.1 and 8.1.2). 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.

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.

8.2. Events or outcomes not qualifying as adverse events or serious adverse events

Not applicable.

8.3. Detecting and recording adverse events, serious adverse events

8.3.1. Time period for detecting and recording adverse events, serious adverse events

All AEs starting within 31 days following administration of each dose of study vaccine (Day 0 to Day 30) must be recorded into the appropriate section of the eCRF, irrespective of intensity or whether or not they are considered vaccination-related.

Any GE episodes occurring from Dose 1 of HRV vaccine up to Visit 3 will be recorded.

The time period for collecting and recording SAEs will begin at the receipt of study vaccines until the subject is discharged from the study. See Section 8.4 for instructions on reporting of SAEs.

All AEs/SAEs leading to withdrawal from the study will be collected and recorded from the time of the receipt of study vaccines.

In addition to the above-mentioned reporting requirements and in order to fulfil international reporting obligations, SAEs that are related to study participation (i.e., protocol-mandated procedures, invasive tests, a change from existing therapy) or are related to a concurrent GSK medication/vaccine will be collected and recorded from the time the subject's parent(s)/LAR(s) consents to participate in the study until they are discharged from the study.

An overview of the protocol-required reporting periods for AEs and SAEs is given in Table 12.

Table 12 Reporting periods for collecting safety information

Study activity	Pre-Vacc*	Visit 1 Dose 1	8 days post Vacc	31 days post Vacc	Visit 2 Dose 2	8 days post Vacc	31 days post Vacc	Visit 3	Extended Safety follow-up
		Day 0			Month1-2			Month 2-4	Month 7-8
Solicited general AEs									
Unsolicited AEs									
GE episodes**									
SAEs and AEs leading to withdrawal									
SAEs									
SAEs related to study participation or concurrent GSK medication/vaccine									

* consent obtained. Pre-Vacc: pre-vaccination; Vacc: vaccination; Post-Vacc: post-vaccination

** If GE will appear during the solicited period then it will be recorded on the solicited AEs screen of eCRF as diarrhoea and if it will appear outside the solicited period up to Visit 3 then it will be recorded as an unsolicited AE.

8.3.2. Post-Study adverse events and serious adverse events

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

8.3.3. Evaluation of adverse events and serious adverse events

8.3.3.1. Active questioning to detect adverse events and serious adverse events

As a consistent method of collecting AEs, the subject's parent(s)/LAR(s) should be asked a non-leading question such as:

'*Has your child acted differently or felt different in any way since receiving the vaccine or since the last visit?*'

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 subject's medical records to GSK Biologicals instead of appropriately completing the eCRF. However, there may be instances when copies of medical records for certain cases are requested by GSK Biologicals. In this instance, all subject identifiers will be blinded on the copies of the medical records prior to submission to GSK Biologicals.

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.

8.3.3.2. Assessment of adverse events

8.3.3.2.1. Assessment of intensity

The intensity of the following solicited AEs will be assessed as described in Table 13 and Table 14:

Table 13 Intensity scales be used by the parent(s)/LAR(s) for solicited symptoms during the solicited follow-up period

Adverse Event	Intensity grade	Parameter
Fever*		Record temperature in °C/°F using any age-appropriate route
Irritability/Fussiness	0	Behaviour 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
Diarrhoea $		Record the number of looser than normal stools/day
Vomiting §		Record the number of vomiting episodes/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
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

* Fever is defined as temperature ≥ 38.0°C/100.4°F. The preferred location for measuring temperature in this study will be the oral cavity, the axilla and the rectum.
$ Diarrhoea is defined as passage of three or more looser than normal stools within a day.
§ Vomiting is defined as one or more episodes of forceful emptying of partially digested stomach contents ≥ 1 hour after feeding within a day.

Table 14 Intensity scales for diarrhoea, vomiting and fever occurring during the solicited period

Adverse Event	Intensity grade	Parameter
Diarrhoea $	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	temperature < 38.0°C/100.4° F
	1	temperature ≥ 38.0°C/100.4° F – ≤ 38.5°C/101.3 F
	2	temperature > 38.5°C/101.3 F – ≤ 39.5°C/103.1 F
	3	temperature > 39.5°C/103.1 F

$ Diarrhoea is defined as passage of three or more looser than normal stools within a day.
§ Vomiting is defined as one or more episodes of forceful emptying of partially digested stomach contents ≥ 1 hour after feeding within a day.

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 one of the following categories:

1 (mild)	=	An AE which is easily tolerated by the subject, 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 day-care centre 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 a 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 one of the pre-defined outcomes as described in Section 8.1.2.

8.3.3.2.2. Assessment of causality

The definitions for 'NO' and 'YES' have been written in such a way that all events that have been attributed a 'NO' can be pooled with events which in the primary vaccination study were determined to be 'not related' or 'unlikely to be related' to vaccination. Those events that are attributed a 'YES' can be pooled with those events that in the past were determined to have a 'suspected' or 'probable' relationship to vaccination in the primary vaccination study.

The investigator is obligated to assess the relationship between investigational vaccine and the occurrence of each AE/SAE. The investigator will use clinical judgement to determine the relationship. 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 investigational vaccine will be considered and investigated. The investigator will also consult the IB and/or Prescribing Information for marketed products to determine his/her assessment.

There may be situations when a SAE has occurred and the investigator has minimal information to include in the initial report to GSK Biologicals. However, it is very important that the investigator always makes an assessment of causality for every event prior to submission of the Expedited Adverse Events Report to GSK Biologicals. The investigator may change his/her opinion of causality in light of follow-up information and update the SAE information accordingly. The causality assessment is one of the criteria used when determining regulatory reporting requirements

In case of concomitant administration of multiple vaccines/products, it may not be possible to determine the causal relationship of general AEs to the individual vaccine administered. The investigator should, therefore, assess whether the AE could be causally related to vaccination rather than to the individual vaccines.

All solicited local (injection site) reactions will be considered causally related to vaccination. Causality of all other AEs should be assessed by the investigator using the following question:

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

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

If an event meets the criteria to be determined as 'serious' (see Section 8.1.2), additional examinations/tests will be performed by the investigator in order 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 vaccines, if applicable.
- Erroneous administration.
- Other cause (specify).

8.3.3.3. 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).

8.3.3.4. Medically attended visits

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

8.4. Reporting of serious adverse events

8.4.1. Prompt reporting of serious adverse events to GSK Biologicals

SAEs that occur in the time period defined in Section 8.3 will be reported promptly to GSK within the timeframes described in Table 15, once the investigator determines that the event meets the protocol definition of a SAE.

Table 15 Timeframes for submitting serious adverse event reports to GSK Biologicals

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

* Timeframe allowed after receipt or awareness of the information.
‡ The investigator will be required to confirm 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.

8.4.2. Contact information for reporting serious adverse events

Study Contact for Reporting SAEs
Refer to the local study contact information document.
Back-up Study Contact for Reporting SAEs
24/24 hour and 7/7 day availability: **GSK Biologicals Clinical Safety & Pharmacovigilance** Outside US & Canada sites: Fax: +PPD or +PPD Email address: PPD US sites only: Fax: PPD Canadian sites only: Fax: PPD

8.4.3. Completion and transmission of SAE reports to GSK Biologicals

Once an investigator becomes aware that a SAE has occurred in a study subject, the investigator (or designate) must complete the 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 a SAE, the report should still be completed within 24 hours. Once additional relevant information is received, the report should be updated WITHIN 24 HOURS.

The investigator will always provide an assessment of causality at the time of the initial report. The investigator will be required to confirm the review of the SAE causality by ticking the 'reviewed' box in the electronic Expedited Adverse Events Report within 72 hours of submission of the SAE.

8.4.3.1. Back-up system in case the electronic reporting system does not work

If the electronic reporting system does not work, the investigator (or designate) must complete, then date and sign a paper Expedited Adverse Events Report and fax it to the Study Contact for Reporting SAEs (refer to the Sponsor Information) or to GSK Biologicals Clinical Safety and Pharmacovigilance department within 24 hours.

This back-up system should only be used if the electronic reporting system is not working and NOT if the system is slow. As soon as the electronic reporting system is working again, the investigator (or designate) must complete the electronic Expedited Adverse Events Report within 24 hours. The final valid information for regulatory reporting will be the information reported through the electronic SAE reporting system.

