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

Primary Study vaccine and number	• Liquid formulation of GlaxoSmithKline (GSK) Biologicals' oral live attenuated human rotavirus (HRV) vaccine Rotarix™ (444563)
Other Study vaccine	• Kitasato Daiichi Sankyo Vaccine Company Ltd's diphtheria, tetanus, pertussis and inactivated poliovirus (DPT-IPV) vaccine (Squarekids™).
eTrack study number and Abbreviated Title	114720 (ROTA-079)
EudraCT number	2014-005282-78
Date of protocol	Final Version 03: 03 June 2016
Title	Immunogenicity and safety of the diphtheria, tetanus, pertussis and inactivated poliovirus (DPT-IPV) vaccine Squarekids™ co-administered with GSK Biologicals' human rotavirus (HRV) vaccine Rotarix™ (444563) in healthy infants.
Detailed Title	A phase IV, randomised, open-label, controlled study to assess the immunogenicity and safety of the diphtheria, tetanus, pertussis and inactivated poliovirus (DPT-IPV) vaccine Squarekids™ when co-administered with GSK Biologicals' oral live attenuated HRV liquid vaccine Rotarix™ in healthy Japanese infants aged 6 - 12 weeks at the time of the first dose of HRV vaccination.
Co-ordinating author	PPD, Scientific Writer
Contributing authors	• PPD, Clinical Research and Development Lead (CRDL) • PPD, Director, Project Level CRDL • PPD, Director, Clinical & Epidemiology Project Lead, MMRV and Rota • PPD, Lead Statistician • PPD, Project Statistician • PPD, Study Delivery Lead, *SynteractHCR* US, for GSK Biologicals • PPD, Study Delivery Lead, *Novellas Healthcare Consultant*, for GSK Biologicals

eTrack study number and Abbreviated Title	114720 (ROTA-079)
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Detailed Title	A phase IV, randomised, open-label, controlled study to assess the immunogenicity and safety of the diphtheria, tetanus, pertussis and inactivated poliovirus (DPT-IPV) vaccine Squarekids™ when co-administered with GSK Biologicals' oral live attenuated HRV liquid vaccine Rotarix™ in healthy Japanese infants aged 6 - 12 weeks at the time of the first dose of HRV vaccination.
Contributing authors	• PPD, Study Delivery Manager, *SynteractHCR* US, for GSK Biologicals • PPD, Clinical Immunology representative • PPD, Clinical Immunology representative • PPD, Clinical Safety representative • PPD, Project Data Manager • PPD, Global Regulatory Affairs representative • PPD, Global Patents representative • PPD, Vaccine Supply Coordinator • PPD, Japan Study Leader

GSK Biologicals' Protocol DS v 14.1.1

Protocol Sponsor Signatory Approval

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Sponsor signatory	Paul Gillard, Director, Clinical & Epidemiology Project Lead, MMRV and Rota GlaxoSmithKline Biologicals, SA.
Signature	_____
Date	_____

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Protocol 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 vaccine 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 vaccine, 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	114720 (ROTA-079)
EudraCT number	2014-005282-78
Date of protocol	Final Version 03: 03 June 2016
Detailed Title	A phase IV, randomised, open-label, controlled study to assess the immunogenicity and safety of the diphtheria, tetanus, pertussis and inactivated poliovirus (DPT-IPV) vaccine Squarekids™ when co-administered with GSK Biologicals' oral live attenuated HRV liquid vaccine Rotarix™ in healthy Japanese infants aged 6 - 12 weeks at the time of the first dose of HRV vaccination.
Investigator name	_____
Investigator Address:	_____
Investigator Phone Number	_____
Investigator Signature	_____
Date	_____

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Medical Monitor/Sponsor Information Page

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. Medical Monitor / Sponsor Study Contact for Reporting of a Causally Related Adverse Event and Serious Adverse Event

Role	Name	Day Time Phone Number and email address	After-hours Phone/Cell/ Pager Number	Fax Number	Site Address
Primary Medical Monitor	PPD	+ PPD (day time) and PPD	PPD (after hours)		GSK / avenue Fleming / 1300 Wavre
Secondary Medical Monitor	PPD	PPD	GSK Biologicals Central Back-up Study Contact for Reporting Causally Related Adverse Events and SAEs: refer to protocol Section 8.4.2	PPD	6-15, Sendagaya 4-chome, Shibuya-ku, Tokyo, 151-8566, Japan
Causally Related Adverse Event/ SAE contact information	Study Monitor	PPD	GSK Biologicals Central Back-up Study Contact for Reporting Causally Related Adverse Events and SAEs: refer to protocol Section 8.4.2	PPD	2-26, Shimomiyabi-cho, Shinjuku-ku, Tokyo, 162-0822, Japan

SYNOPSIS

Detailed Title	A phase IV, randomised, open-label, controlled study to assess the immunogenicity and safety of the diphtheria, tetanus, pertussis and inactivated poliovirus (DPT-IPV) vaccine Squarekids™ when co-administered with GSK Biologicals' oral live attenuated HRV liquid vaccine Rotarix™ in healthy Japanese infants aged 6 - 12 weeks at the time of the first dose of HRV vaccination.
Indication	Active immunisation of infants against gastroenteritis (GE) due to rotavirus (RV).
Rationale for the study and study design	• Rationale for the study The burden of severe RV disease among Japanese children is substantial. An active surveillance of RV hospitalisation in three cities in central Japan showed that RV infection accounted for approximately 40% to 50% of hospitalised acute GE cases in each city. A further extrapolation of the mean incidence of RV hospitalisation in the three cities to the national population data for children less than 5 years of age estimated that approximately 30,000 hospitalisations occurred among Japanese children less than 5 years of age annually, for RV acute GE [Kamiya, 2011]. GlaxoSmithKline (GSK) Biologicals' rotavirus vaccine (Rotarix™) is a vaccine for oral use, containing the live attenuated human rotavirus RIX4414 strain. Infants aged younger than 3 months who received the vaccine did not develop diarrhoea, vomiting or fever [Vesikari, 2004(a)].In a study that evaluated the HRV vaccine in Japan, the vaccine efficacy against any and severe RV GE which led to medical intervention caused by circulating wild-type RV was 79.3% and 91.6% respectively. Additionally, the serum anti-RV antibody seroconversion rate one-month after the second dose of the vaccine was 85.3%. The vaccine was found to be well-tolerated, immunogenic and efficacious against RV disease in Japanese infants [Kawamura, 2011]. This study will evaluate the immunogenicity and safety of the diphtheria, tetanus, pertussis and inactivated poliovirus (DPT-IPV) vaccine *Squarekids* administered with or without the GSK Biologicals' liquid HRV vaccine, in healthy Japanese infants aged 6 - 12 weeks. GSK Biologicals' liquid HRV vaccine *Rotarix* is licensed in Japan since 2011. Although the concomitant administration of GSK Biologicals' DTP-IPV vaccine has been evaluated

during the clinical development of the HRV vaccine [Dennehy, 2008], the vaccine differed in composition and route of administration from the DPT-IPV vaccine *Squarekids* manufactured in Japan. Hence, as requested by the Japanese regulatory authorities, this post-licensure study will evaluate the immunogenicity of the DPT-IPV vaccine manufactured in Japan when co-administered with the liquid HRV vaccine.

- Rationale for the study design

The study is designed as a randomised, controlled, open-label study with two parallel groups. This study will evaluate the immunogenicity and safety of the DPT-IPV vaccine when administered with or without the liquid HRV vaccine in healthy Japanese infants.

The two groups in the study are as follows:

- Co-administration group: Subjects will be administered the DPT-IPV vaccine according to a 3, 4, 6 month schedule and the liquid HRV vaccine according to a 2, 3 month schedule.
- Staggered group: Subjects will be administered the DPT-IPV vaccine according to a 3, 4.5, 6 month schedule and the liquid HRV vaccine according to a 2, 3.5 month schedule.

In the Co-administration group, the co-administration of study vaccines will be performed only once, when the infant is approximately 3 months old. The majority of Japanese infants who are administered both DPT-IPV and RV vaccine are co-administered only once in accordance with the recommended vaccination schedule in Japan. Additionally, the first dose of HRV vaccine administration is strongly recommended for infants at 6 - 12 weeks of age in Japan [Nakagomi, 2011].

The study will be conducted in an open-label manner due to the difference in the vaccination schedule between the two groups. The study will also include a sub-cohort for evaluating immunogenicity of the liquid HRV vaccine in terms of serum anti-RV IgA antibody seropositivity and geometric mean concentrations (GMCs) one month after the second dose of the liquid HRV vaccine.

Objectives

Primary

- To demonstrate that the immunogenicity to the antigens contained in DPT-IPV vaccine is not impaired by the co-administration with GSK Biologicals' liquid HRV

vaccine.

Criteria for non-inferiority (1 month after the third dose of DPT-IPV vaccine at Visit 7):

- Lower limits of the standardised asymptotic 95% confidence intervals (CIs) on the differences (Co-administered group minus Staggered group) in the percentages of subjects with seroprotective concentrations ≥ 0.1 IU/mL for anti-diphtheria (anti-D) antibodies and concentrations ≥ 0.1 IU/mL for anti-tetanus (anti-T) antibodies are ≥-10% (clinical limit for non-inferiority),
- Lower limits of the 95% CIs on the differences (Co-administered group minus Staggered group) in the percentages of subjects with concentrations ≥ 10 IU/mL for antibodies against the pertussis toxoid (PT) and filamentous hemagglutinin (FHA) antigens (anti-PT and anti-FHA) are ≥ -10% (clinical limit for non-inferiority),
- Lower limits of the standardised asymptotic 95% CIs on the differences (Co-administered group minus Staggered group) in the percentages of subjects with seroprotective titres (≥8 ED_{50}) for each of anti-poliovirus serotypes 1, 2 and 3 antibodies are ≥ -10% (clinical limit for non-inferiority).

Secondary

- To assess the immunogenicity of the liquid HRV vaccine in terms of serum anti-RV IgA antibody seropositivity and GMCs in a sub-cohort of subjects, 1 month after the second dose of the liquid HRV vaccine.
- To assess the immunogenicity to all the antigens contained in the DPT-IPV vaccine in terms of GMCs/ geometric mean antibody titres (GMTs), 1 month after the third dose of the DPT-IPV vaccine.
- To assess reactogenicity and safety after each dose of liquid HRV vaccine and first dose of DPT-IPV vaccine in terms of solicited symptoms during the 8-day follow-up period and unsolicited symptoms during the 31-day follow-up period.
- To assess safety in terms of serious adverse events (SAEs) from the first dose of study vaccine up to study end.

