Statistical Analysis Plan

Study ID: 212692

Official Title of Study: A Phase III, observer-blind, randomized, multicenter study to evaluate immunogenicity, reactogenicity and safety of GlaxoSmithKline (GSK) Biologicals' Rotarix Porcine circovirus (PCV)-free liquid as compared to GSK's Rotarix liquid, given in 2-doses in healthy Chinese infants starting at age 6-16 weeks

NCT number: NCT06025695

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TITLE PAGE

Protocol Title:	A Phase III, observer-blind, randomized, multicenter study to evaluate immunogenicity, reactogenicity and safety of GlaxoSmithKline (GSK) Biologicals' *Rotarix Porcine circovirus* (PCV)-free liquid as compared to GSK's *Rotarix* liquid, given in 2-doses in healthy Chinese infants starting at age 6-16 weeks.
Study Number:	212692
Compound Number:	SB444563-BIO ROTA
Abbreviated Title:	ROTA-097
Sponsor Name:	GlaxoSmithKline Biologicals SA (GSK)
EudraCT number	2020-000972-38
Registry	Clinicaltrials.gov
Registry ID	Not yet available

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VERSION HISTORY

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
SAP	25 Aug 2023	13 May 2022	Not Applicable	Original version

1. INTRODUCTION

The purpose of this SAP is to describe the planned analyses to be included in the clinical study report (CSR) for study ROTA-097 (212692). Details of the planned analyses are provided.

1.1. Objectives, Estimands and Endpoints

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

Objectives	Endpoints**
	Medical Dictionary for Regulatory Activities (MedDRA) classification. • SAEs – Percentage of participants reporting the occurrence of SAEs from Dose 1 of the study intervention up to study end.

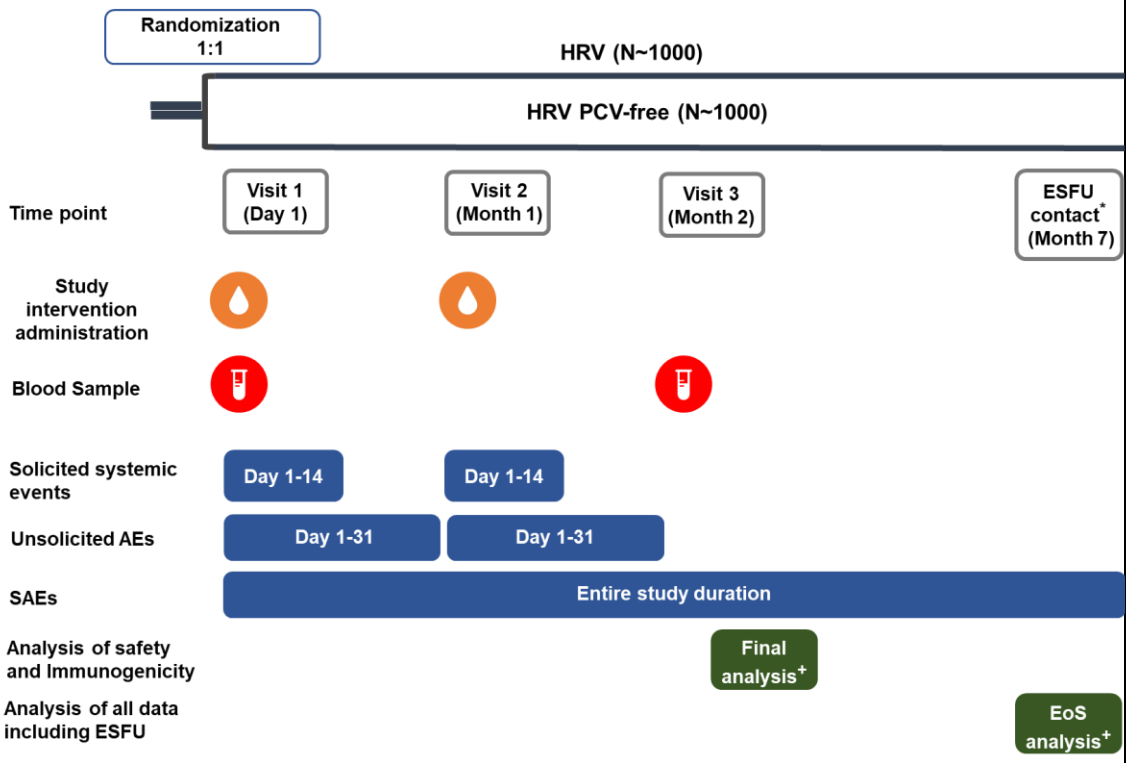
Ab = Antibody; AE = Adverse event; CI = Confidence Interval; IgA = Immunoglobulin A; GMC = Geometric mean Ab concentration; MedDRA = Medical Dictionary for Regulatory Activities; PCV = Porcine circovirus; PCV-free = No detection of PCV-1 and PCV-2 according to the limit of detection of the tests used; SAE = Serious adverse event; RV = Rotavirus; U = Unit; mL = milliliter

