Amsterdam, 11 December 2025.
EMADOC-1700519818-2491727
Committee for Medicinal Products for Human Use (CHMP)

Assessment Report for Paediatric Studies submitted in accordance with Article 46 of Regulation (EC) No 1901/2006, as amended

Rotarix

Common name: rotavirus vaccine, live

Procedure no.: EMA/PAM/0000302758

Marketing authorisation holder (MAH): GlaxoSmithKline Biologicals

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Status of this report and steps taken for the assessment				
Current step	**Description**	**Planned date**	**Actual Date**	**Need for discussion**
☐	Start of procedure	13 Oct 2025	13 Oct 2025	☐
☐	CHMP Rapporteur AR	17 Nov 2025	17 Nov 2025	☐
☐	CHMP members comments	1 Dec 2025	N/A	☐
☐	Updated CHMP Rapporteur AR	4 Dec 2025	N/A	☐
☒	CHMP outcome	11 Dec 2025	11 Dec 2025	☐

Declarations

☒ The assessor confirms that this assessment does **not** include non-public information, including commercially confidential information (e.g. ASMF, information shared by other competent authorities or organisations, reference to ongoing assessments or development plans, etc.), irrespective from which entity was received*.

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1. Introduction

On 26 September 2025, the MAH submitted a completed paediatric study for Rotarix, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The ROTA-098 study report is being submitted to comply with the requirements of Article 46 of the paediatric regulation 1901/2006.

2.2. Information on the pharmaceutical formulation used in the study<ies>

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

ROTA-098 (218485), entitled: "A phase III, open-label, randomised, multicentre, controlled study to evaluate the immunogenicity and safety of the 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."

In China, under the National Immunization Program (NIP), a 3-dose primary vaccination against poliovirus is currently recommended during the first year of life in a 2, 3 and 4 months of age schedule and a booster vaccine is recommended at 4 years of age. Rotarix should be given in a 2-dose schedule between 6-24 weeks of age with an interval of at least 4 weeks between doses. Till date, there is no data available on the immunogenicity and safety of IPV when co-administered with Rotarix PCV-free, in healthy Chinese infants. The current study is therefore designed to assess the immunogenicity and safety of IPV when it is co-administered with Rotarix PCV-free, compared to administration of the vaccines separately.

2.3.2. Clinical study

Study 218485 (ROTA-098) EudraCT: 2022-000708-36

A phase III, open-label, randomised, 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.

Methods

This assessment is based on Protocol Amendment 1 Final, dated 25 October 2023.

Overall design

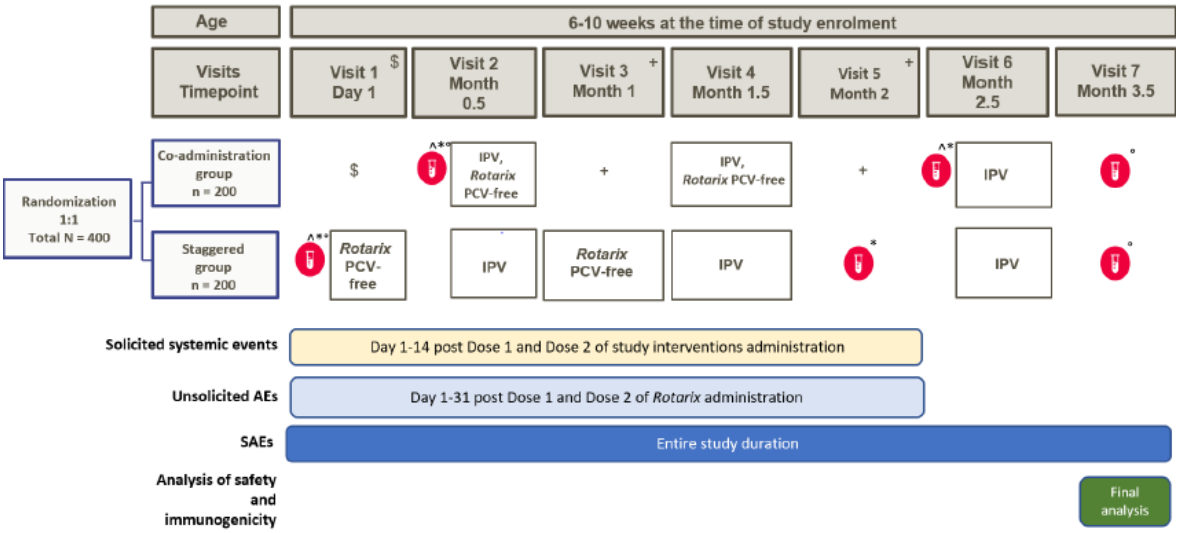
ROTA-098 is a Phase III, open-label, randomised, controlled study with 2 groups (see Figure 1 and Table 1).