8.4.4. Updating of SAE information after removal of write access to the subject's eCRF

When additional SAE information is received after removal of the write access to the subject'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 to the Study Contact for Reporting SAEs (refer to the Sponsor Information) or to GSK Biologicals Clinical Safety and Pharmacovigilance department within the designated reporting time frames specified in Table 15.

8.4.5. Regulatory reporting requirements for serious adverse events

The investigator will promptly report all SAEs to GSK in accordance with the procedures detailed in Section 8.4.1. GSK Biologicals has a legal responsibility to promptly notify, as appropriate, both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. Prompt notification of SAEs by the investigator to the Study Contact for Reporting SAEs is essential so that legal obligations and ethical responsibilities towards the safety of other subjects are met.

Investigator safety reports are prepared according to the current GSK policy and are forwarded to investigators as necessary. An investigator safety report is prepared for a SAE(s) that is both attributable to the investigational vaccines and unexpected. The purpose of the report is to fulfil specific regulatory and GCP requirements, regarding the product under investigation.

8.5. Follow-up of adverse events and serious adverse events

8.5.1. Follow-up of adverse events and serious adverse events

8.5.1.1. Follow-up during the study

After the initial AE/SAE report, the investigator is required to proactively follow each subject and provide additional relevant information on the subject's condition to GSK Biologicals (within 24 hours for SAEs; refer to Table 15).

All SAEs documented at a previous visit/contact and designated as not recovered/not resolved or recovering/resolving will be reviewed at subsequent visits/contacts until the end of the study.

All AEs documented at a previous visit/contact and designated as not recovered/not resolved or recovering/resolving will be reviewed at subsequent visits/contacts until 31 days after the last vaccination.

8.5.1.2. Follow-up after the subject is discharged from the study

The investigator will follow subjects:

- with SAEs, or subjects withdrawn from the study as a result of an AE, until the event has resolved, subsided, stabilised, disappeared, or until the event is otherwise explained, or the subject is lost to follow-up.

If the investigator receives additional relevant information on a previously reported SAE, he/she will provide this information to GSK Biologicals using an electronic Expedited Adverse Events Report as applicable.

GSK Biologicals may request that the investigator performs or arranges the conduct of additional clinical examinations/tests and/or evaluations to elucidate as fully as possible the nature and/or causality of the AE or SAE. The investigator is obliged to assist. If a subject dies during participation in the study or during a recognised follow-up period, GSK Biologicals will be provided with any available post-mortem findings, including histopathology.

8.6. Treatment of adverse events

Treatment of any AE is at the sole discretion of the investigator and according to current good medical practice. Any medication administered for the treatment of an AE should be recorded in the subject's eCRF (refer to Section 6.7).

8.7. Unblinding

GSK Biologicals' policy (which incorporates ICH E2A guidance, EU Clinical Trial Directive and US Federal Regulations) is to unblind the report of any SAE which is unexpected and attributable/suspected to be attributable to the investigational vaccines, prior to regulatory reporting. The GSK Biologicals' Central Safety Physician is responsible for unblinding the treatment assignment in accordance with the specified timeframes for expedited reporting of SAEs (refer to Section 8.4.1).

8.8. Emergency unblinding (Amended: 06 September 2016)

Unblinding of a subject's individual treatment code should occur only in the case of a medical emergency, or in the event of a serious medical condition, when knowledge of the treatment is essential for the clinical management or welfare of the subject, as judged by the investigator.

The emergency unblinding process consists of the automated system SBIR that allows the investigator to have unrestricted, immediate and direct access to the subject's individual study treatment.

The investigator has the option of contacting a GSK Biologicals' On-call Central Safety Physician (or Backup) if he/she needs medical advice or needs the support of GSK to perform the unblinding (i.e., he/she cannot access the automated Internet-based system).

Any emergency unblinding must be fully documented by using the Emergency Unblinding Documentation Form, which must be appropriately completed by the investigator and sent within 24 hours to GSK Biologicals.

GSK Biologicals' Contact information for Emergency Unblinding 24/24 hour and 7/7 day availability
GSK Biologicals' Central Safety Physician: Outside US/Canada: +PPD (GSK Biologicals Central Safety Physician on-call) For US/Canada only: +PPD (***GSK Biologicals' Central Safety Physician on-call***) **(Amended 06 September 2016)** **GSK Biologicals' Central Safety Physician Back-up:** Outside US/Canada: +PPD US/Canada only: +PPD **(Amended 06 September 2016)** **Emergency Unblinding Documentation Form transmission:** Outside US & Canada: Fax: +PPD or +PPD US/Canada only: Fax: +PPD

8.9. Subject card

Study subjects' parent(s)/LAR(s) must be provided with the address and telephone number of the main contact for information about the clinical study.

The investigator (or designate) must therefore provide a "subject card" to each subject's parent(s)/LAR(s). In an emergency situation this card serves to inform the responsible attending physician that the subject is in a clinical study and that relevant information may be obtained by contacting the investigator.

Subjects' parent(s)/LAR(s) must be instructed to keep subject cards in their possession at all times.

9. SUBJECT COMPLETION AND WITHDRAWAL

9.1. Subject completion

A subject who is available for the concluding contact foreseen in the protocol is considered to have completed the study.

9.2. Subject withdrawal

Withdrawals will not be replaced.

9.2.1. Subject withdrawal from the study

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

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

A subject 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 subject from the date of withdrawal/last contact.

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

Information relative to the withdrawal will be documented in the eCRF. The investigator will document whether the decision to withdraw a subject from the study was made by the subject's parent(s)/LAR(s), or by the investigator, as well as which of the following possible reasons was responsible for withdrawal:

- Serious adverse event.
- Non-serious adverse event.
- Protocol violation (specify).
- Consent withdrawal, not due to an adverse event*.
- Moved from the study area.
- Lost to follow-up.
- Other (specify).

*In case a subject is withdrawn from the study because the subject's parent(s)/LAR(s) has withdrawn consent, the investigator will document the reason for withdrawal of consent, if specified by the subject's parent(s)/LAR(s), in the eCRF.

Subjects who are withdrawn from the study because of SAEs/AEs must be clearly distinguished from subjects who are withdrawn for other reasons. Investigators will follow subjects who are withdrawn from the study as result of a SAE/AE until resolution of the event (see Section 8.5.1.2).

9.2.2. Subject withdrawal from investigational vaccines

A 'withdrawal' from the investigational vaccines refers to any subject who does not receive the complete treatment, i.e., when no further planned dose is administered from the date of withdrawal. A subject withdrawn from the investigational vaccines may not necessarily be withdrawn from the study as further study procedures or follow-up may be performed (safety or immunogenicity) if planned in the study protocol.

Information relative to premature discontinuation of the investigational vaccines will be documented on the Vaccine Administration screen of the eCRF. The investigator will document whether the decision to discontinue further vaccination was made by the subject's parent(s)/LAR(s), or by the investigator, as well as which of the following possible reasons was responsible for withdrawal:

- Serious adverse event.
- Non-serious adverse event.
- Other (specify).

10. STATISTICAL METHODS

10.1. Primary endpoints

- Evaluation of immunogenicity in terms of anti-RV antibody concentrations.
  - Serum anti-RV IgA antibody concentrations expressed as GMCs 1-2 months after Dose 2 in each of the HRV liquid formulation groups (Liq_A, Liq_B and Liq_C).
  - Anti-RV IgA antibody seroconversion rate* 1-2 months after Dose 2 in the lyophilised and pooled liquid groups.
  - Serum anti-RV IgA antibody concentrations expressed as GMCs 1-2 months after Dose 2 in the lyophilised and pooled liquid groups.

*Seroconversion rate is defined as the percentage of subjects who were initially seronegative (i.e., with anti-RV IgA antibody concentration < 20 U/mL prior the first dose of HRV vaccine) and developed anti-RV IgA antibody concentration ≥ 20 U/mL at Visit 3.

10.2. Secondary endpoints

- Solicited adverse events
  - Occurrence of each general solicited symptom within the 8 days (Day 0-Day 7) follow-up period after each dose of the lyophilised and PCV-free HRV liquid vaccine
- Unsolicited adverse events.
  - Occurrence of unsolicited AEs within 31 days (Day 0-Day 30) after any dose of HRV vaccine, according to the Medical Dictionary for Regulatory Activities (MedDRA) classification.
- Serious adverse events
  - Occurrence of serious adverse events from Dose 1 up to study end.
- Evaluation of immunogenicity in terms of anti-RV antibody concentrations.
  - Serum anti-RV IgA antibody concentrations ≥ 90 U/mL 1-2 months after Dose 2 in the lyophilised and pooled liquid groups.