Study design

- Experimental design: Phase IV, open-label, randomised, controlled, multi-centric, single-country study with two parallel groups.
- Duration of the study:
  - The intended duration of the study, per subject, is 5 months.
  - Epoch 001: Primary starting at Visit 1 (Day 0) and ending at Visit 7 (Month 5).
- Primary Completion Date (PCD): Visit 7 (Month 5) (Refer to Glossary of terms for the definition of PCD)
- End of Study (EoS): Last testing results released of samples collected at Visit 7 (Refer to Glossary of terms for the definition of EoS)
- Study groups: The study groups and epoch foreseen in the study are provided in Synopsis Table 1.

Synopsis Table 1 Study groups and epochs foreseen in the study

Study groups	Number of subjects	Age (Min/Max)	Epochs
			Epoch 001
Co-administration group	146	6 weeks - 12 weeks	x
Staggered group	146	6 weeks - 12 weeks	x

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

Synopsis Table 2 Study groups and treatment foreseen in the study

Treatment name	Vaccine name	Study Groups	
		Co-administration group	Staggered group
Rotarix	HRV	x	x
Squarekids	*Squarekids*	x	x

- Control: active control (Staggered group).
- Vaccination schedules: The vaccination schedules are as follows:
  - Subjects in the Co-administration group will be administered the DPT-IPV vaccine according to a 3, 4, 6 month schedule and the liquid HRV vaccine according to a 2, 3 month schedule.
  - Subjects in the Staggered group will be administered the DPT-IPV vaccine according to a 3, 4.5, 6 month schedule and the liquid HRV vaccine according to a 2, 3.5 month schedule.

The childhood vaccines Pneumococcal conjugate vaccine (PCV), *Haemophilus influenzae* type B vaccine (Hib), Bacillus Calmette-Guérin (BCG) vaccine, hepatitis B vaccine, meningococcal vaccine and inactivated influenza vaccine can be administered to subjects as per the clinical practice in Japan, outside the scope of this study.

- Treatment allocation: 1:1 randomisation using GSK Biologicals' central randomisation system on Internet (SBIR).
- Blinding: Open-label. The blinding of study epoch is provided in Synopsis Table 3.

Synopsis Table 3 Blinding of study epochs

Study Epochs	Blinding
Epoch 001	open

- Sampling schedule: Details of the samples to be collected are as follows:
  - A blood sample of approximately 2 mL will be collected from a sub-cohort of subjects (approximately half the number of enrolled subjects from each study group), 1 month after the administration of the second dose of the liquid HRV vaccine.
  - A second blood sample of approximately 5 mL will be collected at Visit 7, 1 month after administration of the last dose of DPT-IPV vaccine from all the subjects.
- Type of study: self-contained.
- Data collection: Electronic Case Report Form (eCRF).

Number of subjects In order to have 262 subjects (131 in each study group) evaluable for the immunogenicity analyses corresponding to the primary confirmatory objective, the target sample size to be enrolled is at least 292 subjects (146 subjects in each group), accounting for a dropout rate of 10%.

Endpoints **Primary**

- Immunogenicity with respect to components of the DPT-IPV vaccine 1 month after administration of the third dose of the vaccine (Visit 7):
  - anti-diphtheria antibody concentrations ≥ 0.1 IU/mL,
  - anti-tetanus antibody concentrations ≥ 0.1 IU/mL,

- anti-PT and anti-FHA antibody concentrations ≥10 IU/mL,
- anti-poliovirus serotypes 1, 2 and 3 antibody titre ≥8 ED_{50}.

Secondary

- Serum anti-RV IgA antibody concentration ≥ 20 U/mL and seropositivity in a sub-cohort of subjects, 1 month after the second dose of the liquid HRV vaccine.
- Serum GMCs/GMTs for anti-diphtheria, anti-tetanus, anti-poliovirus serotypes 1, 2 and 3, anti-PT and anti-FHA antibodies, 1 month after the third dose of the DPT-IPV vaccine.
- Occurrence of solicited general symptoms during the 8-day (Days 0-7) follow-up period after each dose of liquid HRV vaccine.
- Occurrence of solicited local and general symptoms during the 8-day (Days 0-7) follow-up period after the first dose of DPT-IPV vaccine.
- Occurrence of unsolicited AEs during the 31-day (Days 0-30) follow-up period after each dose of the liquid HRV vaccine and the first dose of DPT-IPV vaccine, according to the Medical Dictionary for Regulatory Activities (MedDRA) classification.
- Occurrence of SAEs from the first dose of the study vaccine up to study end (Visit 7).

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LIST OF ABBREVIATIONS

AE:	Adverse Event
ATP:	According-To-Protocol
BCG:	Bacillus Calmette-Guérin
BMI:	Body Mass Index
CI:	Confidence Interval
$CCID_{50}$:	Median Cell Culture Infective Dose (quantity of virus causing infection in 50% of exposed cells)
CDC:	Centers for Disease Control and Prevention, USA
DTP/DPT:	Diphtheria, Pertussis and Tetanus toxoids
eCRF:	electronic Case Report Form
EoS	End of Study
FHA:	Filamentous Haemagglutinin
GCP:	Good Clinical Practice
GE:	Gastroenteritis
GMC:	Geometric Mean Concentration
GMT:	Geometric Mean Titre
GSK:	GlaxoSmithKline
Hib:	*Haemophilus influenzae* type B vaccine
HRV:	Human Rotavirus
IgA:	Immunoglobulin A
IPV:	Inactivated Poliovirus Vaccine
IS:	Intussusception
IU:	International Unit(s)
LAR:	Legally Acceptable Representative
LSLV:	Last Subject Last Visit

MedDRA:	Medical Dictionary for Regulatory Activities
mL:	Millilitre
PCD	Primary Completion Date
PCV:	Pneumococcal conjugate vaccine
PT:	Pertussis Toxoid
RDE:	Remote Data Entry
RV:	Rotavirus
SAE:	Serious Adverse Event
SBIR:	Randomisation System on Internet
SCID:	Severe Combined Immunodeficiency
TVC:	Total Vaccinated Cohort
U:	Unit
WHO:	World Health Organization

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 open-label study, no blind is used. Both the investigator and the subject know the identity of the treatment assigned.
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 parent(s) 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.
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, end of study (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 timepoints or a single timepoint from a single protocol. Self-contained means that data collected for all subjects at all timepoints 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 according-to-protocol (ATP) analysis (see Sections 6.8.2 and 10.4 for details on criteria for evaluability).
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 authorised representative are used in some settings.)**	An individual or juridical or other body authorised 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 all primary outcomes, whether the clinical trial was 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.

Self-contained study:	Study with objectives not linked to the data of another study.
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.
Sub-cohort:	A group of subjects for whom specific study procedures are planned as compared to other subjects.
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 vaccine or as a control.
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.
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.

TRADEMARKS

The following trademarks are used in the present protocol.

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

Trademark of the GlaxoSmithKline group of companies	Generic description
Rotarix™	Human rotavirus vaccine

Trademark not owned by the GlaxoSmithKline group of companies	Generic description
Squarekids® (Kitasato Daiichi Sankyo Vaccine Co., Ltd)	Absorbed diphtheria purified pertussis, tetanus and inactivated polio combined vaccine (Salk 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 child deaths were caused due to rotavirus-associated acute gastroenteritis. Approximately 85% of this burden is in low-income countries globally [WHO position paper, 2013]. Although rotavirus 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].

During the past years, vaccines have been developed that could prevent the enormous morbidity and mortality from rotavirus. Two live oral rotavirus vaccines have been licensed in many countries; one is derived from an attenuated human strain of rotavirus and the other combines five bovine-human reassortant strains [Glass, 2006]. Each of these vaccines has proven highly effective in preventing severe rotavirus 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 Organization (WHO) recognises RV vaccination as an effective measure to prevent RV infection and reduce disease burden, and recommends its inclusion into all national infant immunisation programs [WHO position paper, 2013].

GlaxoSmithKline (GSK) Biologicals' rotavirus vaccine (Rotarix™) is a vaccine for oral use, containing the live attenuated human rotavirus 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 human rotavirus vaccine *Rotarix* (RIX4414)was high, ranging from 80.5% to 90.4% against severe rotavirus gastroenteritis (RVGE), and 83.0% to 96.0% against hospitalization 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 rotavirus gastroenteritis in the first two years of life [Cunliffe, 2014].

Please refer to the Prescribing Information for information regarding the pre-clinical and clinical studies and the epidemiological information of *Rotarix*.

1.2. Rationale for the study and study design

1.2.1. Rationale for the study

The burden of severe RV disease among Japanese children is substantial. An active surveillance of RV hospitalisation in three cities in central Japan showed that RV infection accounted for approximately 40% to 50% of hospitalised acute GE cases in each city. A further extrapolation of the mean incidence of rotavirus hospitalisation in the three cities to the national population data for children less than 5 years of age estimated that approximately 30,000 hospitalisations occurred among Japanese children less than 5 years of age annually, for RV acute GE [Kamiya, 2011].

In a study that evaluated the HRV vaccine in Japan, the vaccine efficacy against any and severe RV GE which led to medical intervention caused by circulating wild-type RV, was 79.3% and 91.6% respectively. Additionally, the serum anti-RV antibody seroconversion rate one-month after the second dose of the vaccine was 85.3%. The vaccine was found to be well-tolerated, immunogenic and efficacious against RV disease in Japanese infants [Kawamura, 2011].

This study will evaluate the immunogenicity and safety of the diphtheria, tetanus, pertussis and inactivated poliovirus (DPT-IPV) vaccine *Squarekids* administered with or without the GSK Biologicals' liquid HRV vaccine, in healthy Japanese infants aged 6 - 12 weeks.

GSK Biologicals' liquid HRV vaccine *Rotarix* is licensed in Japan since 2011. Although the concomitant administration of GSK Biologicals' DTP-IPV vaccine has been evaluated during the clinical development of the HRV vaccine [Dennehy, 2008], the vaccine differed in composition and route of administration from the DPT-IPV vaccine *Squarekids* manufactured in Japan. Hence, as requested by the Japanese regulatory authorities, this post-licensure study will evaluate the immunogenicity of the DPT-IPV vaccine manufactured in Japan when co-administered with the liquid HRV vaccine.

1.2.2. Rationale for the study design

The study is designed as a randomised, controlled, open-label study with two parallel groups. This study will evaluate the immunogenicity and safety of the DPT-IPV vaccine when administered with or without the liquid HRV vaccine in healthy Japanese infants.

The two groups in the study are as follows:

- Co-administration group: Subjects will be administered the DPT-IPV vaccine according to a 3, 4, 6 month schedule and the liquid HRV vaccine according to a 2, 3 month schedule.
- Staggered group: Subjects will be administered the DPT-IPV vaccine according to a 3, 4.5, 6 month schedule and the liquid HRV vaccine according to a 2, 3.5 month schedule.