The study population consisted of healthy male or female participants of Chinese origin, between and including 6-10 weeks (42-76 days) of age, at the time of first study intervention administration. The total duration of the study, per participant, was approximately 3.5 months.

This study was conducted at 5 centres that enrolled participants in China.

The study initiation date was 22 March 2024 (first participant first visit) and study completion date was 01 April 2025 (End of Study). The analyses presented in this report are based on a database lock date of 29 April 2025.

Figure 1. Study design overview (Protocol Amendment 1 Final, Figure 1)



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 (Section 1.3 of the Protocol) for Co-administration group. Note: For the Co-administration group, unsolicited AEs were collected from visit 2 till visit 6.
+ 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.

Table 1. Study groups, intervention and blinding (Protocol Amendment 1 Final, Table 6)

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 participants

Inclusion criteria

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

- Participants' parent(s)/Legally Acceptable Representative(s) (LAR), who, in the opinion of the investigator, can and will comply with the requirements of the protocol.
- Written or witnessed/thumb printed informed consent obtained from the parent(s)/LAR(s) of the participant prior to performance of any study specific procedure.
- Healthy participants as established by medical history and clinical examination before entering into the study.
- A male or female of Chinese origin, between and including, 6 and 10 weeks (42-76 days) of age at the time of study enrolment.
- Born after a gestation period of 36 to 42 weeks inclusive.

Exclusion criteria

The potential participant MUST NOT be included in the study if ANY exclusion criterion applies:

Medical conditions:

- History of any reaction or hypersensitivity likely to be exacerbated by any component of the study interventions.
- Any confirmed or suspected immunosuppressive or immunodeficient condition, based on medical history and physical examination (no laboratory testing required).
- Hypersensitivity to latex.
- History of severe combined immunodeficiency.
- History of seizures or progressive neurological disease.
- Family history of congenital or hereditary immunodeficiency.
- Uncorrected congenital malformation (such as Meckel's diverticulum) of the gastrointestinal tract that would predispose for intussusception (IS).
- History of IS.
- Major congenital defects, or serious chronic illness as assessed by the investigator.
- Any contraindications to IPV.
- Previous confirmed occurrence of rotavirus gastroenteritis (RVGE).
- History of poliomyelitis.
- Participants with confirmed or suspected Coronavirus Disease 2019 (COVID-19).

Prior/Concomitant therapy:

- Use of any investigational or non-registered product (drug, vaccine or invasive medical device) other than the study interventions during the period beginning 30 days before the first dose of study interventions (Day -29 to Day 1), or planned use during the study period.
- Planned administration/administration of a vaccine not foreseen by the study protocol in the period starting 30 days before the first dose and ending 30 days after the last dose of study interventions administration*, with the exception of the inactivated influenza vaccine, which is allowed at any time during the study and other licensed routine childhood vaccinations.
    - *In case emergency mass vaccination for an unforeseen public health threat (e.g., a pandemic) is recommended and/or organized by public health authorities outside the routine immunization program, the time period described above can be reduced if, necessary for that vaccine, provided it is used according to the local governmental recommendations and that the Sponsor is notified accordingly.
- Administration of long-acting immune-modifying drugs from birth or planned administration at any time during the study period (e.g., infliximab).