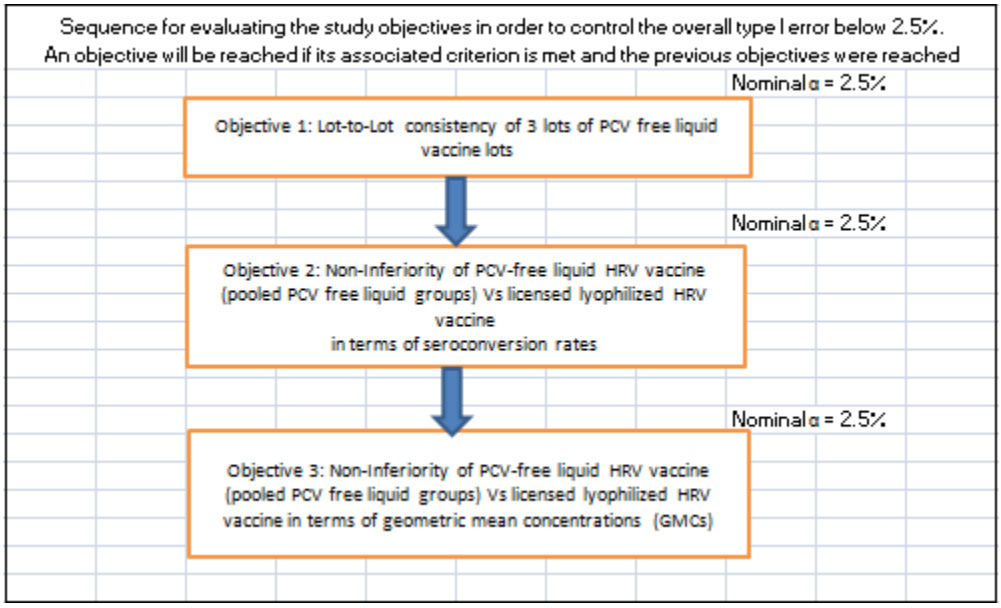
10.3. Determination of sample size

The target enrolment will be 1600 subjects (400 subjects in each of the PCV-free liquid vaccine groups and 400 subjects in the lyophilised vaccine group) to obtain at least 1280 evaluable subjects (320 subjects in each of the PCV-free liquid vaccine groups and 320 subjects in the lyophilised vaccine group) for the evaluation of the co-primary objectives assuming that approximately 20% of the enrolled subjects will not be evaluable.

10.3.1. Control on type I error

A 2.5% nominal type I error will be used for each co-primary evaluation. To control the overall type I error below 2.5%, a hierarchical procedure will be used for the multiple study objectives as shown in Figure 1.

Figure 1 Sequence for evaluating the study objectives in order to control the overall type I error below 2.5%



The sample size has been estimated in order to obtain at least 91% power to demonstrate the co-primary objectives. The power associated with the target sample size for the conclusion on each inferential objective of this study is detailed in Section 10.3.3.

10.3.2. References for sample size

Table 16 Seroconversion rates and standard deviation for log_{10} transformed concentration post vaccination.

Antigen	Endpoint	Rota-060 (Sep-ad group)	Rota-061 (Pooled Liq group)	Rota-061 (Lyo group)	Rota-036 (HRV group)	Rota-054 (HRV group)	Rota-023 (HRV group)	Rota-068 (HRV group)	Rota-028/029/030 (HRV group)
RV IgA	N	121	746	252	787	147	393	318	115
	SCR (>=20U/ml)	86.0%[95% CI: 78.5;91.6] *	88.6%[95%CI :86.1;90.8]	90.5% [95%CI: 86.2;93.8]	86.5%[95 %CI: 83.9;88.8]	85.7%[95% CI: 79.0;90.9]	76.8%[95% CI: 72.4;80.9]	88.1%[95 %CI: 84.0;91.4]	93.9%[95 %CI: 87.9;97.5]
	SD	0.728	0.791	0.791	0.735	0.747	0.760	0.710	0.625

SCR = Seroconversion rate
SD = Standard deviation for log10 transformed concentration post vaccination.
*Seropositivity

10.3.3. Power computation

The power computations were based on the following methods

- Consistency on GMC: Type II error was obtained using Power Analysis and Sample Size (PASS) 2005, one-sided non-inferiority test for 2 means, under the alternative of equal means & alpha=2.5%. The type II error was multiplied by 6 to account for the 6 pair wise lot comparisons.
- NI on Seroconversion rate: Type II error was obtained using PASS 2005, one-sided non-inferiority test for 2 proportions, under the alternative of equal proportions (Miettinen and Nurminen's Likelihood Score Test of the Difference).
- NI on GMC: Type II error was obtained using PASS 2005, one-sided non-inferiority test for 2 means, under the alternative of equal means and variances.

To account for the multiplicity of comparison, the global type II errors were conservatively estimated as the sum of individual type II errors.

Table 17 Power to demonstrate that the two-sided 95% CIs on the anti-RV IgA GMC ratio between PCV free liquid vaccine, 1-2 months after dose 2 of HRV vaccine lots are within the [0.5; 2.0] interval for all the pair wise comparisons

Endpoint	Standard deviation [Log_{10} (titre)]	N evaluable (each PCV free HRV liquid group)	Power
Anti-RV IgA antibody concentration	0.750	320	99.4%
	0.790*	**320**	**98.2%**
	0.850	320	96.4%

*=Reference used for the global power computation

Table 18 Probability that the lower limit of 95% CI for the difference in seroconversion rate (the pooled PCV free liquid vaccine group minus the lyophilised vaccine group), 1-2 months after dose 2 of HRV vaccine is ≥-10%

Seroconversion rate		N evaluable (pooled PCV free HRV liquid group)	N evaluable (lyophilised HRV group)	Power
Lyophilised formulation of HRV vaccine	Liquid formulation of PCV free HRV vaccine			
75%	75%	960	320	96.0%
80%	80%	960	320	98.1%
85%*	**85%***	**960**	**320**	**99.5%**
90%	90%	960	320	99.9%

*=Reference used for the global power computation

Table 19 Probability that the lower limit of the 95% CI on anti-rotavirus IgA antibody GMC ratio (the pooled PCV free liquid vaccine group divided by the lyophilised vaccine group), 1-2 months after dose 2 of HRV vaccine is ≥ 0.67

Endpoint	Standard deviation [Log_{10} (titre)]	N evaluable (pooled PCV free HRV liquid group)	N evaluable (lyophilised HRV group)	Power
Anti-RV IgA antibody concentration	0.750	960	320	95.3%
	0.790*	**960**	**320**	**93.2%**
	0.850	960	320	89.4%

*=Reference used for the global power computation

10.4. Analyses Sets

Note that in order to align to ICH and Clinical Data Interchange Standards Consortium (CDISC) terminology the Total vaccinated cohort (TVC) and the According-To-Protocol (ATP) cohort used in previous Rota studies have been renamed as Exposed Set (ES) and PPS, respectively.

10.4.1. Exposed Set

The ES will include all subjects with at least one study vaccine administration documented:

- a safety analysis based on the ES will include all vaccinated subjects,
- an immunogenicity analysis based on the ES will include all vaccinated subjects for whom immunogenicity data are available.

The ES analysis will be performed per treatment actually administered at dose 1.

10.4.2. Per-Protocol analysis Set of immunogenicity

The PPS for immunogenicity will include all subjects from the ES:

- who have received both the doses of study vaccine,
- for whom the HRV vaccine liquid or lyophilised formulation was administered according to protocol and subjects did not regurgitate after vaccination,
- who have not received a vaccine prohibited by the protocol up to Visit 3,
- for whom the randomisation code has not been broken
- who were seronegative for serum anti-RV IgA antibodies on the day of Dose 1
- who have not received medication prohibited by the protocol up to Visit 3 as listed in Section 6.7.2,
- whose underlying medical condition was not prohibited by the protocol up to Visit 3 as listed in Section 6.8,
- who comply with the vaccination schedule (Table 5),

- who comply with blood sampling schedule (Table 5),
- for whom immunogenicity data are available at the post-vaccination sampling time point,
- who have no RV other than vaccine strain in GE stool samples collected up to Visit 3,
- who have no concomitant infection unrelated to the vaccine up to Visit 3, which may influence the immune response.