In the Co-administration group, the co-administration of study vaccines will be performed only once, when the infant is approximately 3 months old. The majority of Japanese infants who are administered both DPT-IPV and RV vaccine are co-administered only once in accordance with the recommended vaccination schedule in Japan. Additionally, the first dose of HRV vaccine administration is strongly recommended for infants at 6 - 12 weeks of age in Japan [Nakagomi, 2011].

The study will be conducted in an open-label manner due to the difference in the vaccination schedule between the two groups. The study will also include a sub-cohort for evaluating immunogenicity of the liquid HRV vaccine in terms of serum anti-RV IgA antibody seropositivity and geometric mean concentrations (GMCs) one month after the second dose of the liquid HRV vaccine.

1.3. Benefit : Risk Assessment

Please refer to the Prescribing Information for the summary of potential risks and benefits of the *Rotarix* vaccine and the *Squarekids* 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 should report any untoward symptoms experienced after receiving the vaccine immediately to the investigator. • All adverse events (AEs)/serious adverse events (SAEs) should be reported by the investigator immediately to GSK. • Daily monitoring of SAEs by medical monitor; regular systematic review of AE/SAE data from ongoing studies by a GSK safety review team.
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	
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.
Investigational study vaccine (DPT-IPV)		
Shock, Anaphylaxis	Frequency is unknown.	Subjects will be observed for at least 30 minutes after vaccine administration, with medical attention available in case of anaphylaxis reactions.
Thrombocytopenic purpura	Frequency is unknown.	• Subjects should report any untoward symptoms experienced after receiving the vaccine immediately to the investigator. • All AEs/SAEs should be reported by the investigator immediately to GSK. • Daily monitoring of SAEs by medical monitor; regular systematic review of AE/SAE data from ongoing studies by a GSK safety review team.
Encephalopathy	Frequency is unknown.	
Convulsion	Frequency is unknown.	

1.3.2. Benefit Assessment

By receiving the liquid HRV vaccine, the subject may become protected against RV disease. The information collected during this study will help in evaluation of the HRV vaccine co-administration with a DPT-IPV vaccine (*Squarekids*) manufactured in Japan and recommended for routine administration during childhood. Therefore, the subject's participation will benefit other children in the future.

The study vaccines will be administered to subjects according to their prescribed vaccination schedule free of cost, as part of the study.

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 healthcare system in Japan.

1.3.3. Overall Benefit: Risk Conclusion

Considering the measures taken to minimise risk to subjects participating in this study, the potential or identified risks in association with *Rotarix* and *Squarekids* are justified by the potential benefits (prevention) that may be afforded to subjects receiving the vaccines for immunisation against RV, diphtheria, tetanus, pertussis and polio.

2. OBJECTIVES

2.1. Primary objective

- To demonstrate that the immunogenicity to the antigens contained in DPT-IPV vaccine is not impaired by the co-administration with GSK Biologicals' liquid HRV vaccine.

Criteria for non-inferiority (1 month after the third dose of DPT-IPV vaccine at Visit 7):

  - Lower limits of the standardised asymptotic 95% confidence intervals (CIs) on the differences (Co-administered group minus Staggered group) in the percentages of subjects with seroprotective concentrations ≥ 0.1 IU/mL for anti-diphtheria (anti-D) antibodies and concentrations ≥ 0.1 IU/mL for anti-tetanus (anti-T) antibodies are ≥-10% (clinical limit for non-inferiority),
  - Lower limits of the 95% CIs on the differences (Co-administered group minus Staggered group) in the percentages of subjects with concentrations ≥ 10 IU/mL for antibodies against the pertussis toxoid (PT) and filamentous hemagglutinin (FHA) antigens (anti-PT and anti-FHA) are ≥ -10% (clinical limit for non-inferiority),
  - Lower limits of the standardised asymptotic 95% CIs on the differences (Co-administered group minus Staggered group) in the percentages of subjects with seroprotective titres (≥8 ED_{50}) for each of anti-poliovirus serotypes 1, 2 and 3 antibodies are ≥ -10% (clinical limit for non-inferiority).

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

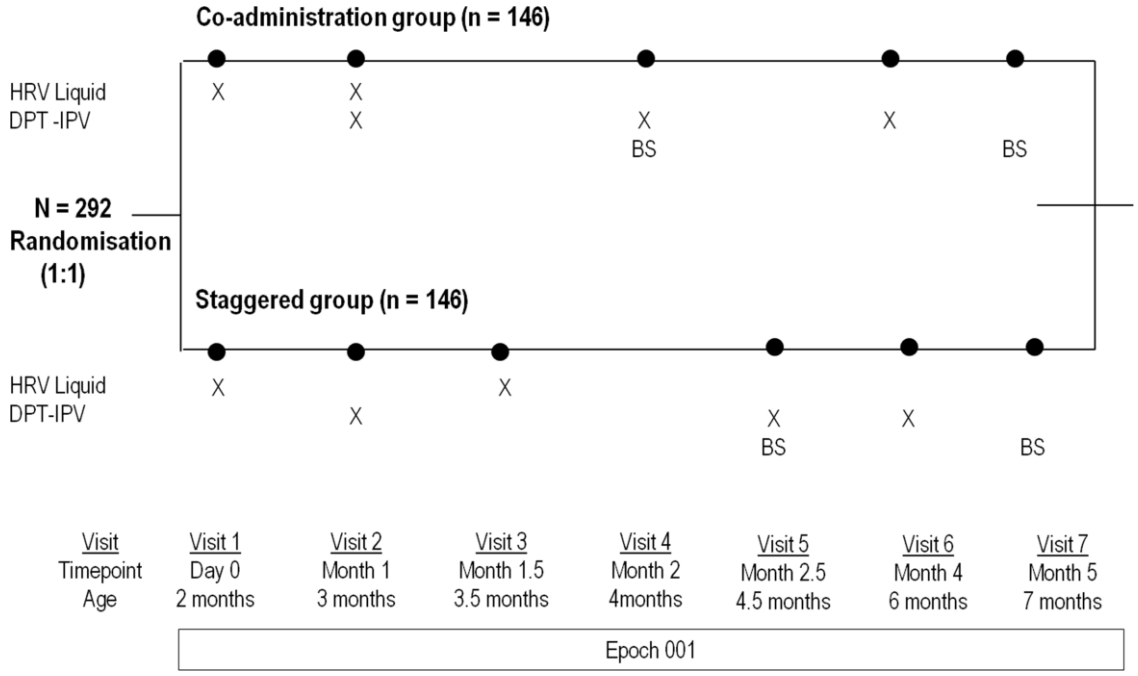
2.2. Secondary objectives

- To assess the immunogenicity of the liquid HRV vaccine in terms of serum anti-RV IgA antibody seropositivity and GMCs in a sub-cohort of subjects, 1 month after the second dose of the liquid HRV vaccine.
- To assess the immunogenicity to all the antigens contained in the DPT-IPV vaccine in terms of GMCs/ geometric mean antibody titres (GMTs), 1 month after the third dose of the DPT-IPV vaccine.

- To assess reactogenicity and safety after each dose of liquid HRV vaccine and first dose of DPT-IPV vaccine in terms of solicited symptoms during the 8-day follow-up period and unsolicited symptoms during the 31-day follow-up period.
- To assess safety in terms of serious adverse events (SAEs) from the first dose of study vaccine up to study end.

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; BS = Blood Sampling.
Visit 3 and Visit 5 are applicable only for subjects in the Staggered group. Visit 4 is applicable only for subjects in the Co-administration group.

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 IV, open-label, randomised, controlled, multi-centric, single-country study with two parallel groups.
- Duration of the study: The intended duration of the study, per subject, is 5 months.
  - Epoch 001: Primary starting at Visit 1 (Day 0) and ending at Visit 7 (Month 5).
- Primary Completion Date: Visit 7 (Month 5) (Refer to GLOSSARY OF TERMS for the definition of PCD).
- End of Study (EoS): Last testing results released of samples collected at Visit 7 (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 epochs foreseen in the study

Study Groups	Number of subjects	Age (Min/ - Max)	Epoch
			Epoch 001
Co-administration group	146	6 weeks - 12 weeks	x
Staggered group	146	6 weeks - 12 weeks	x

- The study groups and treatment foreseen in the study are provided in Table 2.

Table 2 Study groups and treatment foreseen in the study

Treatment name	Vaccine name	Study Groups	
		Co-administration group	Staggered group
Rotarix	HRV	x	x
Squarekids	*Squarekids*	x	x

- Control: active control (Staggered group).
- Vaccination schedules: The vaccination schedules are as follows:
  - Subjects in the Co-administration group will be administered the DPT-IPV vaccine according to a 3, 4, 6 month schedule and the liquid HRV vaccine according to a 2, 3 month schedule.
  - Subjects in the Staggered group will be administered the DPT-IPV vaccine according to a 3, 4.5, 6 month schedule and the liquid HRV vaccine according to a 2, 3.5 month schedule.

The childhood vaccines Pneumococcal conjugate vaccine (PCV), *Haemophilus influenzae* type B vaccine (Hib), Bacillus Calmette–Guérin (BCG) vaccine, hepatitis B vaccine, meningococcal vaccine and inactivated influenza vaccine can be administered to subjects as per the clinical practice in Japan, outside the scope of this study.

- Treatment allocation: Randomised 1:1 using GSK Biologicals' central randomisation system on Internet (SBIR).
- Blinding: Open-label.

The blinding of study epoch is provided in Table 3.

Table 3 Blinding of study epochs

Study Epoch	Blinding
Epoch 001	open

- Sampling schedule: Details of the samples to be collected are as follows:
  - A blood sample of approximately 2 mL will be collected from a sub-cohort of subjects (approximately half the number of enrolled subjects from each study

group), 1 month after the administration of the second dose of the liquid HRV vaccine.

– A blood sample of approximately 5 mL will be collected at Visit 7, 1 month after administration of the last dose of DPT-IPV vaccine from all the subjects.

- Type of study: self-contained.
- Data collection: Electronic Case Report Form (eCRF).

4. STUDY COHORT

4.1. Number of subjects/centres

In order to have 262 subjects (131 in each study group) evaluable for the immunogenicity analyses corresponding to the primary confirmatory objective, the target sample size to be enrolled is at least 292 subjects (146 subjects in each group), accounting for a dropout rate of 10%.

Details of the HRV Immunogenicity sub-cohort are provided in Table 4. The sub-cohort will consist of 146 subjects (the first 73 subjects enrolled into the study from each study group). Since the assessment of immunogenicity in terms of serum anti-RV IgA seropositivity and GMCs is not a confirmatory endpoint in this study and no statistical testing will be performed, the sample size of this sub-cohort has been chosen to assess the immunogenicity of the liquid HRV vaccine in a descriptive manner.