** complementary details on estimand including impact of intercurrent events on the analysis is available in Sections 3 and 4.

1.2. Study Design

Overview of Study Design and Key Features

Figure 1 Study design overview



N = number of participants; AE = adverse event; SAE = serious adverse event; EoS: end of study; ESFU: extended safety follow-up; HRV: Human Rotavirus; PCV-free = No detection of PCV-1 and PCV-2 according to the limit of detection of the tests used.

* An ESFU contact (by telephone call or any convenient procedure) 6 months post Dose 2.

+ Refer to Section 4.7 "Interim Analyses" for detailed information about sequence of analyses.

Overview of Study Design and Key Features

Design Features

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

Table 1 Study groups, intervention and blinding foreseen in the study

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

*Observer-blind except for a limited number of GSK personnel. For unblinding after Visit 3, referto Section 4.7.

ESFU: extended safety follow-up

<table>
<tr><th colspan="4">Overview of Study Design and Key Features</th></tr>
<tr><td>Study intervention</td><td colspan="3">
<table>
<tr><td>Study intervention name</td><td>HRV (Rotarix)</td><td>HRV PCV-free (Rotarix PCV-free)</td></tr>
<tr><td>Presentation</td><td colspan="2">CCI [redacted]</td></tr>
<tr><td>Study interventions formulation</td><td>Human Rotavirus, Live Attenuated, RIX4414 strain (≥ $10^{6.0}$ $CCID_{50}$); Sucrose (1.073 g); Di-sodium adipate; DMEM; Sterile water q.s. 1.5 mL</td><td>Human Rotavirus, Live Attenuated, RIX4414 strain (≥ $10^{6.0}$ $CCID_{50}$); Sucrose (1.073 g); Di-sodium adipate; DMEM; Sterile water q.s. 1.5 mL</td></tr>
<tr><td>Type</td><td>Control</td><td>Study</td></tr>
<tr><td>Route of administration</td><td>Oral use</td><td>Oral use</td></tr>
<tr><td>Number of doses to be administered</td><td>2</td><td>2</td></tr>
<tr><td>Volume to be administered</td><td>1.5 mL</td><td>1.5 mL</td></tr>
<tr><td>Packaging, labeling and TM</td><td>Refer to SPM for more details</td><td>Refer to SPM for more details</td></tr>
<tr><td>Manufacturer</td><td>GSK</td><td>GSK</td></tr>
</table>
mL: milliliter; qs: quantum satis (the amount which is enough); SPM: study procedures manual</td></tr>
<tr><td>Study intervention Assignment</td><td colspan="3">Participants will be randomly assigned (1:1) to the 2 study groups (HRV and HRV PCV-free).

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

To allow GSK to take advantage of greater rates of recruitment than anticipated at individual centers in this multicenter study and to thus reduce the overall study recruitment period, an over-randomization of supplies will be prepared.</td></tr>
<tr><td>Interim Analysis</td><td colspan="3">No interim analysis is planned.
The final analysis addressing confirmatory objectives will be conducted once anti-RV IgA ELISA testing at Visit 3 (1 month after Dose 2) is completed and all the immunogenicity data are available. This final analysis will include immunogenicity and reactogenicity data up to Visit 3 and a CSR will be written.