10.5. Derived and transformed data

Demography:

- For a given subject and a given demographic variable, missing measurements will not be replaced.

Immunogenicity:

- The cut-off value of anti-rotavirus IgA antibody is defined by the laboratory before the analysis and is described in Section 5.7.3.
- Seroconversion rate is defined as the percentage of subjects who were initially seronegative (i.e., with anti-RV IgA antibody concentration < 20 U/mL prior the first dose of HRV vaccine) and developed anti-RV IgA antibody concentration ≥ 20 U/mL at Visit 3.
- Antibody 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. Antibody 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 subject and a given immunogenicity measurement time point, missing or non-evaluable measurements will not be replaced.

Reactogenicity and safety:

- Subjects who missed reporting symptoms (solicited/unsolicited or concomitant medications) will be treated as subjects without symptoms (solicited/unsolicited or concomitant medications, respectively).

10.6. Analysis of demographics

The following calculations will be performed for each group and for the pooled liquid vaccine group:

- The distribution of subjects enrolled among the study centres and countries will be tabulated as a whole and for each group.
- The numbers of subjects who withdraw from the study will be tabulated by group according to the reason for drop-out.
- The deviations from specifications for age and intervals between study visits will be tabulated by group.
- The median, mean, range and standard deviation of age (in weeks) at each HRV vaccine dose and of the gestational age will be computed by group. The median, mean and standard deviation of height (in centimetres) and weight (in kilograms) at Visit 1 will be computed by group. The racial and sex composition will be presented. These calculations will also be performed by country.
- Summary of co-administered vaccinations (i.e., vaccinations given on the day of each HRV vaccine dose) and intercurrent vaccinations (i.e., vaccinations from birth up to Visit 3, excluding vaccination given on the day of HRV vaccine doses) will be summarized by group for the ES.

10.7. Analysis of immunogenicity

The primary analysis will be based on the PPS for analysis of immunogenicity. If, in any vaccine group, the percentage of vaccinated subjects 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.

10.7.1. Within groups assessment

The following calculations will be performed for each group and for the pooled liquid vaccine group.

- For each group, at each time point that anti-rotavirus IgA is measured,
  - Seropositivity/seroconversion rates and their exact 95% CI will be computed,
  - Percentage of subjects with anti-RV IgA antibody concentrations ≥ 90 U/mL and their exact 95% CI will be computed.
  - GMCs and their 95% CIs will be computed.
- The above mentioned descriptive analyses will also be performed by country.
- The distribution of anti-RV IgA antibody concentrations at Visit 3 will be displayed using Reverse Cumulative Curves (RCCs).

10.7.2. Between groups assessment

- The 95% CI for the ratio of anti-RV IgA antibody GMCs at Visit 3 between any pair of the three lots of the HRV liquid vaccine will be computed (first co-primary objective).
- The asymptotic standardized 95% CI for the difference in seroconversion rate at Visit 3 between the PCV-free liquid HRV vaccine (pooled HRV liquid groups) and lyophilised HRV vaccine will be computed (second co-primary objective).
- The 95% CI for the ratio of anti-RV IgA antibody GMCs at Visit 3 between the PCV-free liquid HRV vaccine (pooled HRV liquid groups) and lyophilised HRV vaccine will be computed (third co-primary objective).

Refer to Section 2.1 for the criteria of the respective co-primary objectives.

10.8. Analysis of safety

The ES will be used for the analysis of safety.

10.8.1. Within groups assessment

The following calculations will be performed for each group and for the pooled liquid vaccine group:

The percentage of doses and of subjects reporting at least one symptom (solicited or unsolicited) during the 8 days (Day 0-Day 7) solicited follow-up period post vaccination will be computed, along with exact 95% CI. The same calculations will be done for symptoms (solicited or unsolicited) rated as grade 3 in intensity and for symptoms (solicited or unsolicited) assessed as causally related to vaccination.

The percentage of doses and of subjects reporting each individual solicited general symptom will be computed, over the 8 days (Day 0-Day 7) solicited follow-up period post vaccination, along with exact 95% CI. The same calculations will be done for each individual general solicited symptom rated as grade 3 in intensity, for each individual solicited general symptom assessed as causally related to vaccination and those that resulted in a medically attended visit.

The verbatim reports of unsolicited AEs will be reviewed by a physician and the signs and symptoms will be coded according to MedDRA. Every verbatim term will be matched with the appropriate Preferred Term. The percentage of subjects with unsolicited AEs occurring within 31 days (Day 0-Day 30) follow-up period after any dose with its exact 95% CI will be tabulated by group, and by preferred term. Similar tabulation will be done for unsolicited AEs rated as grade 3, for unsolicited AEs with causal relationship to vaccination and those that resulted in a medically attended visit.

The percentage of subjects reporting GE episodes from Dose 1 of HRV vaccine up to Visit 3 will be tabulated by group.

The percentage of subjects with presence of RV in GE stool samples collected from Dose 1 of HRV vaccine up to Visit 3 will be tabulated by group.

The percentage of GE episodes with no available stool results from Dose 1 of HRV vaccine up to Visit 3 will be tabulated.

The percentage of subjects who started taking at least one concomitant medication from HRV vaccination to Day 7 after vaccinations will be tabulated with exact 95% CI. The percentages of subjects who started taking at least one concomitant medication during the study period will be tabulated with exact 95% CI.

SAEs reported during the study period will be described in detail.

10.9. Interpretation of analyses

Except for analyses addressing criteria specified in the co-primary objectives referred as confirmatory analyses, all the analyses will be descriptive/exploratory in nature. The use of these descriptive/exploratory analyses should be limited to support the confirmatory analyses or to generate hypothesis.

10.9.1. Statistical Methods

- The exact CIs for a proportion within a group will be calculated using SAS [Clopper, 1934].
- The standardized asymptotic CI for the group difference in proportion will be calculated using SAS. The method used within GSK Biologicals is Method 6 [Newcombe, 1998].
- The CI for GMCs will be obtained within each group separately. The CI for the mean of log-transformed concentration will be first obtained assuming that log-transformed values were normally distributed with unknown variance. The CI for the GMCs will then be obtained by exponential-transformation of the CI for the mean of log-transformed concentration.
- The GMC group ratio will be obtained using an ANOVA model on the logarithm-transformed concentrations. The ANOVA model will include the vaccine group and the country as fixed effects. The GMC ratio and their 95% CI will be derived by exponential-transformation of the corresponding group contrast in the model.

10.10. Conduct of analyses

Any deviation(s) or change(s) from the original statistical plan outlined in this protocol will be described and justified in the final study report.

10.10.1. Sequence of analyses

Safety data that is as clean as possible will be analysed for IDMC review. Details of the review will be described in an IDMC charter.

An analysis will be conducted once all the study data up to Visit 3 are available and cleaned and Rota-IgA ELISA testing at 1-2 month post-dose 2 has been fully completed. The Clinical Study Report (CSR) with data up to Visit 3 will be used for the registration of PCV-free liquid vaccine in European Union (EU) and 'rest of world' countries. This CSR will be submitted as soon as it is available.

In addition, an integrated clinical study report containing all data will be written and made available to the investigators and submitted to regulatory authorities as appropriate, e.g., for licensure of PCV-free liquid vaccine in US. This report will include the following:

- An analysis of the serum anti-RV IgA antibody concentrations, 1-2 months after Dose 2 in the lyophilised and pooled liquid groups.
- The reactogenicity and safety analysis of SAEs and AEs leading to drop out reported after Visit 3 up to the safety follow-up contact.
- The final analyses of all data conducted after conclusion of the safety follow-up phase.

This report will also summarize all the SAEs reported from Visit 1 up to the safety follow-up contact to account for the SAEs not reported in the earlier study report due to late reporting of SAEs.

10.10.2. Statistical considerations for interim analyses

All confirmatory analyses will be conducted after all the study data up to Visit 3 are available and therefore no statistical adjustment for interim analyses is required.

11. ADMINISTRATIVE MATTERS

To comply with ICH GCP administrative obligations relating to data collection, monitoring, archiving data, audits, confidentiality and publications must be fulfilled.

11.1. Electronic Case Report Form instructions

A validated GSK defined electronic data collection tool will be used as the method for data collection.

In all cases, subject initials will not be collected nor transmitted to GSK. Subject data necessary for analysis and reporting will be entered/transmitted into a validated database or data system. Clinical data management will be performed in accordance with applicable GSK standards and data cleaning procedures.