- Administration of immunoglobulins and/or any blood products or plasma derivatives from birth or planned administration 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 milligram/kilogram (kg)/day, or equivalent. Inhaled, intra-articular and topical steroids are allowed.
- Previous vaccination against RV.
- Previous vaccination against poliomyelitis.

Prior/Concurrent clinical study experience:

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

Other exclusions:

- Child in care.

Treatments

Table 2. Study intervention administered (Protocol Amendment 1 Final, Table 7)

Study intervention name:	Inactivated Poliomyelitis Vaccine Made From Sabin Strains (Vero Cells) (IPV)	*Rotarix* PCV-free (HRV PCV-free)
Study intervention formulation:	IPV1 (15 DAgU); IPV2 (45 DAgU); IPV3 (45 DAgU); Water for injections	HRV RIX4414 strain (≥ 1 x$10^{6.0}$ $CCID_{50}$); Sterile water
Presentation:	Suspension for injection	Oral suspension, Squeezable tube
Type:	Co-administered	Study
Product category:	Combination product*	Combination product*
Route of administration:	Intramuscular	Oral
Administration site:		
• **Location**	Refer to the SPM for more details	NA
• **Directionality**	Refer to the SPM for more details	NA
• **Laterality**	Refer to the SPM 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 SPM for more details	Refer to the SPM for more details
Manufacturer:	Beijing Biological Products Institute Co.,Ltd.	GSK

DAgU: D antigen unit; HRV: human rotavirus; IPV: inactivated poliovirus vaccine; mL: milliliter; NA: Not applicable; PCV: *Porcine circovirus*; PCV-free: no detection of PCV-1 and PCV-2 according to the limit of detection of the tests used; SPM: Study procedures manual
*Combining a biological product and device
Refer to Section 6.1 for schedule of study intervention administration.

"PCV-free" is defined as no detection of PCV-1 and PCV-2 according to the limit of detection of the tests used

Objectives, endpoints, and estimands

Table 3 summarises the study objectives, endpoints, and estimands.

Table 3. Study objectives, endpoints, and estimands (Protocol Amendment 1 Final, Table 5)

Objectives	Endpoints and estimands
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.

Refer to Section 8 for details on SAEs.

Refer to Section 9.3 and Section 9.4 for additional details on statistical analyses.

The study includes one confirmatory objective which is to demonstrate the immunological non-inferiority of IPV when co-administered with Rotarix PCV-free compared with IPV administered alone.

This primary objective is 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.

Seroconversion rate for IPV neutralizing antibodies 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., with anti-RV IgA Ab concentration <20 U/mL prior the first dose of Rotarix) and developed anti-RV IgA antibodies concentration ≥20 U/mL 1 month post Dose 2.

Sample size

A maximum of 400 participants (200 in the Co-administration group and 200 in the Staggered group) were to be randomised 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 were not be replaced.

The positive conversion rate is defined as the percentage of participants at 1 month post Dose 3 of immunization with:

- Neutralizing antibody (NAb) titer > 1:8 for participants with titer < 1:8 pre-immunization
  Or
- At least 4 times increase in NAb titer for participants with titer > 1:8 pre-immunization.

The definition of seroconversion used in this protocol differs slightly from the above definition of positive conversion by taking into account the expected decline in maternal antibodies between the pre-vaccination blood sample and the post IPV Dose 3 blood sample. By definition, the seroconversion rate will be at least equal to the positive conversion rate. Therefore, as a worst-case scenario, the observed positive conversion rates are used in the following sample size computations.