Table 4 Sub-cohorts

Sub-cohort name	Description	Estimated number of subjects
HRV Immunogenicity sub-cohort	The serum anti-RV IgA antibody concentration and seropositivity 1 month after the second dose of the liquid HRV vaccine will be assessed in this sub-cohort of subjects.	146 subjects (approximately half the number of subjects (73) from each study group)*

* The first 73 subjects enrolled into each study group will be allocated to the sub-cohort.

Overview of the recruitment plan:

- Subjects will be enrolled at multiple sites in Japan.
- Enrolment will be terminated when at least 292 eligible subjects have been enrolled.
- The intended duration of the study, per subject will be approximately 5 months.
- Recruitment will be monitored by SBIR.

4.2. Inclusion criteria for enrolment

Specific information regarding warning, precautions, contraindication, adverse events, and other pertinent information on the GSK investigational product or other study treatment that may impact subject eligibility is provided in the Prescribing information.

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)/ Legally Acceptable Representative(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).
- A male or female between, and including, 6 and 12 weeks (42 - 90 days) of age at the time of the first dose of HRV vaccination.
- Written informed consent obtained from the parent(s)/LAR(s) of the subject prior to performing any study specific procedure.
- Healthy subjects as established by medical history and clinical examination before entering into the study.
- Born full-term (i.e. between a gestation period of 37 weeks 0 days and 41 weeks 6 days) as per the delivery records.

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 within 30 days before the first dose of study vaccine (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 within the period starting 30 days before the first dose of HRV vaccine administration and ending at Visit 7, with the exception of other routinely

administered vaccines like PCV, Hib, BCG, hepatitis B, meningococcal vaccine and inactivated influenza vaccines, which are allowed at any time during the study, if administered at sites different from the sites used to administer the DPT-IPV vaccine.

- 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 rotavirus, diphtheria, tetanus, pertussis and/ or poliovirus.
- Previous confirmed occurrence of RV GE, diphtheria, tetanus, pertussis, and/ or polio disease.
- GE within 7 days preceding the HRV vaccine administration (warrants deferral of the vaccination).
- History of any reaction or hypersensitivity likely to be exacerbated by any component of the HRV or DPT-IPV vaccines.
- Hypersensitivity to latex.
- History of any neurological disorders or seizures.
- History of SCID.
- Acute disease and/or fever at the time of enrollment.
  - Fever is defined as temperature ≥ 37.5°C on oral, axillary or tympanic setting, or ≥ 38.0°C on rectal setting.
  - Subjects with a minor illness (such as 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 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.
- 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), 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.

The investigator has the final responsibility for the final presentation of the ICF respecting the mandatory requirements of local regulations. The ICF generated by the investigator with the assistance of the sponsor's representative must be acceptable to GSK Biologicals and be approved (along with the protocol, and any other necessary documentation) by the IRB/IEC.

5.2. Subject identification and randomisation of treatment

5.2.1. Subject identification

Subject identification numbers will be assigned sequentially to the subjects who have consented to participate 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 randomisation of supplies within blocks will be performed at GSK Biologicals, using 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 (30%) of supplies will be prepared.

5.2.2.2. Treatment allocation to the subject

The treatment numbers will be allocated by component.

5.2.2.2.1. Study group and treatment number allocation

Allocation of the subject to a study group at the investigator site will be performed using a randomisation system on internet (SBIR). The randomisation algorithm will use a minimisation procedure accounting for centre and HRV immunogenicity sub-cohort.

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 an open label study.

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.

5.5. Outline of study procedures

The list of study procedures for subjects in the Co-administration group is provided in Table 5.

Table 5 List of study procedures (Co-administration group)

Age	2 months	3 months	3.5 months	4 months	4.5 months	6 months	7 months
Epoch	*Epoch 001*						
Type of contact	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7
Time-points	Day 0	Month 1	Month 1.5	Month 2	Month 2.5	Month 4	Month 5
Sampling time-points				Post-Vacc 1	Post-Vacc 2		Post Vacc 3
Informed consent	●						
Check inclusion/exclusion criteria	●						
Collect demographic data	●						
Record gestational age	●						
Medical history	●						
History directed physical examination	●						
Check contraindications and warnings and precautions	O	O		O		O	
Pre-vaccination body temperature	●	●		●		●	
Measure/record height and weight	●						
Vaccines							
Study group and treatment number allocation	O						
Treatment number allocation for subsequent doses		O		O		O	
Recording of administered treatment number	●	●		●		●	
HRV Vaccine administration	●	●					
DPT-IPV vaccine administration		●		●		●	
Laboratory Assays							
Blood sampling for antibody determination				● (~2 mL)			● (~5 mL)
Safety assessments							
Record any concomitant medications/vaccinations	●	●		●		●	●
Record any intercurrent medical conditions		●		●		●	●
Distribution of diary cards	O	O		O		O	
Return of diary cards		O		O		O	O
Diary card transcription by investigator		●		●		●	●
Recording of solicited general adverse events during the 8 day (Days 0–7) follow-up period after each dose of HRV vaccine, by subjects' parent(s)/LAR(s) in diary card	●	●					
Recording of solicited local and general adverse events during the 8 day (Days 0–7)follow-up period after the first dose of DPT-IPV vaccine, by subjects' parent(s)/LAR(s) in diary card		●					
Recording of unsolicited adverse events within 31 days post-vaccination (Days 0-30) after each dose of HRV vaccine, by subjects' parent(s)/LAR(s) in diary card	●	●					
Recording of unsolicited adverse events within 31 days post-vaccination (Days 0-30) after the first dose of DPT-IPV vaccine, by subjects' parent(s)/LAR(s) in diary card		●					

Age	2 months	3 months	3.5 months	4 months	4.5 months	6 months	7 months
Epoch	*Epoch 001*						
Type of contact	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7
Time-points	Day 0	Month 1	Month 1.5	Month 2	Month 2.5	Month 4	Month 5
Sampling time-points				Post-Vacc 1	Post-Vacc 2		Post Vacc 3
Recording of AEs/SAEs leading to withdrawal from study	●	●		●		●	●
Recording of SAEs and causally related AEs	●	●		●		●	●
Recording of SAEs related to study participation, or to a concurrent GSK medication/vaccine	●	●		●		●	●
Study Conclusion							●

● is used to indicate a study procedure that requires documentation in the individual eCRF.
○ is used to indicate a study procedure that does not require documentation in the individual eCRF.
Post-Vacc 1 = blood sample collected from subjects in the HRV immunogenicity sub-cohort in the Co-administration group, one month after the second dose of the liquid HRV vaccine; Post-Vacc 3 = blood sample collected from all the subjects, one month after the third dose of the DPT-IPV vaccine.
Visit 3 and Visit 5 are not applicable for subjects in the Co-administered group and hence have been shaded in grey.

The list of study procedures for subjects in the Staggered group is provided in Table 6.

Table 6 List of Study procedures (Staggered group)

Age	2 months	3 months	3.5 months	4 months	4.5 months	6 months	7 months
Epoch	***Epoch 001***						
Type of contact	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**
Time-points	**Day 0**	**Month 1**	**Month 1.5**	**Month 2**	**Month 2.5**	**Month 4**	**Month 5**
Sampling time-points				**Post-Vacc 1**	**Post-Vacc 2**		**Post Vacc 3**
Informed consent	●						
Check inclusion/exclusion criteria	●						
Collect demographic data	●						
Record gestational age	●						
Medical history	●						
History directed physical examination	●						
Check contraindications and warnings and precautions	O	O	O		O	O	
Pre-vaccination body temperature	●	●	●		●	●	
Measure/record height and weight	●						
Vaccines							
Study group and treatment number allocation	O						
Treatment number allocation for subsequent doses		O	O		O	O	
Recording of administered treatment number	●	●	●		●	●	
HRV Vaccine administration	●		●				
DPT-IPV vaccine administration		●			●	●	
Laboratory Assays							
Blood sampling for antibody determination					● (~2 mL)		● (~5 mL)
Safety assessments							
Record any concomitant medications/vaccinations	●	●	●		●	●	●
Record any intercurrent medical conditions		●	●		●	●	●
Distribution of diary cards	O	O	O		O	O	
Return of diary cards		O	O		O	O	O
Diary card transcription by investigator		●	●		●	●	●
Recording of solicited general adverse events during the 8 day (Days 0–7)follow-up period after each dose of HRV vaccine, by subjects' parent(s)/LAR(s) in diary card	●		●				
Recording of solicited local and general adverse events during the 8 day (Days 0–7)follow-up period after the first dose of DPT-IPV vaccine, by subjects' parent(s)/LAR(s) in diary card		●					
Recording of unsolicited adverse events within 31 days post-vaccination (Days 0-30) after each dose of HRV vaccine, by subjects' parent(s)/LAR(s) in diary card	●		●				
Recording of unsolicited adverse events within 31 days post-vaccination (Days 0-30) after the first dose of DPT-IPV vaccine, by subjects' parent(s)/LAR(s) in diary card		●					

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Age	2 months	3 months	3.5 months	4 months	4.5 months	6 months	7 months
Epoch	*Epoch 001*						
Type of contact	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7
Time-points	Day 0	Month 1	Month 1.5	Month 2	Month 2.5	Month 4	Month 5
Sampling time-points				Post-Vacc 1	Post-Vacc 2		Post Vacc 3
Recording of AEs/SAEs leading to withdrawal from study	●	●	●		●	●	●
Recording of SAEs and causally related AEs	●	●	●		●	●	●
Recording of SAEs related to study participation, or to a concurrent GSK medication/vaccine	●	●	●		●	●	●
Study Conclusion							●

● is used to indicate a study procedure that requires documentation in the individual eCRF.
○ is used to indicate a study procedure that does not require documentation in the individual eCRF.
Post-Vacc 2 = blood sample collected from subjects in the HRV immunogenicity sub-cohort in the Staggered group, one month after the second dose of the liquid HRV vaccine; Post-Vacc 3 = blood sample collected from all the subjects, one month after the third dose of the DPT-IPV vaccine.
Visit 4 is not applicable for subjects in the Staggered group and hence has been shaded in grey.

The intervals to be considered within the study are provided in Table 7.

Table 7 Intervals between study visits

Study Group	Interval	Optimal length of interval [1]	Allowed interval[2]
Co-administration group	Visit 1→Visit 2*	30 days	28 days - 42 days
	Visit 2→Visit 4	30 days	28 days – 42days
	Visit 4→Visit 6	56 days	28 days - 56 days
	Visit 6→Visit 7	30 days	21 days - 48 days
Staggered group	Visit 1→Visit 2*	30 days	28 days - 42 days
	Visit 2→Visit 3	15 days	7 days - 21 days
	Visit 3→Visit 5**	30 days	28 days - 42 days
	Visit 5→Visit 6	45 days	28 days – 56 days
	Visit 6→Visit 7	30 days	21 days - 48 days

[1]. Whenever possible the investigator should arrange study visits within this interval.
[2]. Subjects will not be eligible for inclusion in the According To Protocol (ATP) cohort for analysis of immunogenicity if they make the study visit outside this interval.
* Visit 2 should take place when the subject is 3 months of age or older.
**The period between Visit 2 and Visit 5 should be within 8 weeks.
There should be a time-period of at least 7 days between the administration of an inactivated vaccine and any other vaccine, and 28 days between the administration of a live virus vaccine and any other vaccine, in Japan. Please refer to the package inserts of *Rotarix* and *Squarekids* for more details.