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

2. STATISTICAL HYPOTHESES

Objective ranking	Null hypothesis
Primary	
1. To demonstrate the immunological non-inferiority of *Rotarix* PCV-free as compared to *Rotarix* in terms of seroconversion rates 1 month post Dose 2. – Non-inferiority will be demonstrated if the lower limit of the two-sided asymptotic standardized 95% CI for the difference in seroconversion rate between the *Rotarix* PCV-free and *Rotarix* is greater than or equal to -10%.	• The difference in seroconversion rate between the *Rotarix* PCV-free and (minus) *Rotarix* is < -10%.
2. To demonstrate the non-inferiority of the *Rotarix* PCV-free as compared to *Rotarix* in terms of serum anti-RV IgA Ab concentrations 1 month post Dose 2. – Non-inferiority will be demonstrated if the lower limit of the two-sided 95% CI for the ratio of anti-RV IgA Ab geometric mean concentration (GMC) 1 month post Dose 2 between the *Rotarix* PCV-free and *Rotarix* is greater than or equal to 0.67.	• The group ratio of anti-RV IgA Ab GMC 1 month post Dose 2 between the *Rotarix* PCV-free and (over) *Rotarix* is < 0.67.
Secondary	
3. To assess the immunological non-inferiority of *Rotarix* PCV-free as compared to *Rotarix* in terms of percentage of subjects with anti-RV IgA antibody concentrations ≥ 90 U/mL 1 month post Dose 2. – Non-inferiority will be demonstrated if the lower limit of the two-sided asymptotic standardized 95% CI for the difference in the percentage between the *Rotarix* PCV-free and *Rotarix* is greater than or equal to -10%.	The difference in the percentage of participants with serum anti-RV IgA antibody concentrations ≥ 90 U/mL 1 month post Dose 2 between *Rotarix* PCV-free and (minus) *Rotarix* groups is < -10%. .

2.1. Multiplicity Adjustment

To control the type 1 error for the primary objectives and first secondary objective assessment, a hierarchical procedure will be used based on the ranking presented in Section 2. Namely an objective will be reached if its null hypothesis is rejected, and the null hypotheses of the previous objectives were rejected.

Refer to Section 5 “Sample Size Determination” for additional details.

3. ANALYSIS SETS

Table 2 Population for analyses

Analysis Set	Definition / Criteria	Analyses Evaluated
Enrolled	• All participants who entered the study (who were randomized or received study intervention or underwent a post-screening procedure) • NOTE: screening failures (who never passed screening even if rescreened) and participants screened but never enrolled into the study (Met eligibility but not needed) are excluded from the Enrolled Analysis set as they did not enter the study.	• Study Population
Exposed	• All participants who received at least one dose of study intervention. • Participants will be analysed according to the study intervention administered at dose 1.	• Safety
Per-Protocol (PP)	All eligible participants from the exposed set who meet the following requirements: • Who received the study interventions according to their random assignment and the expected study intervention administration schedule ([28-48] days between first and second intervention). Note that in case regurgitation or vomiting occurs within 30 minutes after study intervention administration and impairs up-take of the intervention, a single replacement dose should be used for the participant to be part of the PPS. • Who were not unblinded • Who did not receive a vaccine not specified or forbidden by the protocol up to visit 3 blood sampling • Who did not receive medication forbidden by the protocol up to Visit 3 blood sampling. • Who had anti-RV concentration below 20 U/mL before study intervention. • Who complied with the blood sampling schedule for Visit 3 ([28-48] days between second intervention at Visit 2 and blood sample at Visit 3. • Who had no concomitant infection* up to Visit 3 blood sample, which may influence the immune system. • Participants will be analysed according to the intervention they received at dose 1.	• The PP Set will be used for the immunogenicity analyses. If, in any study intervention group, the percentage of vaccinated participants with serological results excluded from the PP Set for analysis of immunogenicity is 5% or more, a second analysis based on the Exposed Set will be performed to complement the PP Set analysis.

GCP = Good Clinical Practice; LAR = Legally Acceptable Representative

* RV gastroenteritis, immunosuppressive or immunodeficient conditions identified before Visit 3.