The power presented in Table 4 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 4. 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 (Coadministration group minus Staggered group) is greater than or equal to -10% (Protocol Amendment 1 Final, Table 16)

Ag	True seroconversion rate (Co-administrationgroup) *	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].

Randomisation and blinding (masking)

Randomisation to study intervention

Approximately 400 eligible participants were to be randomly assigned (1:1) to the 2 study groups (Co-administration and Staggered). The numbering of Rotarix PCV-free and IPV supplies was to be performed at GSK, using a block scheme randomisation in MATerial EXcellence, a program developed by GSK. Entire blocks were to be shipped to the study centres/warehouse(s). To allow GSK to take advantage of greater rates of recruitment than anticipated in this study and to thus reduce the overall study recruitment period, an over-randomisation of supplies was to be prepared.

Intervention allocation to the participant

The system's randomisation algorithm used a minimisation procedure accounting for centre and the study as a whole as minimisation factors. Minimisation factors had equal weight in the minimisation algorithm. Once a participant identification number was allocated, the randomisation system determined study group and provided the study intervention number to be used for the first dose. The study intervention number(s) to be used for subsequent dosing was to be provided by the same automated Internet-based system (Source Data Base for Internet Randomisation [SBIR]).

Blinding and unblinding

The study was conducted in an open-label manner with respect to Rotarix PCV-free and IPV.

Statistical methods

Statistical hypotheses

The study includes one confirmatory objective. The non-inferiority margin associated with the objective is provided in Table 5.

Table 5. Study objective and null hypothesis (Protocol Amendment 1 Final, Table 14)

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 was 2.5%. The primary objective was 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.

Analysis Sets

Table 6. Analysis sets (Protocol Amendment 1 Final, Table 15)

Analysis set	Description
Screened	All participants who were screened for eligibility.
Enrolled Set	• All participants who entered the study (who were randomized or received study intervention or underwent a post-screening study procedure). • Note: screening failures (who never passed screening even if rescreened) and participants screened but never enrolled into the study (Met eligibility but not needed) are excluded from the Enrolled Set as they did not enter the study.
Exposed Set (ES)	All participants with at least 1 dose of any of the 2 study interventions documented. Analysis per group is based on the administered intervention.
Per Protocol Set (PPS)	All eligible participants from the ES who meet all the following requirements: • who received the study interventions according to their random assignment and the expected study intervention administration schedule (see Table 3 and Table 4), 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.

* immunosuppressive or immunodeficient conditions identified before Visit 7.

Statistical analyses

Immunogenicity:

The analysis of immunogenicity were primarily based on the PPS. Within groups assessment for the PPS was repeated by sex and study sites.

Since, more than 5% of the ES participants with immunogenicity results after study intervention were excluded from the PPS and hence, the confirmatory analyses were repeated on the ES, as planned per protocol.

Primary endpoint analysis

Within groups assessment:

For each group, before Dose 1 and at Visit 7 (1 month post Dose 3 [IPV]) time point:

• Seropositivity (before Dose 1 and at Visit 7) and seroconversion rates for IPV (at Visit 7) and their exact 95% confidence interval (CI) were computed using the method of Clopper and Pearson.

• For participants who were seropositive before Dose 1 of IPV, the expected decline in maternal antibodies was accounted.

Between groups assessments:

The Mittienen and Nurminen 95% CI for the group difference (Co-administration group minus Staggered group) in the seroconversion rate of anti-poliovirus types 1, 2 and 3 antibodies at Visit 7 were computed.

Secondary endpoint analysis

Within groups assessment:

The following calculations was to 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) were computed using the method of Clopper and Pearson.

• The percentage of participants with anti-poliovirus 1, 2, and 3 neutralizing antibody titers ≥1:8 and ≥1:64 and their exact 95% CI for each group at 1 month post Dose 3 were computed.

• GMTs were applicable and their exact 95% CIs were 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 were computed.