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.

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. Collect demographic data

Record demographic data such as age, gender and ethnicity in the subject's eCRF. Record gestational age of the subject in the eCRF.

5.6.4. Medical history

Obtain the subject's medical 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.

5.6.5. 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 within the allowed interval. 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.

5.6.6. 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 6.6 and 6.7 for more details.

5.6.7. Assess pre-vaccination body temperature

The axillary, rectal, oral or tympanic body temperature of all subjects needs to be measured prior to any study vaccine administration. The preferred route for recording temperature in this study will be axillary or tympanic. If the subject has fever [fever is defined as temperature ≥ 37.5°C for oral, axillary or tympanic route, or ≥ 38.0°C for rectal route] on the day of vaccination, the vaccination visit will be rescheduled within the allowed interval for this visit (see Table 7).

5.6.8. 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.

5.6.9. Sampling

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

5.6.9.1. Blood sampling for immune response assessments

Blood samples will be taken during certain study visits as specified in Section 5.5.

- A volume of approximately 2 mL of whole blood (to provide at least 0.7 mL of serum) should be drawn from all subjects included in the HRV immunogenicity sub-cohort for analysis of humoral immune response one month after the second dose of the liquid HRV vaccine, i.e., at Visit 4 for the Co-administration group and at Visit 5 for the Staggered group. A volume of approximately 5 mL of whole blood (to provide at least 1.8 mL of serum) should be drawn from all subjects included in the study for analysis of humoral immune response at Visit 7. After centrifugation, serum samples should be kept at –20°C or below until shipment. Refer to the SPM for more details on sample storage conditions.

5.6.10. Study Vaccines administration

- After completing all prerequisite procedures prior to vaccination, one dose of HRV will be administered orally or/and one dose of DPT-IPV vaccine will be administered subcutaneously (refer to Section 6.4 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 7).
- 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.

5.6.11. 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 6.8.

Intercurrent medical conditions must be checked and recorded in the eCRF as described in Section 6.9.

5.6.12. 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 AEs related to the study vaccines and 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).
  - After each HRV vaccination, the subject's parent(s)/LAR(s) will record body (axillary or tympanic) temperature and any solicited general AEs (i.e. on the day of each vaccination and during the next 8 days [Day 0-7]) or any unsolicited AEs (i.e. on the day of vaccination and during the next 30 days occurring after vaccination).
  - After the first dose of DPT-IPV vaccine administration, subject's parent(s)/LAR(s) will record solicited local/general AEs during the 8 day (Day 0-Day 7) follow-up period and any unsolicited AEs during the 31 day (Day 0-Day 30) follow-up period only.
  - In addition other AEs outside the specified duration will also be captured in the diary card.
- The subject's parent(s)/LAR(s) will be instructed to return the completed diary card to the investigator at the next study visit.
- Collect and verify completed diary cards during discussion with the subject's parent(s)/LAR(s) on Visit 7.
- 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.

5.6.13. 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 only be used for protocol mandates described in this protocol.

Any sample testing will be done in line with the consent of the individual 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).

If additional testing is performed, the marker priority ranking given in Section 5.7.4 may be changed.

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 ATP analysis (See Section 10.4 for the definition of cohorts 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 8.

Table 8 Biological samples

Sample type	Quantity	Unit	Time points
Blood	Approximately 2	mL	Visit 4 in Co-administration group, Visit 5 in Staggered group
	Approximately 5	mL	Visit 7

5.7.3. Laboratory assays

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

Serological assays for the determination of antibodies will be performed by Enzyme-Linked Immunosorbent Assay (ELISA) or neutralisation assay (NEU) at a GSK Biologicals' laboratory or in a laboratory designated by GSK Biologicals using standardised and validated procedures (refer to Table 9).

Table 9 Humoral Immunity (Antibody determination)

System	Component	Method	Kit / Manufacturer	Unit	Assay Cut-off**	Laboratory
SER	*Corynebacterium diphtheriae.Diphtheria Toxoid Ab.IgG*	ELI	NA	IU/ml	0.1	GSK Biologicals*
SER	*Clostridium tetani.Tetanus Toxoid Ab.IgG*	ELI	NA	IU/ml	0.1	GSK Biologicals*
SER	Bordetella pertussis.Filamentous Hemaglutinin Ab.IgG	ELI	NA	IU/ml	2.046	GSK Biologicals*
SER	Bordetella pertussis.Pertussis Toxin Ab.IgG	ELI	NA	IU/ml	2.693	GSK Biologicals*
SER	Poliovirus Sabin Type 1 Ab	NEU	NA	ED50	8	GSK Biologicals*
SER	Poliovirus Sabin Type 2 Ab	NEU	NA	ED50	8	GSK Biologicals*
SER	Poliovirus Sabin Type 3 Ab	NEU	NA	ED50	8	GSK Biologicals*
SER	Rotavirus Ab.IgA	ELI	NA	U/ml	20	GSK Biologicals*

*GSK Biologicals laboratory refers to the Clinical Laboratory Sciences (CLS) in Rixensart, Belgium; Wavre, Belgium; or a laboratory designated by GSK Biologicals.
** These cut-offs are subject to change due to assay re-development.
SER = Serum
ELI = Enzyme-Linked Immunosorbent Assay
NEU = Neutralisation Assay
NA = Not applicable
U = Units; IU = International Units
EU = ELISA Units
ED_{50} = Effective dose to inhibit 50% of the maximum.

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 10.

Table 10 Immunological read-outs

Blood sampling time-point		Sub-cohort Name	Group	No. of subjects	Component	Components priority rank
Type of contact and time point	Sampling time point					
Visit 4 (Month 2)	Post-Vacc 1	HRV Immunogenicity sub-cohort	Co-administration Group	73*	Anti-RV IgA	Not Applicable
Visit 5 (Month 2.5)	Post-Vacc 2	HRV Immunogenicity sub-cohort	Staggered Group	73*	Anti-RV IgA	Not Applicable
Visit 7 (Month 5)	Post-Vacc 3	All subjects		292	D	1
					T	2
					PT	3
					FHA	4
					Poliovirus types 1, 2 and 3	5

D: diphtheria, T: tetanus, PT: pertussis toxoid, FHA: filamentous haemagglutinin, HRV: human rotavirus.
Post-Vacc 1 = blood sample collected from subjects in the HRV immunogenicity sub-cohort in the Co-administration group, one month after the second dose of the liquid HRV vaccine; Post-Vacc 2 = blood sample collected from subjects in the HRV immunogenicity sub-cohort in the Staggered group, one month after the second dose of the liquid HRV vaccine; Post-Vacc 3 = blood sample collected from all the subjects, one month after the third dose of the DPT-IPV vaccine.
* The first 73 subjects enrolled into each of the study groups will be allocated to the HRV immunogenicity sub-cohort. This is half the total number of subjects to be enrolled in each study group.

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 10.

5.7.5. Immunological correlates of protection

Details of the immunological correlates of protection are provided below:

- Anti-diphtheria and anti-tetanus antibody concentrations will be measured by ELISA and expressed in international units per mL (IU/mL), with respect to a reference serum. It is generally accepted that for both diphtheria and tetanus, antibody concentrations ≥ 0.01 IU/mL, as measured by *in vivo* neutralisation tests are protective. It has been previously demonstrated that a good correlation exists between *in vivo* neutralisation tests and the ELISA for antibodies to diphtheria and tetanus toxoid but this correlation may be reduced at antibody concentrations < 0.1 IU/mL. For this reason, an antibody concentration of 0.1 IU/mL by ELISA (corresponding to approximately 3 times the lower quantitation limit of the assays) will be arbitrarily and conservatively set as the cut-off (for both anti-diphtheria and

anti-tetanus ELISAs [Camargo, 1984; Melville-Smith, 1983; WHO position paper, , 2006].

- Antibodies against poliovirus types 1, 2 and 3 will be determined by a virus micro-neutralisation test adapted from the World Health Organization Guidelines for WHO/EPI Collaborative Studies on Poliomyelitis [WHO, 1993]. The lowest dilution at which serum samples will be tested is 1:8, from which a test will be considered positive. Titres will be expressed in terms of the reciprocal of the dilution resulting in 50% inhibition. Antibody titres greater than or equal to this value are considered as protective.
- No correlate of protection is defined for the immune response to pertussis antigens. Antibodies against the pertussis components PT and FHA will be measured by ELISA technique. The current assay cut-off for the pertussis antibodies is 5 international units per mL (IU/mL) Subjects with antibody concentration below this cut-off will be considered seronegative [Plotkin, 2010].
- No immunological correlate of protection has been demonstrated so far for the antigen used as part of the HRV vaccine. However, a publication 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 once 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 AND ADMINISTRATION

6.1. Description of study vaccines

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 are listed in Table 11.

Table 11 Study vaccines

Treatment name	Vaccine name	Formulation	Presentation	Volume to be administered	Number of doses
Squarekids	*Squarekids*	BP>=4Unit; DT>=14IU; TT>=9IU; Inactivated Poliovirus type 1=40DU; Inactivated Poliovirus type 2=8DU; Inactivated Poliovirus type 3=32DU; Sodium hydrate=210µg; Trisodium phosphate=810µg; Aluminum chloride=900µg 0.5 ml	Pre-filled syringe	0.5 ml	3
Rotarix	HRV	HRV RIX4144 live attenuated >=$10^{6.0}$$CCID_{50}$ 1.5 ml	Liquid in a pre-filled oral applicator	1.5 ml	2

6.2. Medical Devices

Medical device (not manufactured by or for GSK) is used for DPT-IPV vaccine (*Squarekids*) administered in this study. It is a combination product of a drug and a kit of a glass syringe pre-filled with drug solution, which is approved for marketing.

Instructions for medical device usage are provided in the package insert of *Squarekids*.

The medical device related incidents including those resulting from malfunctions of the device, must be detected, documented, and reported by the investigator throughout the period of the study – see Section 8.7.

6.3. 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 authorised 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 devices 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 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 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.

6.4. Dosage and administration of study vaccines

The dosage and administration of study vaccines are given in Table 12.

