Statistical Analysis Plan

Study ID: 218485

Official Title of Study: A Phase III, open-label, randomized, controlled study to evaluate the immunogenicity and safety of inactivated poliovirus vaccine (IPV) when co-administered with Porcine circovirus (PCV)-free liquid formulation of an oral live attenuated human rotavirus (HRV) vaccine in healthy Chinese infants

NCT number: NCT06331156

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TITLE PAGE

Protocol Title:	A Phase III, open-label, randomized, controlled study to evaluate the immunogenicity and safety of inactivated poliovirus vaccine (IPV) when co-administered with *Porcine circovirus* (PCV)-free liquid formulation of an oral live attenuated human rotavirus (HRV) vaccine in healthy Chinese infants
Study Number:	218485
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VERSION HISTORY

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
SAP	18 Dec 2023	25 October 2023	Not Applicable	Original version
SAP	21 Oct 2024	25 October 2023	Added Table 5. Intervals between study visits for Staggered group	In the protocol

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-098 (218485). Details of the planned analyses are provided.

1.1. Objectives, Estimands and Endpoints

Objectives	Endpoints**
Primary (Confirmatory)	
• To demonstrate the immunological non-inferiority of IPV when co-administered with *Rotarix* PCV-free compared with IPV administered alone.	• Anti-poliovirus types 1, 2 and 3 neutralizing Ab seroconversion rate* 1 month post Dose 3 of IPV in the Co-administration and Staggered groups.
Secondary (Descriptive)	
• To evaluate the immunogenicity of IPV when co-administered with *Rotarix* PCV-free and when administered alone.	• Anti-poliovirus types 1, 2 and 3 neutralizing Ab GMTs at 1 month post Dose 3 of IPV in the Co-administration and Staggered groups. • Percentage of participants with anti-poliovirus types 1, 2 and 3 neutralizing Ab titers ≥1:8 and ≥1:64 at 1 month post Dose 3 of IPV in the Co-administration and Staggered groups.
• To evaluate the immunogenicity of *Rotarix* PCV-free when co-administered with IPV and when administered alone.	• Anti-RV IgA Ab seroconversion rate** 1 month post Dose 2 in the Co-administration and Staggered groups. • Anti-RV IgA Ab GMCs at 1 month post Dose 2 of *Rotarix* PCV-free in the Co-administration and Staggered groups. • Percentage of participants with anti-RV IgA Ab concentrations ≥90 U/mL at 1 month post Dose 2 of *Rotarix* PCV-free in the Co-administration and Staggered groups.
• To evaluate the reactogenicity of *Rotarix* PCV-free and IPV in terms of solicited systemic events. • To assess the safety of *Rotarix* PCV-free in terms of unsolicited AEs and serious adverse events (SAEs) and safety of IPV in terms of 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 Dose 1 and Dose 2 of *Rotarix* and IPV • Unsolicited AEs – Percentage of participants reporting the occurrence of unsolicited AEs within 31 days (Day 1- Day 31) after each dose of *Rotarix*, according to the MedDRA classification. • SAEs: – Percentage of participants reporting SAEs from the first dose of the study intervention up to study end in the Co-administration and Staggered groups.

Ab: Antibody; GMC: Geometric mean Ab concentration; GMT: Geometric mean Ab titer; IgA: Immunoglobulin A; IPV: Inactivated poliovirus vaccine; MedDRA: Medical Dictionary for Regulatory Activities; mL: milliliter; PCV: *Porcine circovirus*; SAE: Serious Adverse Event; U: Unit

*Seroconversion rate for IPV neutralizing Ab is defined as percentage of participants with

- Titer ≥1:8 at 1 month after 3 dose primary schedule of IPV in participants with titer <1:8 pre-vaccination
- Titer ≥4-fold increase in titer 1 month after 3 dose primary vaccination schedule in participants with titer ≥1:8 pre-vaccination.
  Note: the 4-fold increase will take into consideration the expected decline in maternal antibodies with estimated half-life of 28 days.