• The distribution of anti-RV IgA Ab concentrations 1 month post Dose 2 and anti-poliovirus titers 1 month post Dose 3 were displayed using reverse cumulative curves for the PPS.

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 antibody 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 were computed.

GMC/GMT concentrations/titers below the assay cut-off were given an arbitrary value of half the assay cut-off for the purpose of GMC/GMT calculation. For a given participant and a given immunogenicity measurement time point, missing or non-evaluable measurements were not replaced.

Safety:

Safety analysis was performed on the ES.

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

Standardized electronic Case Report Form (eCRF) were used for safety data collected. Solicited systemic events were collected using a diary card for the data collection.

The following calculations were to 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 were to be computed, along

with exact 95% CI. The same calculations were to 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 were to 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 were to 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 were to also be summarized with threshold defined by half degree increment.
- The verbatim reports of unsolicited AEs were to be reviewed by a physician and were to be coded according to MedDRA. Every verbatim term was to 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 was to be tabulated by Preferred Term. The same calculations were to 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 was to 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 was to be tabulated by study group and by preferred term.
- SAEs and dropouts due to AEs were to be described in detail.

Immunogenicity assessment

Biological samples

Table 7. Biological samples (Protocol Amendment 1 Final, Table 8)

Group	Sample type	Quantity	Unit	Timepoint
Co-administration	Blood*	At least 2**	mL	Visit 2 (Month 0.5)
				Visit 6 (Month 2.5)
				Visit 7 (Month 3.5)
Staggered group	Blood*	At least 2**	mL	Visit 1 (Day 1)
				Visit 5 (Month 2)
				Visit 7 (Month 3.5)

mL: milliliter
*Blood sampling to be done before study intervention administration.
**Volume of the blood sample should be between 2 and 2.5 mL.

Table 8. Intervals between study visits for Co-administration group (SAP, Table 4)

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 9. Intervals between study visits for Staggered group (SAP, Table 5)

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).

Laboratory assays

Table 10. Laboratory assays (Protocol Amendment 1 Final, Table 9)

Test Classification	System	Component	Method	Laboratory*
Humoral Immunity (Antibody determination)	Serum	Rotavirus Ab, IgA	ELISA	GSK designated lab in China
		IPV Ab, type 1 IPV Ab, type 2 IPV Ab, type 3	Microneutralization assay	GSK designated lab in China

Ab: Antibody; IgA: Immunoglobulin A; IPV: Inactivated poliovirus vaccine; ELISA: Enzyme Linked Immunosorbent Assay

*Refer to the list of clinical laboratories for details.

Anti-RV IgA antibody determination:

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

Anti-IPV type 1, type 2 and type 3 antibodies determination:

The polio microneutralization assay measures neutralizing antibody titers to poliovirus types 1, 2, and 3 using 96-well microtiter plates. The principle of the test is that the anti-poliovirus antibodies in a serum sample will bind to the virus and block infection of susceptible cells. Because poliovirus is cytopathic, virus that is not bound by antibody infects and lyses cells. The amount of neutralizing antibody is quantitated as a titer based on the last serum dilution to protect susceptible cell culture wells from poliovirus infection and cytopathic effect.

Immunological read-outs

Table 11. Immunological read-out ((Protocol Amendment 1 Final, Table 10)

Blood sampling timepoint		Subset name	No. participants	Component
Type of contact and timepoint	Sampling timepoint			
Visit 1 (Day 1)	Pre-first Dose administration	Staggered group	200	Rotavirus Ab, IgA IPV Ab, type 1 IPV Ab, type 2 IPV Ab, type 3
Visit 2 (Month 0.5)	Pre-first Dose administration	Co-administration group	200	Rotavirus Ab, IgA IPV Ab, type 1 IPV Ab, type 2 IPV Ab, type 3
Visit 5 (Month 2)	Post Dose 2 of *Rotarix* PCV-free	Staggered group	200	Rotavirus Ab, IgA
Visit 6 (Month 2.5)	Post Dose 2 of *Rotarix* PCV-free	Co-administration group	200	Rotavirus Ab, IgA
Visit 7 (Month 3.5)	Post Dose 3 of IPV	All participants (Co-administration group + Staggered group)	400	IPV Ab, type 1 IPV Ab, type 2 IPV Ab, type 3

Ab: Antibody; 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.