Table 12 Dosage and administration

Type of contact and time point	Volume to be administered	Study group	Treatment name	Route [1]	Site	Side
Visit 1 (Day 0)	1.5 ml	Co-administration group, Staggered group	*Rotarix*	O	Not applicable	Not applicable
Visit 2 (Month 1)	1.5 ml	Co-administration group	*Rotarix*	O	Not applicable	Not applicable
Visit 2 (Month 1)	0.5 ml	Co-administration group, Staggered group	*Squarekids*	SC	Upper arm, or Upper thigh	-
Visit 3 (Month 1.5)	1.5 ml	Staggered group	*Rotarix*	O	Not applicable	Not applicable
Visit 4 (Month 2)	0.5 ml	Co-administration group	*Squarekids*	SC	Upper arm, or Upper thigh	-
Visit 5 (Month 2.5)	0.5 ml	Staggered group	*Squarekids*	SC	Upper arm, or Upper thigh	-
Visit 6 (Month 4)	0.5 ml	Co-administration group, Staggered group	*Squarekids*	SC	Upper arm, or Upper thigh	-

[1]Oral (O)/ subcutaneous (SC)

6.5. 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 5% additional vaccine doses will be supplied to replace those that are unusable.

6.6. Contraindications to subsequent vaccination

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

- Anaphylaxis following the administration of vaccines.
- Hypersensitivity reaction following the administration of the vaccines.
- Contraindications to *Rotarix*:
  - Any uncorrected congenital malformation of the gastrointestinal tract (such as Meckel's diverticulum) that would predispose for IS.
  - Any history of IS.
  - SCID.
- Contraindication for pertussis-containing vaccines:
  - Encephalopathy of unknown aetiology, defined as an acute, severe central nervous system disorder, occurring within 7 days following previous vaccination with pertussis-containing vaccine and generally consisting of major alterations in consciousness, unresponsiveness, generalised or focal seizures that persist more than a few hours, with failure to recover within 24 hours.
  - Individuals with progressive neurologic disorder, including infantile spasms, uncontrolled epilepsy, or progressive encephalopathy should not receive a pertussis-containing vaccine until a treatment regimen has been established and the condition has stabilised.

The following events constitute contraindications to administration of the study vaccines 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 (see Section 5.5), within the time window specified in the protocol, 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 ≥ 37.5°C on oral, axillary or tympanic setting, or ≥ 38.0°C on rectal setting. The preferred route for recording temperature in this study will be axillary or tympanic.
  - Subjects with a minor illness (such as mild upper respiratory infection) without fever can be administered all vaccines.
- Diarrhoea or vomiting at the time of vaccination.

6.7. Warnings and precautions

Refer to the approved product label/package insert.

6.8. Concomitant medications/products and concomitant vaccinations

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

6.8.1. Recording of concomitant medications/products and concomitant vaccinations

The following concomitant medications/products/vaccines 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 (Day -30 to Day 30).
- Any concomitant vaccination administered in the period starting 30 days before the first dose of study vaccine and ending at the last study visit (Day -30 to Month 5).
- 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 ≥ 37.5°C for oral, axillary or tympanic route, or ≥ 38.0°C for rectal route].
- Any concomitant medications/products/vaccines listed in Section 6.8.2.
- Any concomitant medications/products/vaccines relevant to a SAE to be reported as per protocol or administered 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.

6.8.2. Concomitant medications/products/vaccines that may lead to the elimination of a subject from ATP 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 ATP analysis.

- Any investigational or non-registered product (drug or vaccine) other than the study vaccines used during the study period between the first vaccination at Visit 1 to the blood sampling at Visit 7.
- Immunosuppressants or other immune-modifying drugs administered chronically (i.e. more than 14 days) during the study period between Visit 1 to Visit 7. 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 the first vaccination at Visit 1 to the blood sampling at Visit 7.
- Administration of long-acting immune-modifying drugs 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 dose of HRV vaccine administration and ending at blood sampling at Visit 7*, with the exception of other routinely administered vaccines like PCV, Hib, BCG, hepatitis B, meningococcal vaccine and inactivated influenza vaccines, which are allowed at any time during the study if administered at sites different from the sites used to administer the DPT-IPV vaccine.

  *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 Prescribing Information and according to the local governmental recommendations and provided a written approval of the Sponsor is obtained.

6.9. Intercurrent medical conditions that may lead to elimination of a subject from ATP analyses

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

Subjects may be eliminated from the ATP cohort 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:

- 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 investigational 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 investigational vaccines or a concurrent medication (overdose per se should not be reported as an AE/SAE).
- Signs, symptoms temporally associated with 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.

   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 local (injection-site) adverse events

All solicited local AEs are considered to be related to the vaccination.

The following local (injection-site) AEs associated with DPT-IPV vaccine will be solicited:

Table 13 Solicited local adverse events

Pain at injection site
Redness at injection site
Swelling at injection site

8.1.3.2. Solicited general adverse events

The following general AEs will be solicited after administration of the HRV vaccine:

Table 14 Solicited general adverse events (HRV vaccine)

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

The following general AEs will be solicited after administration of the DPT-IPV vaccine:

Table 15 Solicited general adverse events (DPT-IPV vaccine)

Drowsiness
Fever
Irritability/Fussiness
Loss of appetite

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.

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. However, clinically significant abnormal laboratory findings or other abnormal assessments that are associated with the disease being studied, unless judged by the investigator as more severe than expected for the subject's condition, or that are present or detected at the start of the study and do not worsen, will not 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 and serious adverse events

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

All AEs starting within 31 days following administration of each dose of HRV vaccine and after the first dose of DPT-IPV 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. See Section 8.4 for instructions on reporting of causally AEs related to study vaccine.

The time period for collecting and recording SAEs will begin at the first receipt of study vaccines and will end at the end of the study (Visit 7), for each subject. 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 first receipt of study vaccines.

SAEs that are related to the investigational vaccines will be collected and recorded from the time of the first receipt of study vaccines until the subject is discharged from the study.

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 consents to participate in the study until she/he is discharged from the study.

All causally related AEs from the first vaccination until the subject is discharged in the study will be recorded in the diary card and will be reported to Sponsor as mentioned in Section 8.4.

An overview of the protocol-required reporting periods for AEs and SAEs is given in Table 16 and Table 17.

Table 16 Reporting periods for collecting safety information (Co-administration group)

Event	Pre-V1*		Visit 1	7 d post V1	30 d post-V1	Visit 2	7 d post V2	30 d post-V2	Visit 3	7 d post V3	30 d post-V3	Visit 4	7 d post V4	30 d post-V4	Visit 5	7 d post V5	30 d post-V5	Visit 6	7 d post V6	30 d post-V6	Visit 7
			Day 0			M 1			M 1.5			M 2			M 2.5			M 4			M 5
Solicited general AEs																					
Solicited local AEs																					
Unsolicited AEs																					
AEs/SAEs leading to withdrawal from the study																					
Causally related AEs/SAEs																					
SAEs related to study participation or concurrent GSK medication/vaccine																					

* i.e. consent obtained. Pre-V: pre-vaccination; V: visit; d: day; M: Month

Please refer to Section 5 for the detailed study design. Visit 3 and Visit 5 (shaded in grey) are not applicable for subjects in the Co-administered group. Solicited and unsolicited AEs will be recorded after each dose of the liquid HRV vaccine administration and after the first dose of DPT-IPV vaccine administration.

Table 17 Reporting periods for collecting safety information (Staggered group)

Event	Pre-V1*		Visit 1	7 d post V1	30 d post-V1	Visit 2	7 d post V2	30 d post-V2	Visit 3	7 d post V3	30 d post-V3	Visit 4	7 d post V4	30 d post-V4	Visit 5	7 d post V5	30 d post-V5	Visit 6	7 d post V6	30 d post-V6	Visit 7
			Day 0			M 1			M 1.5			M 2			M 2.5			M 4			M 5
Solicited general AEs																					
Solicited local AEs																					
Unsolicited AEs																					
AEs/SAEs leading to withdrawal from the study																					
Causally related AEs/SAEs																					
SAEs related to study participation or concurrent GSK medication/vaccine																					

* i.e. consent obtained. Pre-V: pre-vaccination; V: visit; d: day; M: Month

Please refer to Section 5 for the detailed study design. Visit 4 (shaded in grey) is not applicable for subjects in the Staggered group. Solicited and unsolicited AEs will be recorded after each dose of the liquid HRV vaccine administration and after the first dose of DPT-IPV vaccine administration

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 19. Investigators are not obligated to actively seek causally related AEs or SAEs in former study participants. However, if the investigator learns of any causally related AE and 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 vaccines 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:

The intensity scales for solicited symptoms are listed in Table 18.

Table 18 Intensity scales for solicited symptoms in infants

Infants		
Adverse Event	**Intensity grade**	**Parameter**
Pain at injection site	0	None
	1	Mild: Minor reaction to touch
	2	Moderate: Cries/protests on touch
	3	Severe: Cries when limb is moved/spontaneously painful
Redness at injection site		Record greatest surface diameter in mm
Swelling at injection site		Record greatest surface diameter in mm
Fever*		Record temperature in °C
Irritability/Fussiness	0	Behaviour as usual
	1	Mild: Crying more than usual/no effect on normal activity
	2	Moderate: Crying more than usual/interferes with normal activity
	3	Severe: Crying that cannot be comforted/prevents normal activity
Drowsiness	0	Behaviour as usual
	1	Mild: Drowsiness easily tolerated
	2	Moderate: Drowsiness that interferes with normal activity
	3	Severe: Drowsiness that prevents normal activity
Loss of appetite	0	Appetite as usual
	1	Mild: Eating less than usual/no effect on normal activity
	2	Moderate: Eating less than usual/interferes with normal activity
	3	Severe: Not eating at all
Diarrhoea¶		Record the number of looser than normal stools /day
	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§		Record the number of vomiting episodes/day
	0	Normal (no emesis)
	1	1 episode of vomiting/day
	2	2 episodes of vomiting/day
	3	≥ 3 episodes of vomiting/day
Cough/Runnynose	0	Normal
	1	Mild: Cough/runny nose which is easily tolerated
	2	Moderate: Cough/runny nose which interferes with daily activity
	3	Severe: Cough/runny nose which prevents daily activity

*Fever is defined as temperature ≥ 37.5°C for oral, axillary or tympanic route, or ≥ 38.0°C for rectal route. The preferred route for recording temperature in this study will be axillary or tympanic. ¶Diarrhea 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 maximum intensity of local injection site redness/swelling will be scored at GSK Biologicals as follows:

0 : Absent

1 : ≤ 5 mm

2 : > 5 mm and ≤ 20 mm

3 : > 20 mm

The maximum intensity of fever will be scored at GSK Biologicals as follows:

0 : Axillary < 37.5°C
1 : Axillary ≥ 37.5 – ≤ 38.0°C
2 : Axillary > 38.0 – ≤ 39.0°C
3 : Axillary > 39.0°C

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

The intensity should be assigned to 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 a 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 investigator is obligated to assess the relationship between investigational vaccines 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 vaccines will be considered and

investigated. The investigator will also consult the Prescribing Information for marketed products to determine his/her assessment.