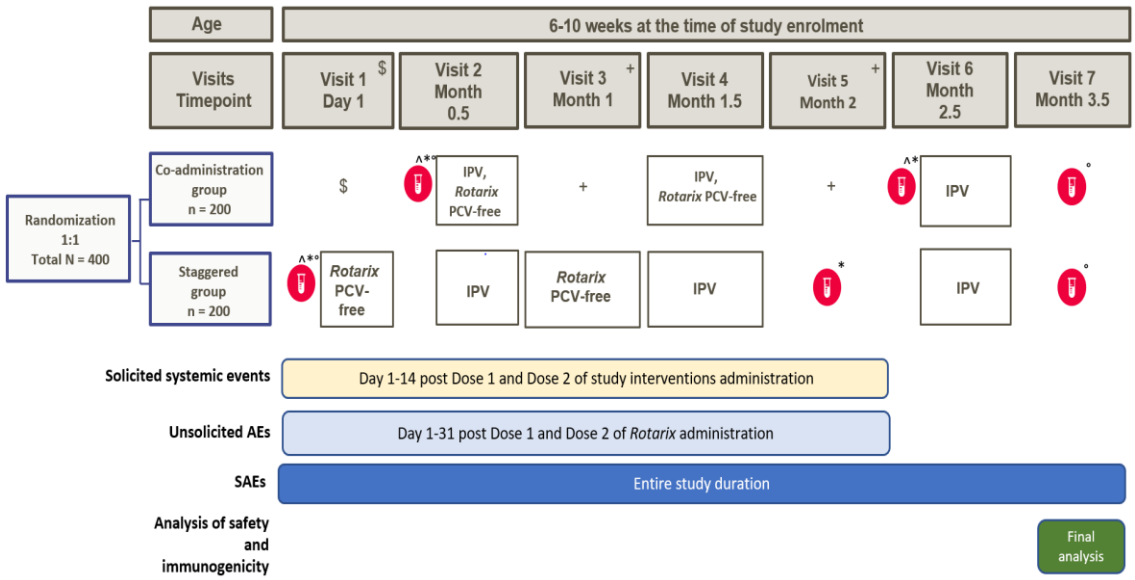
**Seroconversion rate for anti-RV IgA Ab is defined as the percentage of participants who were initially seronegative (i.e., with anti-RV IgA Ab concentration <20 U/mL prior the first dose of *Rotarix*) and developed anti-RV IgA Ab concentration ≥20 U/mL at 1 month post Dose 2.

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

1.2. Study Design

Overview of Study Design and Key Features

Figure 1 Study design overview



AE: Adverse Event; IPV: Inactivated poliovirus vaccine; 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; N: Total number of participants planned to be enrolled; n: Planned number of participants in each group.

Study interventions: IPV (Co-administered vaccine) and *Rotarix* PCV-free (Study vaccine).

$ Refer to the Schedule of activities (SoA) the protocol for Co-administration group.

+ Visit not applicable for participants in the Co-administration group.

^ Blood sampling to be done before study intervention administration.

° Blood sample for anti-poliovirus types 1, 2 and 3 antibodies measurement.

* Blood sample for anti-RV IgA antibody measurement.

Overview of Study Design and Key Features

Design Features

- **Experimental design**: Phase III, open-label, randomized, controlled study with 2 groups.
- **Duration of the study**: The total duration of the study, per participant, will be approximately 3.5 months
- **Primary completion date**: Visit 7 (Month 3.5).
- **Control:** Active control, i.e., staggered administration of licensed IPV and *Rotarix* PCV-free.
- **Blinding**: Open-label.
- **Data collection**: Standardized electronic Case Report Form (eCRF). Solicited systemic events will be collected using a diary card.
- **Study groups**: Refer to Figure 1 and Table 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 interventions	Blinding
Co-administration	200	6-10 weeks*	IPV, *Rotarix* PCV-free	Open-label
Staggered	200	6-10 weeks*	IPV, *Rotarix* PCV-free	Open-label

IPV: Inactivated poliovirus vaccine; Max: maximum; Min: minimum; PCV: *Porcine circovirus*
*6-10 weeks at the time of study enrolment.

Study intervention

Study intervention name:	Inactivated Poliomyelitis Vaccine Made From Sabin Strains (Vero Cells) (IPV)	*Rotarix* PCV-free (HRV PCV-free)
Study intervention formulation:	CCI [redacted] CCI [redacted] CCI [redacted]	HRV RIX4414 CCI [redacted] Sterile water
Presentation:	CCI [redacted]	CCI [redacted]
Type:	Co-administered	Study
Product category:	Combination product*	Combination product*
Route of administration:	Intramuscular	Oral
Administration site:		
• **Location**	Refer to the Pharmacy Manual for more details	NA
• **Directionality**	Refer to the Pharmacy Manual for more details	NA

Overview of Study Design and Key Features	
	• **Laterality** / Refer to the Pharmacy Manual for more details / NA **Number of doses to be administered:** / 3 / 2 **Volume to be administered by dose:** / 0.5 mL / 1.5 mL **Packaging and labeling:** / Refer to the Pharmacy Manual for more details / Refer to the Pharmacy Manual for more details **Manufacturer:** / Beijing Biological Products Institute Co.,Ltd. / GSK mL: milliliter; Pharmacy Manual: study procedures manual
Study intervention Assignment	Participants will be randomly assigned (1:1) to the 2 study groups (Co-administered and Staggered). 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.
Interim Analysis	No interim analysis is planned. All analyses will be conducted on final data. The final analysis will include all data up to one month after the third dose of IPV. 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.