Assessor's comment

Study ROTA-098 was a PAM, open label, randomised, controlled, Phase 3 conducted in 5 different sites in China 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 (referred hereafter as Rotarix PCV-free) in Chinese healthy infants 6-10 weeks of age. The active control group – "Staggered group" – did not receive concomitant administration of IPV with Rotarix PCV-free, but sequential administrations of both vaccines. The targeted sample size was 200 participants in each group. The total duration of the study, per participant, would be approximately 3.5 months.

In the Co-administration group, participants received Rotarix PCV-free co-administered with IPV at Month 0.5 and Month 1.5, and the third dose of IPV at Month 2.5. In the Staggered group, participants received Rotarix PCV-free at Day 1 and Month 1, and IPV at Month 0.5, Month 1.5, and Month 2.5.

The primary objective was the demonstration of non-inferior neutralising antibody responses (in terms of seroconversion rates) specific to polioviruses 1, 2 and 3 following administration of IPV with Rotarix PCV-free versus IPV alone, at 1 month post Dose 3. To be achieved, the lower limit of the 2-sided 95% CI for the group difference (Co-administration group minus Staggered group) in seroconversion rate had to be greater than or equal to -10% for each of the anti-poliovirus types 1, 2 and 3 antibodies. The non-inferiority margin associated with the primary confirmatory objective for non-inferiority is considered acceptable. Secondary objectives included further characterization of humoral responses to IPV and Rotarix PCV-free vaccinations.

Methods are overall acceptable.

Results

Participant flow

Participant disposition

Refer to Figure 2.

The study enrolled 400 participants (200 participants per group in 1:1 ratio), and 392 participants were randomised and received at least 1 dose of study intervention.

The Exposed set (ES) for safety analysis included 193 participants in the Co-administration group and 199 participants in the Staggered group, respectively.

Of 193 participants in the ES of the Co-administration group, 191 participants (99.0%) received both doses of Rotarix PCV-free and 190 participants (98.4%) received all 3 doses of IPV. All participants (100%) received at least 1 dose of both study interventions. Of the participants that received at least 1 dose, 189 participants (97.9%) completed the study, and 4 participants (2.1%) were withdrawn from the study (see Table 12). Participant's "migration/moved from the study area" was the most common reason for withdrawal from study (3 participants [1.6%]).

Of 199 participants in the ES of the Staggered group, 192 participants (96.5%) received both doses of Rotarix PCV-free and 188 participants (94.5%) received all 3 doses of IPV. All participants (100%) received at least 1 dose of Rotarix PCV-free, and 192 participants (96.5%) received at least 1 dose of

IPV. Of these participants, 186 participants (93.5%) completed the study, and 13 participants (6.5%) were withdrawn from the study (see Table 12). Participant's "migration/moved from the study area" was the most common reason for withdrawal from study (4 participants [2.0%]).

Figure 2. Participant disposition (CSR, Figure 2)