There may be situations when a causally related AE and/or 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 causally related AE and 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 investigational 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 eCRF.

8.4. Reporting of causally related adverse events and serious adverse events and other events

8.4.1. Prompt reporting of related adverse event and serious adverse events to GSK Biologicals

Both causally related solicited and unsolicited AEs and SAEs that occur in the time period defined in Section 8.3 will be reported promptly to GSK within the timeframes described in Table 19, once the investigator determines that the event meets the protocol definition of a causally related AE or SAE**.**

Table 19 Timeframes for submitting related adverse event and 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
Causally related solicited AE	24 hours*	electronic solicited AEs report	24 hours*	electronic solicited AEs report
Causally related unsolicited AE	24 hours*	electronic non-serious adverse event and intercurrent medical conditions report	24 hours*	electronic non-serious adverse event and intercurrent medical conditions report
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 causally related adverse events and serious adverse events

Study Contact for Reporting Causally Related AEs and SAEs
Refer to the local study contact information document.
Back-up Study Contact for Reporting Causally Related AEs and SAEs
24/24 hour and 7/7 day availability: GSK Biologicals Clinical Safety & Pharmacovigilance Fax: PPD or PPD Email address: PPD

8.4.3. Completion and transmission of causally related AE reports and SAE reports to GSK Biologicals

Once an investigator becomes aware that a causally related AE or a SAE has occurred in a study subject, the investigator (or designate) must complete the information in the electronic solicited AE report, unsolicited AE report or 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 causally related AE or 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 for a SAE. 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 report form (i.e. solicited AE report, unsolicited AE report or Expedited Adverse Events Report) and fax it to the Study Contact for Reporting SAEs (refer to the Medical Monitor/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 causally related AE and SAE information after removal of write access to the subject's eCRF

When additional causally related AE or 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 causally related AEs or SAEs (refer to the Medical Monitor/Sponsor Information or to GSK Biologicals Clinical Safety and Pharmacovigilance department within the designated reporting time frames specified in Table 19.

8.4.5. Regulatory reporting requirements for causally related AEs and SAEs

The investigator will promptly report all causally related AEs and 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/or other regulatory agencies about the safety of a product under clinical investigation. Prompt notification of causally related AEs and SAEs by the investigator to the Study Contact for Reporting causally related AEs and 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 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 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 causally related AEs and SAEs; refer to Table 19).

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 the end of the study (Visit 7).

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

The investigator will follow subjects:

- with causally related AEs, 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 causally related AE or SAE, he/she will provide this information to GSK Biologicals using solicited AE report, unsolicited AE report or electronic Expedited Adverse Events Report.

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 6.8).

8.7. Medical Device Incidents (Including Malfunctions)

The medical device is being provided for use in this study. The investigator is responsible for the detection and documentation of events which meet the definitions of incident or malfunction that occur during the study with such devices.

The definition of a Medical Device Incident can be found in Section 8.7.1 of the Protocol.

NOTE: Incidents fulfilling the definition of an AE/SAE will also follow the processes outlined in Section 8.3 to 8.6 of the Protocol.

8.7.1. Definitions of a Medical Device Incident

- Any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labelling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a patient/user/other persons or to a serious deterioration in their state of health.
- Not all incidents lead to death or serious deterioration in health. The non-occurrence of such a result might have been due to other fortunate circumstances or to the intervention of health care personnel.

It is sufficient that:

- an incident associated with a device happened and
- the incident was such that, if it occurred again, might lead to death or a serious deterioration in health.

A serious deterioration in state of health can include:

- life-threatening illness
- permanent impairment of body function or permanent damage to a body structure
- a 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 medical device incidents:

- a patient, user, care giver or professional is injured as a result of a medical device failure or its misuse
- a patient's treatment is interrupted or compromised by a medical device failure
- misdiagnosis due to medical device failure leads to inappropriate treatment
- a patient's health deteriorates due to medical device failure

8.7.2. Procedures for Documenting Medical Device Incidents

The detection and documentation procedures described in this protocol apply to all medical devices provided for use in the study (see Section 6.2 for the medical device used in this study).

8.7.2.1. Time Period for Detecting Medical Device Incidents

Medical device incidents or malfunctions of the device that result in an incident will be detected, documented and reported during all periods of the study.

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

NOTE: The method of documenting Medical Device Incidents is provided in Section 8.7.2.2.

8.7.2.2. Documenting Medical Device Incidents

Any medical device incident occurring during the study will be documented in the subject's medical records, in accordance with the investigator's normal clinical practice, and on the appropriate form. For incidents fulfilling the definition of an AE or an SAE, the appropriate AE/SAE eCRF screen will be completed as described in Section 8.3to 8.6.

The form will be completed as thoroughly as possible and signed by the investigator before it is transmitted to GSK by fax.

It is very important that the investigator provides his/her assessment of causality to the 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. A remedial action is any action other than routine maintenance or servicing of a device where such action is necessary to prevent recurrence of an incident. This includes any amendment to the design to prevent recurrence.

8.7.3. Prompt Reporting of Medical Device Incidents to GSK

Medical device incidents will be reported to GSK within 24 hours once the investigator determines that the event meets the protocol definition of a medical device incident.

Facsimile transmission of the "Medical Device Incident Report Form" is the preferred method to transmit this information to the Study Contact for Reporting Medical Device Incidents (Section 8.4.2). The Study Contact for Reporting Medical Device Incidents is same as the Study Contact for Reporting Causally Related AEs and SAEs.

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

8.7.3.1. Regulatory Reporting Requirements for Medical Device Incidents

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

8.7.4. Follow-up of Medical Device Incidents

All medical device incidents involving an AE will be followed until resolution of the event, until the condition stabilises, until the condition is otherwise explained, or until the subject is lost to follow-up. This applies to all subjects, including those withdrawn prematurely.

The investigator is responsible for ensuring that follow-up includes any supplemental investigations as may be indicated to elucidate as completely as practical 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 investigator.

8.8. 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 returns for the concluding visit 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 did not come back for the concluding visit 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 he/she/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 8.5.2).

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/treatment 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 endpoint

- Immunogenicity with respect to components of the DPT-IPV vaccine 1 month after administration of the third dose of the vaccine (Visit 7):
  - anti-diphtheria antibody concentrations ≥ 0.1 IU/mL,
  - anti-tetanus antibody concentrations ≥ 0.1 IU/mL,
  - anti-PT and anti-FHA antibody concentrations ≥ 10 IU/mL,
  - anti-poliovirus serotypes 1, 2 and 3 antibody titre ≥ 8 ED_{50}.

10.2. Secondary endpoints

- Serum anti-RV IgA antibody concentration≥ 20 U/mL and seropositivity in a sub-cohort of subjects, 1 month after the second dose of the liquid HRV vaccine.

- Serum GMCs/GMTs for anti-diphtheria, anti-tetanus, anti-poliovirus serotypes 1, 2 and 3, anti-PT and anti-FHA antibodies, 1 month after the third dose of the DPT-IPV vaccine.
- Occurrence of solicited general symptoms during the 8-day (Days 0-7) follow-up period after each dose of liquid HRV vaccine.
- Occurrence of solicited local and general symptoms during the 8-day (Days 0-7) follow-up period after the first dose of DPT-IPV vaccine.
- Occurrence of unsolicited AEs during the 31-day (Days 0-30) follow-up period after each dose of the liquid HRV vaccine and the first dose of DPT-IPV vaccine, according to the Medical Dictionary for Regulatory Activities (MedDRA) classification.
- Occurrence of SAEs from the first dose of the study vaccine up to study end (Visit 7).

10.3. Determination of sample size

The target enrolment will be at least 292 subjects (146 subjects in each of the groups) to obtain 262 evaluable subjects (131 subjects in each of groups) for the evaluation of the co-primary objectives assuming that approximately 10% of the enrolled subjects will not be evaluable.

A sub-cohort of subjects which includes half the number of enrolled subjects from each study group (a total of 146 subjects, with 73 from the co-ad group and 73 from the staggered group), will be used for evaluating immunogenicity of the liquid HRV vaccine in terms of serum anti-RV IgA antibody seropositivity and GMCs.

10.3.1. Reference for sample size

Table 20 presents the reference response rates.

Table 20 Reference response rates

Reference	Timing	Cut-off	N	%	LL	UL
DPT-IPV group (DPT-IPV (SQK) Phase 2 Study*)	4 weeks after primary vaccination	D ≥ 0.01 IU/ml	114	100.0%	96.7%	100.0%
		T ≥ 0.01 IU/ml	114	100.0%	96.7%	100.0%
		PT≥ 10 EU/ml	114	99.1%	95.2%	99.8%
		FHA≥ 10 EU/ml	114	100.0%	96.7%	100.0%
		Anti-Polio-1 ≥ 8	114	100.0%	96.7%	100.0%
		Anti-Polio-2 ≥ 8	114	100.0%	96.7%	100.0%
		Anti-Polio-3 ≥ 8	114	100.0%	96.7%	100.0%
DPT-IPV group (DPT-IPV (SQK) Phase 3 Study*)		D ≥ 0.1 IU/ml	235	99.1%	97.0%	99.9%
		T ≥ 0.01 IU/ml	235	100.0%	98.4%	100.0%
		PT≥ 10 EU/ml	235	98.7%	96.3%	99.7%
		FHA≥ 10 EU/ml	235	100.0%	98.4%	100.0%
		Anti-Polio-1 ≥ 8	235	100.0%	98.4%	100.0%
		Anti-Polio-2 ≥ 8	235	100.0%	98.4%	100.0%
		Anti-Polio-3 ≥ 8	235	100.0%	98.4%	100.0%
DPT group (DPT-IPV (SQK) Phase 3 Study*)		D ≥ 0.1 IU/ml	120	100.0%	97.0%	100.0%
		T ≥ 0.01 IU/ml	120	100.0%	97.0%	100.0%
		PT≥ 10 EU/ml	120	98.3%	94.1%	99.8%
		FHA≥ 10 EU/ml	120	100.0%	97.0%	100.0%

N= Number of subjects with available results, % = Percentage of subjects with titre/concentration within the specified range, LL = Lower Limit, UL = Upper Limit
*Regulatory review report of DPT-IPV (SQK).

10.3.2. Power computation

The sample size has been estimated in order to obtain at least 90% power to demonstrate the confirmatory primary objectives (Bonferroni adjustment of type II error). A hierarchical procedure will be used for the multiple study objectives.

The power computations are based on the following method:

- Non-inferiority on percentage of subjects with titre/concentration above pre-specified cut-off: Type II error is obtained using PASS 12, one-sided non-inferiority test for two proportions, under the alternative of equal proportions. Miettinen and Nurminen method. It corresponds to method 6 described in a paper by Newcombe [Newcombe, 1998].