While completed eCRFs are reviewed by a GSK Biologicals' Site Monitor at the study site, omissions or inconsistencies detected by subsequent eCRF review may necessitate clarification or correction of omissions or inconsistencies with documentation and approval by the investigator or appropriately qualified designee. In all cases, the investigator remains accountable for the study data.

The investigator will be provided with a CD-ROM of the final version of the data generated at the investigational site once the database is archived and the study report is complete and approved by all parties.

11.2. Study Monitoring by GSK Biologicals

GSK will monitor the study to verify that, amongst others, the:

- Data are authentic, accurate, and complete.
- Safety and rights of subjects are being protected.
- Study is conducted in accordance with the currently approved protocol, any other study agreements, GCP and all applicable regulatory requirements.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents.

The investigator must ensure provision of reasonable time, space and qualified personnel for monitoring visits**.**

Direct access to all study-site related and source data is mandatory for the purpose of monitoring review. The monitor will perform an eCRF review and a Source Document Verification (SDV). By SDV we understand verifying eCRF entries by comparing them with the source data that will be made available by the investigator for this purpose.

The Source Documentation Agreement Form describes the source data for the different data in the eCRF. This document should be completed and signed by the site monitor and investigator and should be filed in the investigator's study file. Any data item for which the eCRF will serve as the source must be identified, agreed and documented in the source documentation agreement form.

For eCRF, the monitor freezes completed and approved screens at each visit.

Upon completion or premature discontinuation of the study, the monitor will conduct site closure activities with the investigator or site staff, as appropriate, in accordance with applicable regulations, GCP, and GSK procedures.

11.3. Record retention

Following closure of the study, the investigator must maintain all site study records (except for those required by local regulations to be maintained elsewhere) in a safe and secure location. The records must be easily accessible, when needed (e.g., audit or

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

GSK will inform the investigator/institution of the time period for retaining these records to comply with all applicable regulatory requirements. However, the investigator/institution should seek the written approval of the sponsor before proceeding with the disposal of these records. The minimum retention time will meet the strictest standard applicable to a particular site, as dictated by ICH GCP, any institutional requirements, applicable laws or regulations, or GSK standards/procedures.

The investigator/institution must notify GSK of any changes in the archival arrangements, including, but not limited to archival at an off-site facility, transfer of ownership of the records in the event the investigator leaves the site.

11.4. Quality assurance

To ensure compliance with GCP and all applicable regulatory requirements, GSK may conduct a quality assurance audit. Regulatory agencies may also conduct a regulatory inspection of this study. Such audits/inspections can occur at any time during or after completion of the study. If an audit or inspection occurs, the investigator and institution agree to allow the auditor/inspector direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any relevant issues.

11.5. Posting of information on publicly available clinical trial registers and publication policy

GSK assures that the key design elements of this protocol will be posted on the GSK website and in publicly accessible database(s) such as clinicaltrials.gov, in compliance with the current regulations.

GSK also assures that results of this study will be posted on the GSK website and in publicly accessible regulatory registry(ies) within the required time-frame, in compliance with the current regulations. The minimal requirement is to have primary endpoint summary results disclosed at latest 12 months post primary PCD and to have secondary endpoint disclosed at latest 12 months after the LSLV as described in the protocol.

GSK also aims to publish the results of these studies in searchable, peer reviewed scientific literature and follows the guidance from the International Committee of Medical Journal Editors.

11.6. Provision of study results to investigators

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.

GSK Biologicals 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 subjects, as appropriate.

12. COUNTRY SPECIFIC REQUIREMENTS

12.1. Requirements for Germany

12.1.1. EXPLANATORY STATEMENT CONCERNING GENDER DISTRIBUTION (ARTICLE 7, PARAGRAPH 2 (12) OF THE GERMAN GCP ORDER)

There is no intention to conduct specific analyses investigating the relationship between the gender of the subjects and the immunogenicity and safety of the GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine. The ratio of male to female subjects recruited into the study (ROTA-081) is expected to be in line with the demographics of the population aged 6-12 weeks in the Member State.

12.2. Requirements for Japan (Amended: 09 March 2017)

12.2.1. Regulatory and Ethical Considerations, including the Informed Consent Process

The study will be conducted in accordance with all applicable regulatory requirements, and with GSK policy.

The study will also be conducted in accordance with ICH GCP, all applicable subject privacy requirements, and the guiding principles of the current version of the Declaration of Helsinki. This includes, but is not limited to, the following:

- IRB/IEC review and favourable opinion/approval of the study protocol and amendments as applicable
- Signed informed consent to be obtained for each subject before participation in the study (and for amendments as applicable)
- Investigator reporting requirements (e.g., reporting of AEs/SAEs/protocol deviations to IRB/IEC)

GSK will provide full details of the above procedures, either verbally, in writing, or both.

12.2.2. Study and site closure

- Upon completion or premature discontinuation of the study, the GSK monitor will conduct site closure activities with the investigator or site staff, as appropriate, in accordance with applicable regulations including GCP, and GSK Standard Operating Procedures.
- GSK reserves the right to temporarily suspend or prematurely discontinue this study at any time for reasons including, but not limited to, safety or ethical issues or severe non-compliance. For multicenter studies, this can occur at one or more or at all sites.
- If GSK determines such action is needed, GSK will discuss the reasons for taking such action with the investigator or the head of the medical institution (where applicable). When feasible, GSK will provide advance notification to the investigator or the head of the medical institution, where applicable, of the impending action.
- If the study is suspended or prematurely discontinued for safety reasons, GSK will promptly inform all investigators, heads of the medical institutions (where applicable) and/or institution(s) conducting the study. GSK will also promptly inform the relevant regulatory authorities of the suspension or premature discontinuation of the study and the reason(s) for the action.
- If required by applicable regulations, the investigator or the head of the medical institution (where applicable) must inform the IRB/IEC promptly and provide the reason for the suspension or premature discontinuation.

12.2.3. Regulatory and Ethical Considerations

The study will be conducted in accordance with “the Ministerial Ordinance on the Standards for the Conduct of Clinical Trials of Medicinal Products (MHW Notification No.28 dated 27th March, 1997)” and ***the Pharmaceuticals and Medical Devices Act***.

The statement “I acknowledge that I am responsible for the overall study conduct.” on the Investigator Protocol Agreement Page means the investigator’s responsibility as defined by Japanese GCP.

GSK will submit the CTN to the regulatory authorities in accordance with ***the Pharmaceuticals and Medical Devices Act*** before conclusion of any contract for the conduct of the study with study sites.

12.2.4. Informed Consent

Prior to participation in the study, the investigator (or sub-investigator) should fully inform the potential subject and/or the subject’s legally acceptable representative of the study including the written information. The investigator (or sub-investigator) should provide the subject and/or the subject's legally acceptable representative ample time and opportunity to inquire about details of the study. The subject and/or the subject’s legally acceptable representative should sign and personally date the consent form. If the subject wishes to consider the content of the written information at home, he/she may sign the consent form at home. The person who conducted the informed consent discussion and the study collaborator giving supplementary explanation, where applicable, should sign

and personally (signature) date the consent form. If an impartial witness is required, the witness should sign and personally date the consent form. The investigator (or sub-investigator) should retain this signed and dated form (and other written information) together with the source medical records, such as clinical charts (in accordance with the rules for records retention, if any, at each medical institution) and give a copy to the subject and/or the subject's legally acceptable representative.

12.2.5. Study Period

Study period is included in Exhibit 1.

12.2.6. Study administrative structure

Sponsor information and List of Medical Institutions and Investigators are included in Exhibit 1.

12.2.7. Concerning the "Biological sample handling and analysis"

In the Section 5.7 "Biological sample handling and analysis", the content is replaced for Japan specific content in Exhibit 1.

12.2.8. Unapproved Medical Devices

GSK provides a medical device which has not been approved in Japan for the use in this study.

Unapproved medical device incidents, including those resulting from malfunctions of the device, must be detected, documented, and reported by the investigator throughout the study.