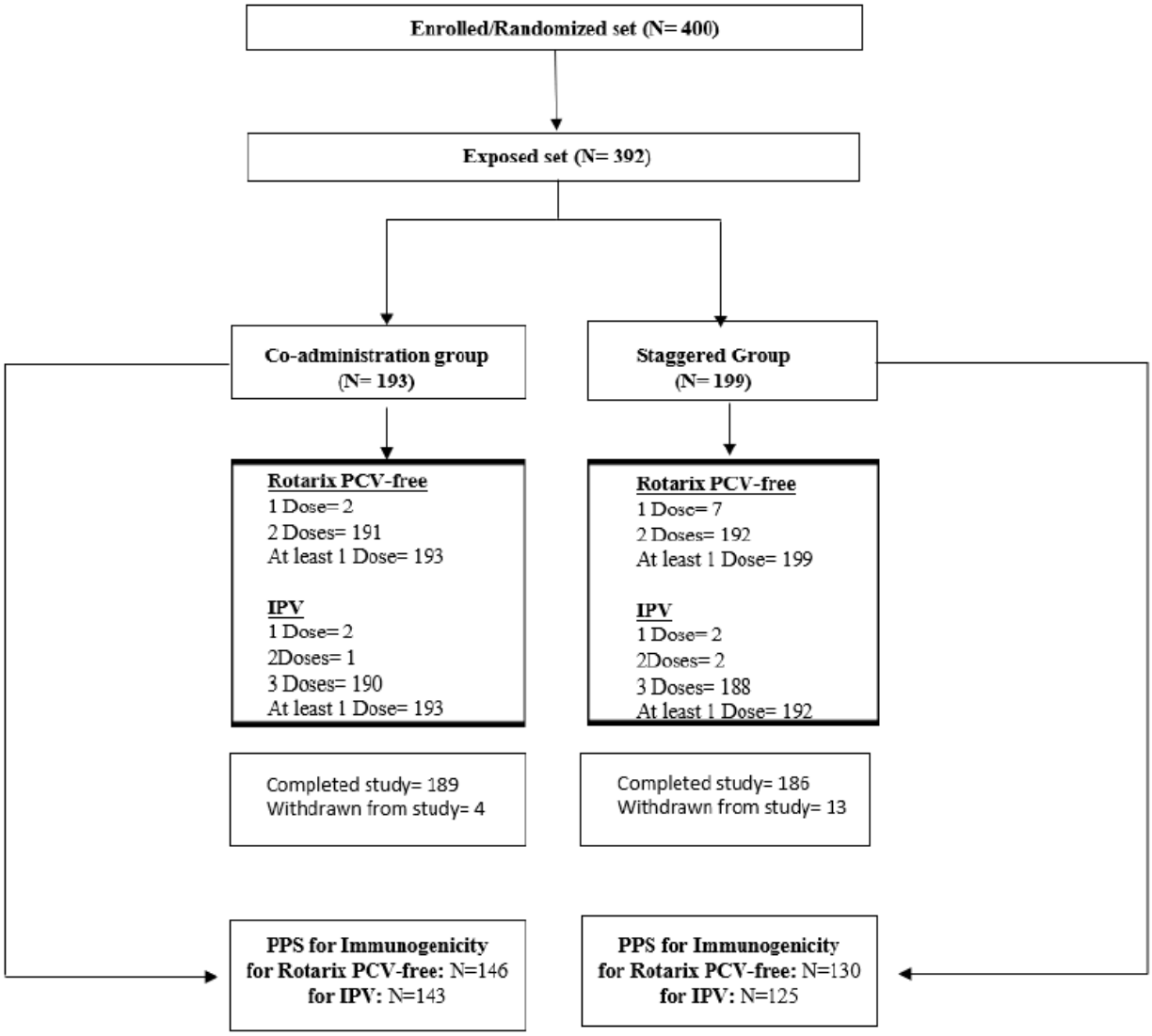


Table 12. Summary of study completion with reasons for withdrawal - Exposed Set (CSR, Table 3)

	Staggered N=199		Co-administration N=193		Total N=392	
	n	%	n	%	n	%
Completed the study	186	93.5	189	97.9	375	95.7
Withdrawn from the study	13	6.5	4	2.1	17	4.3
Primary reason for withdrawal						
Unsolicited Non-Serious Adverse Event	0	0.0	0	0.0	0	0.0
Solicited Adverse Event	1	0.5	0	0.0	1	0.3
Consent Withdrawal, Not Due To An Adverse Event	0	0.0	0	0.0	0	0.0
Migrated / Moved From The Study Area	4	2.0	3	1.6	7	1.8
Lost To Follow-Up	1	0.5	0	0.0	1	0.3
Not Willing To Participate This Visit	0	0.0	0	0.0	0	0.0
Sponsor Study Termination	0	0.0	0	0.0	0	0.0
Other	7	3.5	0	0.0	7	1.8
Adverse Event Requiring Expedited Reporting	0	0.0	1	0.5	1	0.3