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

Table 21 details the power for non-inferiority of DPT-IPV vaccine co-administered with *Rotarix* compared to DPT-IPV vaccine with staggered administration of *Rotarix* following 3 primary vaccine doses in terms of immune response to diphtheria, tetanus, PT, FHA and 3 serotypes of poliovirus. During the redevelopment of the PT and FHA assays, an international standard was included as an internal reference. This led to the conversion of the unit concentration from EU/mL to IU/mL. The unit standard of IU/mL is a conservative reference and considering that most subjects are anticipated to achieve a

post vaccination titre significantly above 10, there is no expected impact on the calculations in Table 21, which uses the EU/mL unit for the PT and FHA assays.

Table 21 Power for non-inferiority

Endpoint	N evaluable in Co-administration group	N evaluable in Staggered group	Estimated sero-positive rate in both groups	Power*
Anti-D ≥0.1 IU/mL	131	131	97.0%	97.3%
Anti-T ≥0.1 IU/mL**	131	131	98.4%	99.7%
Anti-PT ≥10 EU/mL	131	131	96.3%	95.2%
Anti-FHA ≥10 EU/mL	131	131	98.4%	99.7%
Anti-Polio-1 ≥ 8	131	131	98.4%	99.7%
Anti-Polio-2 ≥ 8	131	131	98.4%	99.7%
Anti-Polio-3 ≥ 8	131	131	98.4%	99.7%
Global power for Non-inferiority				91.0%

* PASS 12, non-inferiority test for two proportions using differences, 1-sided, alpha=0.025, power under the alternative hypothesis of equal rates between groups.
** Anti-T percentage of subjects above the cut off 0.01 =100% (N=235 95%CI 98.4- 100.0) from DPT-IPV(SQK) reports of the phase 3 study.

10.4. Cohorts for Analyses

Two cohorts are defined for the purpose of the analysis:

- Total vaccinated cohort.
- ATP cohort for analysis of immunogenicity.

10.4.1. Total vaccinated cohort

The TVC will include all subjects with at least one dose of the study vaccines administration documented:

- A safety and reactogenicity analysis based on the TVC will include all subjects with at least one vaccine administration documented.
- An immunogenicity analysis based on the TVC will include all subjects from this cohort for whom immunogenicity data were available.

The TVC analysis will be performed per treatment actually administered.

10.4.2. According-to-protocol cohort for analysis of immunogenicity

The ATP cohort for immunogenicity will include all subjects:

- who comply with vaccination schedule of DPT-IPV and HRV vaccines,
- who have not received medication forbidden by the protocol (up to Visit 7),
- whose underlying medical condition was not forbidden by the protocol (up to Visit 7),

- who complied with the blood sampling schedule,
- who had no concomitant infection related to the vaccine which may have influenced the immune response,
- who had no concomitant infection unrelated to the vaccine which may have influenced the immune response,
- for whom immunogenicity data are available at least one of the post-sampling time points.

10.5. Derived and transformed data

- Immunogenicity
  - The cut-off value is defined by the laboratory before the analysis and is described in Section 5.7.3.
  - A seronegative subject is a subject whose antibody titre is below the cut-off value.
  - A seropositive subject is a subject whose antibody titre is greater than or equal to the cut-off value.
  - The Geometric Mean Concentrations/Titres (GMC/GMTs) calculations are performed by taking the anti-log of the mean of the log concentration/titre transformations. Antibody concentrations/titres below the cut-off of the assay will be given an arbitrary value of half the cut-off for the purpose of GMC/GMT calculation.
  - Handling of missing data: for a given subject and a given immunogenicity measurement, missing or non-evaluable measurements will not be replaced.
- Reactogenicity and safety
  - Handling of missing data: subjects who missed reporting symptoms (solicited/unsolicited or concomitant medications) will be treated as subjects without symptoms (solicited/unsolicited or concomitant medications, respectively). In case of significant non-compliance of study procedures for reporting symptoms, the analysis plan will be reassessed to ensure more accurate reporting of study data by further analysis.
  - For the analysis of solicited symptom, missing or non-evaluable measurements will not be replaced. Therefore the analysis of the solicited symptoms based on the Total vaccinated cohort will include only subjects/doses with documented safety data (i.e. symptom screen/sheet completed).

10.6. Analysis of demographics/baseline characteristics

The distributions of subjects enrolled by centre will be tabulated by group. The numbers of subjects who are withdrawn from the study will be tabulated by group according to the reason for withdrawal. The median, mean, range and standard deviation (SD) of age at

each study vaccine dose (in weeks) will be computed by group. The median, mean and SD of height in centimetre (cm) and weight in kilograms (kg) at Visit 1 will be computed by group. The Body Mass Index (BMI) at Visit 1 will also be computed as weight (in kg)/height Index (BMI). The number of doses of the liquid HRV vaccine and DPT-IPV vaccine administered will be tabulated per group. The gender composition per group will also be presented. The deviations from specifications for age and intervals between study visits will be tabulated by group.

10.7. Analysis of immunogenicity

The ATP cohort for immunogenicity will be used for the primary analysis of immunogenicity. An analysis of immunogenicity based on the TVC will be performed only if more than 5% of the vaccinated subjects with immunogenicity results available were excluded from the ATP cohort for immunogenicity. In such a case, the TVC analyses will evaluate whether exclusion from the ATP cohort has biased the results.

10.7.1. Within groups assessment

For each treatment group and each antigen:

- Percentage of subjects with antibody concentrations/ titres greater than or equal to the pre-specified cut-off will be calculated with exact 95% CI (Refer Table 9). Anti-PT and anti-FHA antibody concentrations ≥ 10 IU/mL will also be calculated with exact 95% CI.
- GMC/GMTs, as applicable with 95% CIs will be tabulated.
- The distribution of antibody concentrations/ titres, as applicable, will be presented using reverse cumulative curves (RCC).

10.7.2. Between groups assessment

For each antigen in the DPT-IPV vaccine:

- The two-sided asymptotic standardised 95% CIs for the difference between groups (Co-administration group minus Staggered group) in terms of percentage of subjects with antibody concentrations/ titres greater than or equal to the pre-specified cut-off will be computed. Anti-PT and anti-FHA antibody concentrations ≥ 10 IU/mL will also be calculated with exact 95% CI.

10.8. Analysis of safety

The safety analysis will be based on the TVC.

The incidence by dose, overall per dose and overall per subject, with its exact 95% CI of

- any adverse event (solicited or unsolicited, local or general),
- at least one local adverse event (solicited or unsolicited), and,

- at least one general adverse event (solicited or unsolicited),

during the 8-day (Days 0-7) follow-up period will be tabulated. The same calculations will be performed for any Grade 3 (solicited or unsolicited) symptoms, related and for any adverse event requiring medical attention.

For each type of solicited symptom, the incidence during the 8-day (Days 0-7) follow-up period of the symptom (any grade, Grade 3, related, Grade 3 related, requiring medical advice) will be tabulated as follows:

- at each dose, the percentage of doses followed by the reporting of a symptom and its exact 95% CI,
- over all the doses, the percentage of subjects reporting the symptom and its exact 95% CI,
- over all the doses, the percentage of doses followed by the reporting of a symptom and its exact 95% CI,
- for fever, additional analyses will be performed by 0.5°C increments.

The percentage of subjects who receive concomitant medication, who receive antipyretic medication and prophylactic antipyretic medication during the 8-day (Days 0-7) and 31-day (Days 0-30) follow-up period post-vaccination will be tabulated by dose, overall per subject and over all the doses.

The verbatim reports of unsolicited symptoms 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 symptoms occurring during the 31 days (Days 0-30) with its exact 95% CI will be tabulated by preferred term. Similar tabulation will be done for Grade 3 unsolicited symptoms and for unsolicited symptoms causally related to vaccination.

Subjects who experienced at least one SAE during the entire study period (from the first dose till the end of the study [Visit 7]) will be reported and the SAEs will be described in detail.

10.9. Interpretation of analyses

Except for the analyses addressing the criteria specified in the objectives, no comparative analyses will be performed.

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

The final data analysis will include all data up to one month after the third dose of DPT-IPV vaccine. These analyses will include the final analysis of immunogenicity and the final analysis of solicited and unsolicited symptoms and SAEs from the first dose up to Visit 7.

10.10.2. Statistical considerations for interim analyses

All analyses will be conducted on final data 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 monitor's and 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 completion date (PCD) and to have secondary endpoint disclosed at latest 12 months after the Last Subject Last Visit (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.

The procedures and timing for public disclosure of the results summary and for development of a manuscript for publication will be in accordance with GSK Policy.

A manuscript will be progressed for publication in the scientific literature if the results provide important scientific or medical knowledge.

11.7. 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 Good Clinical Practice (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 favorable 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.

11.8. 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. COUNTRY SPECIFIC REQUIREMENTS

12.1. Japan specific requirements – Study conduct considerations

12.1.1. 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.

Prompt notification by the investigator to GSK of unsolicited AEs assessed as related to a investigational products (even for non- interventional post-marketing studies) is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a product under clinical investigation are met.

12.1.2. 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 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.

12.1.3. Study period

September 2016 (First Subject First Visit) - December 2017 (PCD).

12.1.4. Study administrative structure

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

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APPENDIX A LABORATORY ASSAYS

Anti-Rotavirus antibody concentrations are determined by a validated anti-Rotavirus IgA ELISA. Micro titre 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. Concentrations of the samples expressed in units per millilitre are calculated relative to the four-parameter logistic function generated from the standard curve.

APPENDIX B CLINICAL LABORATORIES

Table 22 GSK Biologicals' laboratories

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

Table 23 Outsourced laboratories

Laboratory	Address
Q² Solutions Clinical Trials (US)	27027 Tourney Road, Suite 2E Valencia, CA 91355 USA
Q² Solutions Clinical Trials (UK)	Simpson Parkway The Alba Campus Rosebank Livingston EH54 7EG UK

Protocol Sponsor Signatory Approval

eTrack study number and Abbreviated Title	114720 (ROTA-079)
EudraCT number	2014-005282-78
Date of protocol	Final Version 03: 03 June 2016
Detailed Title	A phase IV, randomised, open-label, controlled study to assess the immunogenicity and safety of the diphtheria, tetanus, pertussis and inactivated poliovirus (DPT-IPV) vaccine Squarekids™ when co-administered with GSK Biologicals' oral live attenuated HRV liquid vaccine Rotarix™ in healthy Japanese infants aged 6 - 12 weeks at the time of the first dose of HRV vaccination.
Sponsor signatory	Paul Gillard, Director, Clinical & Epidemiology Project Lead, MMRV and Rota GlaxoSmithKline Biologicals, SA.
Signature	[redacted]
Date	08 JUNE 2016

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