2. STATISTICAL HYPOTHESES

Primary objective	Null hypothesis
• To demonstrate the immunological non-inferiority of IPV when co-administered with *Rotarix* PCV-free compared with IPV administered alone.	• The difference in seroconversion rate between the Co-administration group and (minus) the Staggered group is below -10% for at least 1 of the anti-poliovirus types 1, 2 and 3 Abs.

Ab: Antibody; IPV: Inactivated poliovirus vaccine; PCV: *Porcine circovirus*

The global type I error will be 2.5%. The primary objective will be achieved if the lower limit of the 2-sided 95% CI for the group difference (Co-administration group minus Staggered group) in seroconversion rate is greater than or equal to -10% for each of the anti-poliovirus types 1, 2 and 3 antibodies.

3. ANALYSIS SETS

Table 2 Population for analyses

Analysis Set	Definition / Criteria	Analyses Evaluated
Screened	• All participants who were screened for eligibility	• Study Population
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 any of the 2 study interventions. • Participants will be analyzed 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 and without intercurrent conditions* that may interfere with immunogenicity and without prohibited concomitant medication/vaccination. • for anti-poliovirus types 1, 2 and 3 analyses at 1 month post Dose 3 of IPV, participants should have pre- and post-vaccination immunogenicity results for at least 1 antigen and should have complied with interval between IPV Dose 3 and the post IPV Dose 3 blood sample. • for anti-RV IgA analyses at 1 month post Dose 2 of *Rotarix* PCV-free, participants should have pre- and post-vaccination immunogenicity results and should have complied with the interval between *Rotarix* Dose 2 and the post *Rotarix* PCV-free Dose 2 blood sample.	• 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.

* Immunosuppressive or immunodeficient conditions identified before Visit 7.

4. STATISTICAL ANALYSES

4.1. General Considerations

4.1.1. Immunogenicity

- GMC/GMT concentrations/titers below the assay cut-off will be given an arbitrary value of half the assay cut-off for the purpose of GMC/GMT calculation.
- The GMC/GMT calculations will be performed by taking the anti-log of the mean of the log concentration/titer transformations.
- Seroconversion rate for IPV neutralizing Ab is defined as percentage of participants with
  - Titer ≥1:8 at 1 month after 3 dose primary schedule of IPV in participants who are seronegative before Dose 1 (titer <1:8 pre-vaccination).
  - ≥4-fold increase in titer 1 month after 3 dose primary vaccination schedule in participants who are seropositive before Dose 1 (titer ≥1:8 pre-vaccination) after adjusting for maternal antibody decay assuming a half-life of 28 days.
- Seroconversion rate for *Rotarix* 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 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 endpoint will be conducted primarily on the Per Protocol Set.

4.2.1. Within groups assessment

The following calculations will be performed:

For each group, before Dose 1 and Visit 7 (1 month post Dose 3) time point,

- Seropositivity (before Dose 1 and Visit 7) and Seroconversion rates for IPV (at Visit 7) and their exact 95% confidence interval (CI) will be computed using the method of Clopper and Pearson [Clopper, 1934],
- For participants who are seropositive before Dose 1 of IPV, the expected decline in maternal antibodies will be accounted for as follows. Assuming the maternal antibody half-life is 28 days, the estimated maternal antibody titer will be calculated as:

$$Titer\ (t) = titer\ (baseline)\ \times \exp(\frac{-\ln\ (2)}{t_{\frac{1}{2}}} \times t)$$

Where t is the time in days since baseline and $t_{\frac{1}{2}}$ is the expected half-life of the maternal antibodies of 28 days. The SAS code for calculating the adjusted titer is shown below:

```
data is_ipv;
       set is_ipv;

       if titer_prevaccination ge 8 then do;
       titer_adj= titer_prevaccination x exp((-ln(2)/28) x
   t));
       end;

       if titer_prevaccination < 8 then do;
       titer_adj=titer_prevaccination;
       end;
run;
```

4.2.2. Between groups assessment

The asymptotic standardized 95% CI for the difference in seroconversion rate for IPV at Visit 7 between Co-administration group minus staggered group will be computed using the method of Miettinen and Nurminen [Miettinen, 1985]

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 analysis 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, 1 month post Dose 2 for *Rotarix* PCV-free and 1 month post Dose 3 for IPV timepoint,