4. STATISTICAL ANALYSES

4.1. General Considerations

4.1.1. Immunogenicity

- Anti-RV IgA Ab concentrations below the assay cut-off will be given an arbitrary value of half the assay cut-off for the purpose of GMC calculation.
- The GMC calculations will be performed by taking the anti-log of the mean of the log concentration transformations.
- A participant is considered seronegative when the Anti-RV IgA Ab concentration is < 20 U/mL and seropositive when ≥ 20 U/mL.
- Seroconversion is defined as the percentage of participants who were initially seronegative (i.e., prior the first dose of *Rotarix*) and developed anti-RV IgA Ab concentration ≥ 20 U/mL at Visit 3 (1 month post Dose 2).
- For a given participant and a given immunogenicity measurement time point, missing or non-evaluable measurements will not be replaced.

4.1.2. Reactogenicity

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

Refer to Section 6.2.4.2 for the intensity grading of solicited AEs.

4.2. Primary Endpoint(s) Analyses

Analyses on the immunogenicity endpoints will be conducted primarily on the Per Protocol Set.

4.2.1. Within groups assessment

The following calculations will be performed.

For each group, at Visit 1 and Visit 3 time point,

- Seropositivity (at Visit 1 and Visit 3) and Seroconversion rates (at Visit 3) and their exact 95% confidence interval (CI) will be computed using the method of Clopper and Pearson [Clopper, 1934],
- GMCs and their exact 95% CIs will be computed,

4.2.2. Between groups assessment

- The asymptotic standardized 95% CI for the difference in seroconversion rate at Visit 3 between *Rotarix* PCV-free minus *Rotarix* will be computed using the method of Miettinen and Nurminen [Miettinen, 1985].
- The 95% CI for the ratio of anti-RV IgA Ab GMCs at Visit 3 between *Rotarix* PCV-free over *Rotarix* will be computed.

4.2.3. Sensitivity analyses

If more than 5% of the ES participants with immunogenicity results after study intervention are excluded from the PPS, the confirmatory analyses (refer to Section 2) will be repeated on the ES.

Within groups assessment for the PPS will be repeated by sex and study sites.

4.3. Secondary Endpoint(s) Analyses

Refer to Section 4.5 for safety analyses.

Analyses on the immunogenicity endpoints will be conducted primarily on the PPS.

4.3.1. Within groups assessment

The following calculations will be performed.

For each group, at Visit 1 and Visit 3 time point,

- The percentage of participants with anti-RV IgA antibody concentrations ≥ 90 U/mL and their exact 95% CI will be computed.
- The distribution of anti-RV IgA Ab concentrations at Visit 3 will be displayed using reverse cumulative curves for the PPS.

4.3.2. Between group assessment

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

4.3.3. Sensitivity analyses

If more than 5% of the ES participants with immunogenicity results after study intervention are excluded from the PPS, the confirmatory analyses (refer to Section 2) will be repeated on the ES.

Within groups assessment for the PPS will be repeated by sex and study sites.

4.4. Tertiary/Exploratory Endpoint(s) Analyses

There are no tertiary/exploratory endpoints in this study

4.5. Safety Analyses

The analyses will be descriptive and conducted on the ES.

The following calculations will be performed for each group:

- The percentage of doses and participants reporting at least 1 AE (solicited or unsolicited) during the 14-day (Day 1 to Day 14) solicited follow-up period will be computed, along with exact 95% CI. The same calculations will be done for AEs (solicited or unsolicited) rated as grade 3 in intensity and for AEs leading to a medically attended visit.
- The percentage of doses over the study and the percentage of participants (by dose and over the study) reporting each individual solicited systemic event will be computed, over the 14-day (Day 1 to Day 14) solicited follow-up period, following study intervention administration, along with exact 95% CI. The same calculations will be done for each individual solicited systemic event rated as grade 3 (grade 3 or grade 4 for fever) in intensity and events leading to a medically attended visit. Temperature above specific thresholds will also be summarized with threshold defined by half degree increment.

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

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

4.6. Other Analyses

Not applicable.

4.7. Interim Analyses

No interim analysis is planned.

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

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

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

4.8. Changes to Protocol Defined Analyses

There were no changes or deviations to the originally planned statistical analysis specified in the protocol (Dated: 13 May 2022).