Table 20 Unapproved Medical Device(s)

General Name	Manufacture Name	Brand Name
Pre-filled syringe	SCHOTT Schweiz AG	SYR.1,75ML ROTA FORMAVITRUM FM27
Plunger rod of the Pre-filled syringe	PLASTICS SYSTEMS PACKAGING (PSP)	PLUNGER ROD SHORT PS SYRINGE 1.75 ML
Plunger stopper	BD Medical Pharmaceutical Systems	BD HYPAK SCF plunger stopper
Backstop	BD Medical Pharmaceutical Systems	BD HYPAK Backstop
Enteral Transfer Adapter Device*	SCHOTT Schweiz AG	Enteral Transfer Adapter (ETA)

**only used for lyophilised HRV vaccine.*

Note: Incidents fulfilling the criteria of an AE/SAE will also follow the processes outlined in Section 8.3 to8.8 of the protocol.

12.2.8.1. *Definitions of an Unapproved Medical Device Incident*

- ***An unapproved medical device incident is any malfunction or deterioration in the characteristics and/or performance of a device as well as any inadequacy in the instructions for use, which, directly or indirectly, may lead to or might have led to the death of a participant/user/other person or to a serious deterioration in his/her state of health.***
- ***Not all incidents lead to death or serious deterioration in health. The non-occurrence of such a result may be due to other fortunate circumstances or due to the intervention of health care personnel.***

It is sufficient that:

- ***An incident associated with an unapproved device happens and the incident is such that, if it occurs again, may lead to death or a serious deterioration in health.***

A serious deterioration in state of health can include any of the following:

- ***life-threatening illness;***
- ***permanent impairment of body function or permanent damage to body structure;***
- ***condition necessitating medical or surgical intervention to prevent one of the above;***
- ***foetal distress, foetal death, or any congenital abnormality or birth defects.***

Examples of incidents are:

- ***A participant, user, caregiver, or healthcare professional is injured as a result of an unapproved medical device failure or its misuse.***
- ***A participant's study treatment is interrupted or compromised by an unapproved medical device failure.***
- ***A misdiagnosis due to unapproved medical device failure leads to inappropriate treatment.***
- ***A participant's health deteriorates due to unapproved medical device failure.***

12.2.8.2. *Detecting and recording Unapproved Medical Device Incidents*

The detection and documentation procedures described in this protocol apply to all unapproved medical devices provided for use in the study.

12.2.8.2.1. Time Period for Detecting Unapproved Medical Device Incidents

Unapproved medical device incidents or malfunctions of the device that result in an incident will be detected, documented, and reported during the entire study period.

If the investigator learns of any incident at any time after a participant has been discharged from the study, and such incident is considered reasonably related to an unapproved medical device provided for the study, the investigator will promptly notify the sponsor.

12.2.8.2.2. Unapproved Medical Device Incident Documenting

Any unapproved medical device incident occurring during the study will be documented in the participant's medical records, in accordance with the investigator's normal clinical practice, and on the appropriate form. For incidents fulfilling the criteria of an AE or an SAE, the appropriate AE/SAE eCRF page will be completed as described in Section 8.3 to8.8.

The form will be completed as thoroughly as possible and signed by the unblind (sub-) investigator before transmittal to the unblind monitor via Fax or an e-mail. Blinding needs to be maintained during this process.

It is very important that the investigator provides his/her assessment of causality (relationship to the unapproved medical device provided by GSK) at the time of the initial report and describes any corrective or remedial actions taken to prevent recurrence of the incident.

12.2.8.3. *Prompt Reporting of Unapproved Medical Device Incidents to Sponsor*

Unapproved medical device incidents will be reported to the sponsor within 24 hours after the investigator determines that the event meets the criteria of an unapproved medical device incident, as described in Section 12.2.8.1.

The Medical Device Incident Report Form will be sent to unblind monitor via Fax or an e-mail. Refer to the Exhibit 1 for the contact information of unblind monitor.

In the absence of facsimile or e-mail equipment, notification by telephone is acceptable for incidents, with a copy of the 'Medical Device Incident Report Form' sent by an overnight mail.

12.2.8.3.1. Regulatory Reporting Requirements for Unapproved Medical Device Incidents

The investigator will promptly report all incidents occurring with any medical device provided for use in the study in order for the sponsor to fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.

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

12.2.8.4. *Follow-up of Unapproved Medical Device Incidents*

All unapproved medical device incidents involving an AE will be followed and reported in the same manner as other AEs. This applies to all participants, including those who discontinue study treatment or the study.

The investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated, to elucidate the nature and/or causality of the incident.

New or updated information will be recorded on the originally completed form with all changes signed and dated by the unblind (sub-) investigator.

13. REFERENCES

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APPENDIX A LABORATORY ASSAYS

Serum Analysis

The anti-rotavirus antibody concentrations are determined by a validated anti-rotavirus IgA ELISA. Microtitre plates (96-well) are coated with an anti-rotavirus monoclonal antibody. The wells are washed and incubated with (positive wells) or without (negative wells) rotavirus. Following incubation, the plates are washed and serum, standard and control dilutions are incubated in both types of wells (positive and negative). Bound anti-rotavirus IgA in the well are detected by incubation with peroxidase conjugated anti-human IgA polyclonal antibodies. Colour development proportional to the quantity of bound anti-rotavirus IgA occurs in the presence of a chromogen, TMB (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 millilitre are calculated relative to the four-parameter logistic function generated from the standard curve.

Antigen Detection in Stool Samples

The rotavirus antigen in stool samples collected during GE episodes will be detected by ELISA at Central Lab (GSK or designated laboratory).

RV strain genotyping

The rotavirus RNA will be isolated from Elisa rotavirus positive stool samples. In order to determine the rotavirus P and G type, VP4 and VP7 genes will be then amplified by Reverse Transcription Polymerase Reactions (RT-PCR) using two separate primer sets. VP4 and VP7 amplimers will be further analysed by direct sequencing. The sequences will be interpreted using BLAST database searches in Genbank and phylogenetic analysis.

APPENDIX B CLINICAL LABORATORIES

Table 21 GSK Biologicals' laboratories

Laboratory	Address
GSK Biological's Clinical Laboratory Sciences (CLS), Rixensart	Biospecimen Reception-B7/44 Rue de l'Institut, 89-B-1330 Rixensart-Belgium
GSK Biological's CLS, Wavre-Nord Noir Epine	Avenue Fleming, 20-B-1300 Wavre-Belgium

Table 22 Outsourced laboratories

Laboratory	Address
Q² Solutions Clinical Trials (US)	27027 Tourney Road, Suite 2E Valencia, CA 91355 USA
Q² Solutions Clinical Trials (UK)	1 Simpson Parkway The Alba Campus Rosebank Livingston EH54 7EG UK
DDL Diagnostic Laboratory	Visseringlaan 25 2288 ER Rijswijk The Netherlands

APPENDIX C AMENDMENTS AND ADMINISTRATIVE CHANGES TO THE PROTOCOL

GlaxoSmithKline Biologicals Vaccines R &D **Protocol Administrative Change 1**	
eTrack study number and Abbreviated Title	115461 (ROTA-081)
IND number	BB-IND-16992
EudraCT number	2016-000598-19
Administrative change number:	Administrative change 1
Administrative change date:	22 June 2016
Co-ordinating author:	PPD
Rationale/background for changes: This protocol administrative change 1 is being done to include mandatory text specific for Japan and Germany.	

Amended text has been included in *bold italics* and deleted text in ~~strikethrough~~ in the following sections:

TITLE PAGE	
Contributing authors	• PPD, Clinical & Epidemiology Project Lead • PPD, Project Statistician • PPD, Lead Statistician • PPD ***and*** PPD, Study Delivery Leads • PPD ***and*** PPD, Project Delivery Leads • PPD, ~~Clinical Immunology representative~~ ***Clinical Read-Out Team Leader*** • PPD, Laboratory Study Manager • PPD, Clinical Safety representative • PPD, Project Data Manager • PPD, Global Regulatory Affairs representative • PPD, Global Patents representative

	• PPD, Keyrus BioPharma for GSK Biologicals ***and*** PPD, ~~Vaccine Supply Coordinators~~ ***Clinical Trial Supply Managers***
Placeholder for name and signature of "Leiter der klinischen Prufung" for Germany, on the Protocol Investigator Agreement page has been added as shown below:	
Leiter der klinischen Prüfung name, function and title	
Signature	
Date	
List of Abbreviations has been updated for IEC, IMP and IRB as shown below: ***IEC: Independent Ethics Committee*** ***IMP: Investigational Medicinal Products*** ***IRB: Institutional Review Board***	
Section 5.4 General study aspects has been updated as shown below: ***The burden of the study for the subject will be minimised as much as possible. For taking blood samples, three attempts at most should be performed. If the physician is not successful after the third attempt, he/she will make no further attempts. A local numbing cream or patch will also be offered at the discretion of the investigator prior to blood sampling, in order to minimise pain when blood samples are drawn.***	
Table 4 List of study procedures has been updated as shown below: Blood sampling for anti-RV antibody determination (~~at least~~ ***approximately*** 2 ml)	

Section 5.6.10.1 Blood sampling for safety and immune response assessments has been updated as shown below:

A volume of ~~at least~~ ***approximately*** 2 mL of whole blood (to provide ~~at least~~ ***approximately*** 0.7 mL of serum) should be drawn from all subjects for anti-RV antibody determination at Visit 1 (Pre-Vacc) and Visit 3 (Post-Vacc 2). After centrifugation, serum samples should be kept at –20°C/–4°F or below until shipment. Refer to the SPM for more details on sample storage conditions.