- Seropositivity (before Dose 1 and 1 month post Dose 2) and Seroconversion rates for *Rotarix* PCV-free (1 month post Dose 2) and their exact 95% confidence interval (CI) will be computed using the method of Clopper and Pearson [Clopper, 1934],
- GMCs/GMTs were applicable and their exact 95% CIs will be computed.
- The percentage of participants with anti-poliovirus 1, 2, and 3 neutralizing Ab titers≥ 1:8 and≥ 1:64 and their exact 95% CI for each group at 1 month post Dose 3 will be computed.
- The percentage of participants with anti-RV IgA antibody concentrations ≥ 90 U/mL and their exact 95% CI for each group at 1 month post Dose 2 will be computed.
- The distribution of anti-RV IgA Ab concentrations 1 month post Dose 2 and anti-poliovirus titers 1 month post Dose 3 will be displayed using reverse cumulative curves for the PPS

4.3.2. Between group assessment

- The asymptotic standardize 95% CI for the difference in the percentage of participants with anti-poliovirus types 1, 2 and 3 neutralizing Ab titers ≥ 1:8 and ≥ 1:64 at Visit 7 between Co-administration group minus staggered group will be computed.
- The 95% CI for the ratio of anti-poliovirus type 1, 2 and 3 Ab GMTs at Visit 7 between Co-administration group over staggered group will be computed.

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, 2019].

- 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 of *Rotarix* PCV-free 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 dropouts due to AEs will be described in detail.

4.6. Other Analyses

Not applicable.

4.7. Interim Analyses

No interim analysis is planned. All analyses will be conducted on final data and therefore no statistical adjustment for interim analyses is required.

The final analysis will include all data up to one month after the third dose of IPV. 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.

4.8. Changes to Protocol Defined Analyses

There were no changes or deviations to the originally planned statistical analysis specified in the protocol amendment 1 (Dated: 25 October 2023).

5. SAMPLE SIZE DETERMINATION

A maximum of 400 participants (200 in the Co-administration group and 200 in the Staggered group) will be randomized such that approximately 160 evaluable participants complete the study, in each group for the evaluation of the primary objective assuming that approximately 20% of the enrolled participants will not be evaluable.

Participants who withdraw from the study will not be replaced.

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 hypothesis of a 96.23% (Polio 1), 93.83% (Polio 2), and 97.60% (Polio 3) seroconversion rate for the Staggered group and a true difference of 0% between the Co-administration group and Staggered group, using Miettinen and Nurminen's Likelihood Score Test of the Difference. Under these conservative assumptions the overall power is above 90.4% (i.e., global type II error is conservatively computed as the sum of nominal type II errors).

Table 3 Probability that the lower limit of the 95% CI around group difference in the percentage of participants with anti-poliovirus types 1, 2 and 3 antibody seroconversion 1 month post Dose 3 of IPV (Co-administration group minus Staggered group) is greater than or equal to -10%

Ag	True seroconversion rate (Co-administration group) *	True seroconversion rate (Staggered group) *	N evaluable (each group)	Power	Alpha
Polio 1	96.23%	96.23%	160	98.2%	0.025
Polio 2	93.83%	93.83%	160	92.5%	0.025
Polio 3	97.60%	97.60%	160	99.7%	0.025
	Overall			90.4%	

Ag: Antigen; N: number of participants

* Observed positive conversion rate from the Beijing Biological Products Institute Co.,Ltd. IPV package insert [Inactivated Poliomyelitis Vaccine Made From Sabin Strains (Vero Cells) package insert, 2019].

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 study intervention 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 categorized 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 freezing the database to ensure all deviations leading to analysis population exclusions are captured and categorized 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 vaccine (HRV/IPV) or non-routine vaccine starting from 30 days before the first vaccination up to Visit 7 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: • Participant who did not receive the complete dose of each of the study vaccines (two doses for HRV PCV-free and three doses for IPV). • Route of study vaccine administration wrong or unknown.
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
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 7 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 7 blood sample, which may influence the immune system namely RV gastroenteritis, immunosuppressive or immunodeficient conditions identified before Visit 7.

Code	Decode: Condition under which the code is used
2080	Non-compliance with vaccination schedule (including wrong and unknown dates) for IPV and/or HPV PCV-free
2090	Non-compliance with the blood sampling schedule (including wrong and unknown dates)
2100	Serological results not available 1 month post Dose 2 for Rotarix PCV-free and 1 month post Dose 3 for IPV.
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

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.