5. SAMPLE SIZE DETERMINATION

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

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

The sample size provides at least 90% power to reach the first primary endpoint (see Table 3) and at 80.7% power to reach the second primary endpoint. 80.7% is a very conservative power estimate and is obtained as 100% minus the sum of type II errors for the 2 primary objectives, see Table 3 and Table 4. Using the same approach, the power to meet the first secondary objectives will be at least 67% power.

5.1.1. Power for non-inferiority in seroconversion

The power presented in Table 3 is based on PASS 2019 (one-sided Non-Inferiority Tests for the Difference Between Two Proportions), under the alternative of a 70% and 67.8%

seroconversion rate for *Rotarix* and *Rotarix* PCV-free, respectively, Miettinen and Nurminen's Likelihood Score Test of the Difference).

Table 3 Probability that the lower limit of the 95% CI around group difference in seroconversion rate (*Rotarix* PCV-free minus *Rotarix*), 1 month after Dose 2 of *Rotarix*, is ≥ -10%

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

* = Reference from Rota-075
N = number of participants

5.1.2. Power for non-inferiority in GMC

The power presented in Table 4 is based on PASS 2019 (one-sided non-inferiority test for 2 independent means, under the alternative of equal variance & alpha=2.5%).

Table 4 Probability that the lower limit of the 95% CI around the anti-RV IgA Ab GMC ratio (*Rotarix* PCV-free / *Rotarix*), 1 month after Dose 2 of *Rotarix*, is ≥ 0.67

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

* = Reference from Rota-075

N = number of participants

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

The power presented in Table 5 is based on PASS 2019 (one-sided Non-Inferiority Tests for the Difference Between Two Proportions), under the alternative hypothesis of a 45.7% and 43.5% percentage for *Rotarix* and *Rotarix* PCV-free, respectively, Miettinen and Nurminen's Likelihood Score Test of the Difference).

Table 5 Probability that the lower limit of the 95% CI around group difference in the percentage of participants with serum anti-RV IgA antibody concentrations greater or equal to 90 U/mL (*Rotarix* PCV-free minus *Rotarix*), 1 month after Dose 2 of *Rotarix*, is ≥ -10%

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

* = Reference from Rota-075
N = number of participants

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 Study Population Analyses

As per EudraCT reporting requirement, a summary of number of participants enrolled by country and by age category will be provided for the enrolled set.

6.1.1. Participant Disposition

Number of enrolled participants and reason for exclusion from ES will be described by group.

Number of vaccinated participants and reason for withdrawal from the study will be described by group for the ES.

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

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

6.1.2. Demographic and Baseline Characteristics

The demography and baseline characteristic summaries will be provided for both ES and PPS.

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

6.1.3. Protocol Deviations

Important protocol deviations will be summarized.

Protocol deviations will be tracked by the study team throughout the conduct of the study. These protocol deviations will be reviewed to identify those considered as important as follows:

- Data will be reviewed prior to freezing the database to ensure all important deviations (where possible without knowing the study intervention details) are captured and categorised in the protocol deviations dataset.
- This dataset will be the basis for the summaries of important protocol deviations.

Protocol deviations which result in exclusion from the analysis set will also be summarized.

- Data will be reviewed prior to [unblinding and] freezing the database to ensure all deviations leading to analysis population exclusions are captured and categorised in the protocol deviations ADaM dataset (note these exclusions are not captured in the SDTM dataset).

The following deviations will be considered important protocol deviations.

Codes 800, 900 and 1030 will lead to elimination from the ES and the PPS. The other codes are specific to the PPS. Refer to Section 3 for the summary of protocol deviation leading to elimination from analysis set.

Code	Decode: Condition under which the code is used
800	Fraudulent data
900	Invalid informed consent
1030	Study vaccine dose not administered but participant number allocated: participants enrolled but not vaccinated
1050	Randomization failure: forced or manual randomization*. First dose of vaccine administration not aligned with the randomized treatment.
1040	Administration of concomitant vaccine(s) forbidden in the protocol: Administration of a non study HRV vaccine or non routine vaccine starting from 30 days before the first vaccination up to Visit 3 blood sample.
1060	Randomization code broken at the investigator site: Participants unblinded in the central randomization system or unblinding reported as protocol deviation
1070	Study vaccine dose not administered according to protocol: • Participants vaccinated with the correct vaccine but who regurgitated for one of the 2 doses and did not receive a vaccine replacement • Participants for whom the second administered dose is not aligned with the first dose (e.g. HRV as second dose after a first dose with HRV PCV-free) • Participant who did not receive the second dose • Route of vaccination which is not oral
1080	Vaccine temperature deviation: Participants who have received a vaccine which had a temperature deviation qualified as inappropriate for use by Quality Assurance.
1090	Expired vaccine administered: Participants who received an expired vaccine