Table 6 Biological samples has been updated as shown below:

Sample Type	Quantity	Unit	Sampling time point	Subset/No. subjects
Blood	~~At least~~ ***Approximately*** 2	mL	Pre-Vacc	All
	~~At least~~ ***Approximately*** 2	mL	Post-Vacc 2	All
GE stool†	NA	NA	From Visit 1 up to Visit 3	All subjects with GE

Section 10.10.1 Sequence of analyses has been modified as shown below:

Safety data that is as clean as possible will be analysed for IDMC review. Details of the review will be described in an IDMC charter.

An analysis will be conducted once all the study data up to Visit 3 are available and cleaned and Rota-IgA ELISA testing at 1-2 month post-dose 2 has been fully completed. The Clinical Study Report (CSR) with data up to Visit 3 will be used for the registration of PCV-free liquid vaccine in European Union (EU) and 'rest of world' countries. This CSR will be submitted as soon as it is available ~~(without waiting for the safety follow-up data) since safety follow-up is not requested in EU and 'rest of world' countries, in order to accelerate the launch of PCV-free vaccine~~.

In addition, an integrated clinical study report containing all data will be written and made available to the investigators and submitted to regulatory authorities as appropriate, ***e.g., for licensure of PCV-free liquid vaccine in US***. This report will include the following:

- An analysis of the serum anti-RV IgA antibody concentrations, 1-2 months after Dose 2 in the lyophilised and pooled liquid groups.
- The reactogenicity and safety analysis of SAEs and AEs leading to drop out reported after Visit 3 up to the safety follow-up contact.
- The final analyses of all data conducted after conclusion of the safety follow-up phase.

This report will also summarize all the SAEs reported from Visit 1 up to the safety follow-up contact to account for the SAEs not reported in the earlier study report due to late reporting of SAEs.

~~The safety follow-up data will be needed for licensure in US and thus the integrated clinical study report will be submitted in US.~~

Section 12 COUNTRY SPECIFIC REQUIREMENTS has been updated for Germany and Japan as shown below:

Requirements for Germany

EXPLANATORY STATEMENT CONCERNING GENDER DISTRIBUTION (ARTICLE 7, PARAGRAPH 2 (12) OF THE GERMAN GCP ORDER)

There is no intention to conduct specific analyses investigating the relationship between the gender of the subjects and the immunogenicity and safety of the GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine. The ratio of male to female subjects recruited into the study (ROTA-081) is expected to be in line with the demographics of the population aged 6-12 weeks in the Member State.

Requirements for Japan

Regulatory and Ethical Considerations, including the Informed Consent Process

The study will be conducted in accordance with all applicable regulatory requirements, and with GSK policy.

The study will also be conducted in accordance with ICH GCP, all applicable subject privacy requirements, and the guiding principles of the current version of the Declaration of Helsinki. This includes, but is not limited to, the following:

- ***IRB/IEC review and favourable opinion/approval of the study protocol and amendments as applicable***
- ***Signed informed consent to be obtained for each subject before participation in the study (and for amendments as applicable)***
- ***Investigator reporting requirements (e.g., reporting of AEs/SAEs/protocol deviations to IRB/IEC)***

GSK will provide full details of the above procedures, either verbally, in writing, or both.

Study and site closure

- ***Upon completion or premature discontinuation of the study, the GSK monitor will conduct site closure activities with the investigator or site staff, as appropriate, in accordance with applicable regulations including GCP, and GSK Standard Operating Procedures.***
- ***GSK reserves the right to temporarily suspend or prematurely discontinue this study at any time for reasons including, but not limited to, safety or ethical issues or severe non-compliance. For multicenter studies, this can occur at one or more or at all sites.***

- ***If GSK determines such action is needed, GSK will discuss the reasons for taking such action with the investigator or the head of the medical institution (where applicable). When feasible, GSK will provide advance notification to the investigator or the head of the medical institution, where applicable, of the impending action.***
- ***If the study is suspended or prematurely discontinued for safety reasons, GSK will promptly inform all investigators, heads of the medical institutions (where applicable) and/or institution(s) conducting the study. GSK will also promptly inform the relevant regulatory authorities of the suspension or premature discontinuation of the study and the reason(s) for the action.***
- ***If required by applicable regulations, the investigator or the head of the medical institution (where applicable) must inform the IRB/IEC promptly and provide the reason for the suspension or premature discontinuation.***

Regulatory and Ethical Considerations

The study will be conducted in accordance with "the Ministerial Ordinance on the Standards for the Conduct of Clinical Trials of Medicinal Products (MHW Notification No.28 dated 27th March, 1997)" and Law for Ensuring the Quality, Efficacy, and Safety of Drugs and Medical Devices.

The statement "I acknowledge that I am responsible for the overall study conduct." on the Investigator Protocol Agreement Page means the investigator's responsibility as defined by Japanese GCP.

GSK will submit the CTN to the regulatory authorities in accordance with Article 80-2 of the Law for Ensuring the Quality, Efficacy, and Safety of Drugs and Medical Devices before conclusion of any contract for the conduct of the study with study sites.

Informed Consent

Prior to participation in the study, the investigator (or sub-investigator) should fully inform the potential subject and/or the subject's legally acceptable representative of the study including the written information. The investigator (or sub-investigator) should provide the subject and/or the subject's legally acceptable representative ample time and opportunity to inquire about details of the study. The subject and/or the subject's legally acceptable representative should sign and personally date the consent form. If the subject wishes to consider the content of the written information at home, he/she may sign the consent form at home. The person who conducted the informed consent discussion and the study collaborator giving supplementary explanation, where applicable, should sign and personally (signature) date the consent form. If an impartial witness is required, the witness should sign and personally date the consent form. The investigator (or sub-investigator) should retain this signed and dated form (and other written information) together with the source medical records, such as clinical charts (in accordance with the rules for records retention, if any, at each medical institution) and give a copy to the subject and/or the subject's legally acceptable representative.

Study Period

Study period is included in Exhibit 1.

Study administrative structure

Sponsor information and List of Medical Institutions and Investigators are included in Exhibit 1.

Concerning the "Biological sample handling and analysis"

In the Section 5.7 "Biological sample handling and analysis", the content is replaced for Japan specific content in Exhibit 1.

GlaxoSmithKline Biologicals

Vaccines R &D

Protocol Administrative Change 2

eTrack study number and Abbreviated Title	115461 (ROTA-081)
IND number	BB-IND-16992
EudraCT number	2016-000598-19
Administrative change number:	Administrative change 2
Administrative change date:	06 September 2016
Co-ordinating author:	PPD

Rationale/background for changes:
The GSK Biologicals' Contact information for Emergency Unblinding for United States (US) and Canada have changed. This protocol administrative change provides the new numbers.

Amended text has been included in *bold italics* and deleted text in ~~strikethrough~~ in the following sections:

The list of contributing authors has been updated.

Section 8.8 Emergency unblinding has been updated as shown below.