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

Table 4 Intervals between study visits for Co-administration group

Interval	Optimal interval	Allowed interval range	Allowed interval during special circumstances[#]
Visit 1→Visit 2	15 days	14-18 days between study enrolment and Dose 1 of IPV and *Rotarix* PCV-free	14-45 days
Visit 2→Visit 4	30 days	28-36[†] days between Dose 1 of IPV and *Rotarix* PCV-free and Dose 2 of IPV and *Rotarix* PCV-free	28-60 days
Visit 4→Visit 6	30 days	28-36[†] days between Dose 2 of IPV and *Rotarix* PCV-free and Dose 3 of IPV and BS for assessment of Rotavirus Ab, IgA	28-60 days
Visit 6→Visit 7	30 days	30-36[†] days between Dose 3 of IPV and BS for assessment of anti-poliovirus types 1, 2 and 3 Ab	30-60 days

Ab: Antibody; BS: Blood sampling; IgA: Immunoglobulin A; IPV: Inactivated poliovirus vaccine; PCV: Porcine circovirus; PCV-free: no detection of PCV-1 and PCV-2 according to the limit of detection of the tests used

[†] Participants will not be eligible for inclusion in the Per Protocol Set for immunogenicity if they make the study visit outside this interval. Interval is computed as the difference between the 2 dates of the study procedure.

[#] Refer to Section 8 of the protocol for more details on special circumstances (e.g., COVID-19 pandemic).

Table 5 Intervals between study visits for Staggered group

Interval	Optimal interval	Allowed interval range	Allowed interval during special circumstances[#]
Visit 1→Visit 2	15 days	14-18[†] days between Dose 1 of *Rotarix* PCV-free and Dose 1 of IPV	14-45 days
Visit 1→Visit 3	30 days	28-36[†] days between Dose 1 and Dose 2 of *Rotarix* PCV-free	28-60 days
Visit 2→Visit 4	30 days	28-36[†] days between Dose 1 and Dose 2 of IPV	28-60 days
Visit 3→Visit 5	30 days	28-36[†] days between Dose 2 of *Rotarix* PCV-free and BS for assessment of Rotavirus Ab, IgA	28-60 days
Visit 4→Visit 6	30 days	28-36[†] days between Dose 2 and Dose 3 of IPV	28-60 days
Visit 6→Visit 7	30 days	30-36[†] days between Dose 3 of IPV and BS for assessment of anti-poliovirus types 1, 2 and 3 Ab	30-60 days

Ab: Antibody; BS: Blood sampling; IgA: Immunoglobulin A; IPV: Inactivated poliovirus vaccine; PCV: *Porcine circovirus*; PCV-free: no detection of PCV-1 and PCV-2 according to the limit of detection of the tests used

† Participants may not be eligible for inclusion in the Per Protocol Set for immunogenicity if they make the study visit outside this interval. Interval is computed as the difference between the 2 dates of the study procedure.

Refer to Section 8 for more details on special circumstances (e.g., COVID-19 pandemic).

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 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.</td></tr>
<tr><td>Missing start day and month</td><td>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.</td></tr>
<tr><td>Missing end day</td><td>The general rule is applied</td></tr>
<tr><td>Missing end day and month</td><td>The general rule is applied</td></tr>
<tr><td>Completely missing start/end date</td><td>No imputation</td></tr>
</table></td></tr>
<tr><td>Concomitant Medications/Medical History</td><td>The general rules above apply,
<table>
<tr><td>Missing start day</td><td>The general rule is applied</td></tr>
<tr><td>Missing start day and month</td><td>The general rule is applied</td></tr>
<tr><td>Missing end day</td><td>The general rule is applied</td></tr>
<tr><td>Missing end day and month</td><td>The general rule is applied</td></tr>
</table></td></tr>
</table>

Element	Reporting Detail	
	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/GMTs and Rates (%), including LL & UL of CI	1
Immunogenicity	GMC/GMT ratios, including LL & UL of CI	2
Immunogenicity	Differences between Rates, including LL & UL of CI	2

6.2.11. Trademarks

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7. REFERENCES

Clopper CJ, Pearson E. The Use of Confidence or Fiducial Limits Illustrated in the case of the Binomial. *Biometrika.* 1934; 26: 404-13.

Inactivated Poliomyelitis Vaccine Made From Sabin Strains (Vero Cells) package insert. Beijing Biological Products Institute Co.,Ltd. January, 2019.

Miettinen, O.S. and Nurminen, M. Comparative analysis of two rates. *Statistics in Medicine* 1985; 4: 213-226.

NMPA Guiding Principle of Adverse Event Grading Standards for Clinical Trials of Preventive Vaccines, 26 December 2019 (b).
Accessed 08 May 2020.