Code	Decode: Condition under which the code is used
2010	Protocol violation linked to the inclusion/exclusion criteria: Ineligible participants who was vaccinated (Refer to protocol Section 5 "Study population" for the exhaustive list of inclusion/exclusion criteria).
2020	Anti-RV IgA antibody concentration at pre-vaccination above or equal to 20 U/mL or initially unknown antibody status
2040	Administration of any medication from day 1 to the Visit 3 blood sample which is forbidden by the protocol (see Section 5.2 from the protocol)
2070	Concomitant infection not related to the vaccine which may influence immune response = > who have concomitant infection up to Visit 3 blood sample, which may influence the immune system namely RV gastroenteritis, immunosuppressive or immunodeficient conditions identified before Visit 3.
2080	Non-compliance with vaccination schedule (including wrong and unknown dates): Participants who did not comply with the interval for dose 2 (Dose 2 should be between 28-48 days after Dose 1 i.e. Dose 2 date – Dose 1 date should be between 28-48 days).
2090	Non-compliance with the blood sampling schedule (including wrong and unknown dates) => Blood sample not collected within 28 days-48 days after the corresponding intervention
2100	Serological results not available post dose
2120	Obvious incoherence/abnormality or error in data

* Forced randomization: In case of supplies shortage for the next assigned vaccine according to the randomization schedule at the clinical site, the randomization system will use the forced randomization procedure in order to continue to enrol and vaccinate participants. The system moves seamlessly to the next treatment/randomization number for which vaccine supplies are available. The site will not be aware of the forced randomization event.

*Manual randomization: In case the randomization system is unavailable, the investigator has the option to perform randomization by selecting supplies available at the site according to a pre-defined rule. In case the randomization system is available, a vaccine different from the randomized treatment may have been administered at dose 1.

6.1.4. Prior and Concomitant Medications

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

The percentages of participants who started taking at least 1 concomitant medication, by type (any, antipyretic), from Day 1 to Day 14 after study intervention administrations will be tabulated by group with the exact 95% CI.

The percentages of participants who started taking at least 1 concomitant medication, by type (any, antipyretic), within 1 month after each dose will also be tabulated by group with exact 95% CI.

6.1.5. Study Intervention Compliance

The number of doses administered will be tabulated for each group for the ES. A dose is defined as a vaccination visit. Accordingly, a visit at which a replacement dose was given

following regurgitation will be counted as one dose. Note that participants without a replacement dose administered despite regurgitation will be summarized among the important protocol deviation summary.

6.1.6. Reactogenicity/Safety Compliance

The number and percentage of participants with symptom sheets returned with documented occurrence of at least one solicited symptom will be tabulated by group and by dose for the ES.

6.2. Appendix 2 Data Derivations Rule

6.2.1. Study Day and Reference Dates

The reference day is defined as the day of 1st vaccine dose.
The study day is calculated as below:

- Assessment Date = Missing → Study Day = Missing
- Assessment Date < Reference Date → Study Day = Assessment Date – Ref Date
- Assessment Date ≥ Reference Date → Study Day = Assessment Date – Ref Date + 1

6.2.2. Assessment Window

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

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

6.2.3. Handling of partial or missing Dates

<table>
<tr><th>Element</th><th>Reporting Detail</th></tr>
<tr><td>General</td><td>• Partial dates will be displayed as captured in participant listing displays.
• When partially completed dates (i.e. with missing day or month) are used in calculations, the following standard rules will be applied:
- a missing day will be replaced by 15
- a missing day and month will be replaced by June 30th.
• Derivations for partial dates for Adverse Events, concomitant medication/medical history and age are detailed below</td></tr>
<tr><td>Adverse Events</td><td>The general rules above apply, with the following exceptions for missing start day/ missing start day and month.<table><tr><td>Missing start day</td><td>If the event starts in the same month as at least 1 of the study doses, the contents of AE.AESTRTPT (the flag indicating if the event occurred before or after vaccination) will be used to complete the date. If ‘after vaccination’ is selected, the imputed start date will</td></tr></table></td></tr>
</table>