GSK Biologicals' Contact information for Emergency Unblinding

24/24 hour and 7/7 day availability

GSK Biologicals' Central Safety Physician:

Outside US/Canada:
+PPD (GSK Biologicals Central Safety Physician on-call)
For US/Canada only:
+PPD +PPD (GSK Biologicals' Central Safety Physician on-call) **(Amended 06 September 2016)**
GSK Biologicals' Central Safety Physician Back-up:
Outside US/Canada:
+PPD
US/Canada only:
+PPD +PPD **(Amended 06 September 2016)**
Emergency Unblinding Documentation Form transmission:
Outside US & Canada:
Fax: +PPD or +PPD
US/Canada only:
Fax: +PPD

GlaxoSmithKline Biologicals

Vaccines R &D

Protocol Amendment 1

eTrack study number and Abbreviated Title	115461 (ROTA-081)
IND number	BB-IND-16992
EudraCT number	2016-000598-19
Administrative change number:	Amendment 1
Administrative change date:	09 March 2017
Co-ordinating author:	PPD

Rationale/background for changes:
The protocol is being amended to include the text related to the unapproved medical devices and incidents associated with it as per Japan specific requirements.

Amended text has been included in *bold italics* and deleted text in ~~strikethrough~~ in the following sections:

The list of contributing authors has been updated.

Contributing authors	• PPD, Clinical & Epidemiology Project Lead • PPD, Clinical Research and Epidemiology Lead • PPD, ~~Project~~ Statistician • PPD, Lead Statistician • PPD ~~and~~ PPD ~~,~~ PPD **,** Study Delivery Lead~~s~~ • PPD ~~and~~ PPD, Project Delivery Lead~~s~~ • PPD, Clinical Read-Out Team Leader • PPD, Laboratory Study Manager • PPD, Clinical Safety representative • PPD, ~~Project~~ ***Oversight*** Data Manager • PPD, Global Regulatory Affairs representative

	• PPD, Global Patents representative • PPD, ~~Keyrus BioPharma for GSK Biologicals and~~ PPD, Clinical Trial Supply Manager~~s~~

Section 12 COUNTRY SPECIFIC REQUIREMENTS has been updated for Japan as shown below:

12.2.3 Regulatory and Ethical Considerations

The study will be conducted in accordance with "the Ministerial Ordinance on the Standards for the Conduct of Clinical Trials of Medicinal Products (MHW Notification No.28 dated 27th March, 1997)" and ~~Law for Ensuring the Quality, Efficacy, and Safety of Drugs and Medical Devices~~ ***the Pharmaceuticals and Medical Devices Act***.

The statement "I acknowledge that I am responsible for the overall study conduct." on the Investigator Protocol Agreement Page means the investigator's responsibility as defined by Japanese GCP.

GSK will submit the CTN to the regulatory authorities in accordance with ~~Article 80-2 of the Law for Ensuring the Quality, Efficacy, and Safety of Drugs and Medical Devices~~ ***the Pharmaceuticals and Medical Devices Act*** before conclusion of any contract for the conduct of the study with study sites.

12.2.8 Unapproved Medical Devices

GSK provides a medical device which has not been approved in Japan for the use in this study.

Unapproved medical device incidents, including those resulting from malfunctions of the device, must be detected, documented, and reported by the investigator throughout the study.

Table 20 Unapproved Medical Device(s)

General Name	*Manufacture Name*	*Brand Name*
Pre-filled syringe	*SCHOTT Schweiz AG*	*SYR.1,75ML ROTA FORMAVITRUM FM27*
Plunger rod of the Pre-filled syringe	*PLASTICS SYSTEMS PACKAGING (PSP)*	*PLUNGER ROD SHORT PS SYRINGE 1.75 ML*
Plunger stopper	*BD Medical Pharmaceutical Systems*	*BD HYPAK SCF plunger stopper*
Backstop	*BD Medical Pharmaceutical Systems*	*BD HYPAK Backstop*
*Enteral Transfer Adapter Device**	*SCHOTT Schweiz AG*	*Enteral Transfer Adapter (ETA)*

**only used for lyophilised HRV vaccine.*

Note: Incidents fulfilling the criteria of an AE/SAE will also follow the processes outlined in Section 8.3 to8.8 of the protocol.

12.2.8.1 Definitions of an Unapproved Medical Device Incident

- ***An unapproved medical device incident is any malfunction or deterioration in the characteristics and/or performance of a device as well as any inadequacy in the instructions for use, which, directly or indirectly, may lead to or might have led to the death of a participant/user/other person or to a serious deterioration in his/her state of health.***
- ***Not all incidents lead to death or serious deterioration in health. The non-occurrence of such a result may be due to other fortunate circumstances or due to the intervention of health care personnel.***

It is sufficient that:

- ***An incident associated with an unapproved device happens and the incident is such that, if it occurs again, may lead to death or a serious deterioration in health.***

A serious deterioration in state of health can include any of the following:

- ***life-threatening illness;***
- ***permanent impairment of body function or permanent damage to body structure;***
- ***condition necessitating medical or surgical intervention to prevent one of the above;***
- ***foetal distress, foetal death, or any congenital abnormality or birth defects.***

Examples of incidents are:

- ***A participant, user, caregiver, or healthcare professional is injured as a result of an unapproved medical device failure or its misuse.***
- ***A participant's study treatment is interrupted or compromised by an unapproved medical device failure.***
- ***A misdiagnosis due to unapproved medical device failure leads to inappropriate treatment.***
- ***A participant's health deteriorates due to unapproved medical device failure.***

12.2.8.2 Detecting and recording Unapproved Medical Device Incidents

The detection and documentation procedures described in this protocol apply to all unapproved medical devices provided for use in the study.

12.2.8.2.1 Time Period for Detecting Unapproved Medical Device Incidents

Unapproved medical device incidents or malfunctions of the device that result in an incident will be detected, documented, and reported during the entire study period.

If the investigator learns of any incident at any time after a participant has been discharged from the study, and such incident is considered reasonably related to an unapproved medical device provided for the study, the investigator will promptly notify the sponsor.

12.2.8.2.2 Unapproved Medical Device Incident Documenting

Any unapproved medical device incident occurring during the study will be documented in the participant's medical records, in accordance with the investigator's normal clinical practice, and on the appropriate form. For incidents fulfilling the criteria of an AE or an SAE, the appropriate AE/SAE eCRF page will be completed as described in Section 8.3 to8.8.

The form will be completed as thoroughly as possible and signed by the unblind (sub-) investigator before transmittal to the unblind monitor via Fax or an e-mail. Blinding needs to be maintained during this process.

It is very important that the investigator provides his/her assessment of causality (relationship to the unapproved medical device provided by GSK) at the time of the initial report and describes any corrective or remedial actions taken to prevent recurrence of the incident.

12.2.8.3 Prompt Reporting of Unapproved Medical Device Incidents to Sponsor

Unapproved medical device incidents will be reported to the sponsor within 24 hours after the investigator determines that the event meets the criteria of an unapproved medical device incident, as described in Section 12.2.8.1.

The Medical Device Incident Report Form will be sent to unblind monitor via Fax or an e-mail. Refer to the Exhibit 1 for the contact information of unblind monitor.

In the absence of facsimile or e-mail equipment, notification by telephone is acceptable for incidents, with a copy of the 'Medical Device Incident Report Form' sent by an overnight mail.

12.2.8.3.1 Regulatory Reporting Requirements for Unapproved Medical Device Incidents

The investigator will promptly report all incidents occurring with any medical device provided for use in the study in order for the sponsor to fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.

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

12.2.8.4 Follow-up of Unapproved Medical Device Incidents

All unapproved medical device incidents involving an AE will be followed and reported in the same manner as other AEs. This applies to all participants, including those who discontinue study treatment or the study.

The investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated, to elucidate the nature and/or causality of the incident.

New or updated information will be recorded on the originally completed form with all changes signed and dated by the unblind (sub-) investigator.

Protocol Amendment 1 Sponsor Signatory Approval

eTrack study number and Abbreviated Title	115461 (ROTA-081)
IND number	BB-IND-16992
EudraCT number	2016-000598-19
Date of protocol amendment	Amendment 1 Final: 09 March 2017
Detailed Title	A phase IIIA, randomised, observer-blind, multi-centre study to evaluate the clinical consistency of three production lots of the Porcine circovirus (PCV)-free liquid formulation of GlaxoSmithKline (GSK) Biologicals' oral live attenuated human rotavirus (HRV) vaccine and to evaluate the PCV-free liquid formulation of GSK Biologicals' HRV vaccine as compared to the currently licensed lyophilised formulation of the HRV vaccine in terms of immunogenicity, reactogenicity and safety when administered as a two-dose vaccination in healthy infants starting at age 6-12 weeks.
Sponsor signatory	Paul Gillard, Clinical & Epidemiology Project Lead (CEPL), GlaxoSmithKline Biologicals, SA.
Signature	PPD
Date	27 MAR 2017

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