Element	Reporting Detail	
		match the first (or only) study dose given during that month. If 'before vaccination' is selected, the imputed date will be 1 day before the first (or only) study dose given during that month.
	Missing start day and month	If the event starts in the same year as at least 1 of the study doses, the contents of AE.AESTRTPT (the flag indicating if the event occurred before or after vaccination) will be used to complete the date. If 'after vaccination' is selected, the imputed start date will match the first (or only) study dose given during that year. If 'before vaccination' is selected, the imputed date will be 1 day before the first (or only) study dose given during that year.
	Missing end day	The general rule is applied
	Missing end day and month	The general rule is applied
	Completely missing start/end date	No imputation
Concomitant Medications/Medical History	The general rules above apply,	
	Missing start day	The general rule is applied
	Missing start day and month	The general rule is applied
	Missing end day	The general rule is applied
	Missing end day and month	The general rule is applied
	Completely missing start/end date	No imputation

6.2.4. Handling of other missing data

6.2.4.1. Immunogenicity data

Missing immunogenicity data are not imputed.

6.2.4.2. Daily recording of solicited AEs

When a specific solicited AE is marked as having not occurred following a specific vaccination (i.e. SDTM CE.CEOCCUR=N for the specified post-vaccination period for the solicited AE in question), all daily measurements will be imputed as Grade 0.

When a specific solicited AE is marked as having occurred following a specific vaccination (i.e. SDTM CE.CEOCCUR=Y for the specified post-vaccination period for the solicited AE in question), any missing daily recordings will be given an imputed value which allows them to contribute to the 'Any' rows but not to specific grade rows of the solicited AE summary tables.

When the occurrence of a specific solicited AE is not present (i.e. SDTM CE.CEOCCUR is neither Y nor N for the specified post-vaccination period for the solicited AE in question) all missing daily recordings will be given an imputed value which allows them to contribute to the 'Any' rows but not to specific grade rows of the solicited AE summary tables.

The following table shows how solicited events are coded for intensity.

Table 6 Intensity scales for solicited AEs – Attribution for codes for Diarrhea, Vomiting and Fever

	Infant		
Event	**Intensity grade (collected or measured)**	**Intensity grade (code attributed)**	**Parameter**
Loss of appetite	0	0	Appetite as usual
	1	1	Eating less than usual/no effect on normal activity
	2	2	Eating less than usual/interferes with normal activity
	3	3	Not eating at all
Irritability/Fussiness	0	0	Behavior as usual
	1	1	Crying more than usual/no effect on normal activity
	2	2	Crying more than usual/interferes with normal activity
	3	3	Crying that cannot be comforted/prevents normal activity
Cough/runny nose	0	0	Normal
	1	1	Cough/runny nose which is easily tolerated
	2	2	Cough/runny nose which interferes with daily activity
	3	3	Cough/runny nose which prevents daily activity
Diarrhea	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	episodes of vomiting/day	0	Normal (no emesis)
		1	1 episode of vomiting/day
		2	2 episodes of vomiting/day
		3	≥3 episodes of vomiting/day
Fever[+]	Axilary Temperature (°C)	0	Normal (< 37.5°C)
		1	37.5°C – < 38.0°C
		2	38.0°C – < 39.5°C
		3	≥ 39.5°C
		4	≥ 39.5°C, lasts more than 5 consecutive days

[*]Axilla is the preferred route to measure temperature in China. If temperature is collected by other routes, the following conversion will be applied:

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

The following table shows how participants contribute to each category for a specific solicited AE over the Day X to Day Y post-vaccination period:

Solicited AE category	Participants included in the calculation of the numerator
Any	All participants with at least 1 occurrence of the solicited AE at grade 1, grade 2, grade 3 or grade 4 between Day X and Day Y or with the solicited AE marked as present and at least 1 missing daily recording between Day X and Day Y
At least grade 1	All participants with at least 1 occurrence of the solicited AE at grade 1, grade 2, grade 3 or grade 4 between Day X and Day Y
At least grade 2	All participants with at least 1 occurrence of the solicited AE at grade 2, grade 3 or grade 4 between Day X and Day Y
At least grade 3	All participants with at least 1 occurrence of the solicited AE at grade 3 or grade 4 between Day X and Day Y

6.2.4.3. Unsolicited adverse events

Unsolicited AE summaries will include unsolicited AEs and SAEs. Solicited events collected within the Day 1 -14 assessment period will be reported in the clinical event (CE) domain while unsolicited events will be reported in the AE domain. Following CBER's request to comply with the CDISC Vaccines Therapeutic Area Guide, solicited events that continue beyond the assessment period will also be reported in the AE domain. These solicited events will not be included in the summaries of unsolicited AEs but will be reported separately.

Missing severity, relationship with study vaccine, and outcome of unsolicited adverse events will not be replaced and will appear as 'UNKNOWN' in all statistical output.

6.2.5. Age at vaccination in weeks

Age at vaccination will be displayed in weeks. It will be calculated as the number of complete weeks between the date of birth (DOB) and the date of vaccination. For example:

DOB = 10JUN2019, Date of vaccination = 28JUL2019 -> Age = 6 weeks

DOB = 10JUN2019, Date of vaccination = 29JUL2019 -> Age = 7 weeks

Incomplete birthdate will follow the general imputation for incomplete date (refer to Section 6.2.3).

6.2.6. Onset day

The onset day for an event (e.g. AE, medication, vaccination) is the number of days between the last study vaccination and the start date of the event. This is 1 for an event occurring on the same day as a vaccination (and reported as starting after vaccination).

6.2.7. Counting rules for combining solicited and unsolicited adverse events

For output combining solicited and unsolicited adverse events, all serious adverse events will be considered general events since the administration site flag is not included in the expedited adverse event case report form (CRF) pages.

Multiple events with the same preferred term which start on the same day are counted as only 1 occurrence.

6.2.8. Counting rules for occurrences of solicited adverse events

When the occurrences of solicited adverse events are summarized, each event recorded as having occurred during a specific period will be counted as only 1 occurrence regardless of the number of days on which it occurs.

6.2.9. Immunogenicity data

- In general, the assay cut-off is the value under which there is no quantifiable result available. For an assay with a specific 'assay cut_off', the numerical immunogenicity result is derived from a character field (IS.ISSTRES):
  - if ISSTRES is 'NEG' or '-' or '(-)', numeric result= assay cut_off/2,
  - if ISSTRES is 'POS' or '+' or '(+)', numeric result = assay cut_off,
  - if ISSTRES is '< value' and value<=assay cut_off, numeric result =assay cut_off/2,
  - if ISSTRES is '< value' and value>assay cut_off, numeric result =value,
  - if ISSTRES is '> value' and value<assay cut_off, numeric result =assay cut_off/2,
  - if ISSTRES is '> value' and value>=assay cut_off, numeric result =value,
  - if ISSTRES is '<= value' or '>= value' and value<assay cut_off, numeric result =assay cut_off/2,
  - if ISSTRES is '<= value' or '>= value' and value>=assay cut_off, numeric result =value,
  - if ISSTRES is a value < assay cut_off, numeric result = assay cut_off/2,
  - if ISSTRES is a value >= assay cut_off, numeric result = ISSTRES
  - else numeric result is left blank.

6.2.10. Number of decimals displayed

The following decimal description from the decision rules will be used for the demography, immunogenicity and safety/reactogenicity.

Display Table	Parameters	Number of decimal digits
All summaries	% of count, including LL & UL of CI	1
Demographic characteristics	Mean, median, SD	1
Reactogenicity	% of count, including LL & UL of CI	1
Immunogenicity	GMCs and Rates (%), including LL & UL of CI	1
Immunogenicity	GMC ratios, including LL & UL of CI	2
Immunogenicity	Differences between Rates, including LL & UL of CI	2

6.2.11. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies	Trademarks not owned by the GlaxoSmithKline Group of Companies
Rotarix	Not applicable

7. REFERENCES

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