Completed = number of participants who completed the last study visit/contact
Withdrawn = number of participants who did not complete their last visit/contact
N = number of participants
n/% = number / percentage of participants in a given category
Source: Table 8.1.12

Protocol deviations

Important protocol deviations leading to elimination from analyses were reported in 50 participants (25.0%) in the Co-administration group, and 70 participants (35.0%) in the Staggered group, respectively (see Table 13). The most common category of protocol deviations leading to elimination from ES in both the Co-administration and Staggered groups were "assessment or time point completion" (38 participants [19.0%] and 61 participants [30.5%], respectively), and "visit completion" (27 participants [13.5%] and 47 participants [23.5%], respectively).

The main reasons for elimination from ES to the PP set for anti-poliovirus vaccination and for Rotarix PCV-free vaccination were also "out of window treatment administration" followed by "out of window vist/phone contact "and biological sample specimen procedures" (refer to Table 8.1.2 and Table 8.1.3 of the CSR).

Table 13. Summary of important protocol deviations leading to elimination from any analyses – Enrolled Set (CSR, Table 4)

Category Sub category	Staggered N=200			Co-administration N=200			Total N=400		
	occ	n	%	occ	n	%	occ	n	%
At least one important protocol deviation	158	70	35.0	77	50	25.0	235	120	30.0
Assessment or time point completion	115	61	30.5	52	38	19.0	167	99	24.8
Out of window treatment administration	104	52	26.0	47	35	17.5	151	87	21.8
Out of window assessment	5	5	2.5	3	3	1.5	8	8	2.0
Incomplete assessment	2	2	1.0	2	2	1.0	4	4	1.0
Missed assessment	4	4	2.0	0	0	0.0	4	4	1.0
Visit completion	33	47	23.5	16	27	13.5	49	74	18.5
Out of window visit/phone contact	27	45	22.5	16	27	13.5	43	72	18.0
Missed visit/phone contact	5	4	2.0	0	0	0.0	5	4	1.0
Other visit window deviation	1	1	0.5	0	0	0.0	1	1	0.3
Study procedures	5	5	2.5	6	6	3.0	11	11	2.8
Biological sample specimen procedures	5	5	2.5	6	6	3.0	11	11	2.8
Wrong study treatment/administration/dose	2	2	1.0	2	2	1.0	4	4	1.0
Study treatment not administered per protocol	2	2	1.0	2	2	1.0	4	4	1.0
Eligibility criteria not met	2	2	1.0	0	0	0.0	2	2	0.5
Eligibility criteria not met	2	2	1.0	0	0	0.0	2	2	0.5
Excluded medication, vaccine or device	1	1	0.5	1	1	0.5	2	2	0.5
Medication, excluded by the protocol, was administered	1	1	0.5	0	0	0.0	1	1	0.3
Vaccine, excluded by the protocol, was administered	0	0	0.0	1	1	0.5	1	1	0.3

Occ = number of occurrences = number of important protocol deviations
N = number of participants
n/% = number / percentage of participants in a given category
Source: Table 8.1.13

Number analysed

Number of participants with available results in the Staggered and Co-administration groups for seroconversion rates for poliovirus types 1, 2, and 3 neutralizing antibody titers equal or above 1:8, equal to or above 1:64 and Ratio of GMT 1 month post Dose 3 (per Protocol Set for immunogenicity for IPV) was 125 participants and 143 participants respectively.

Number of participants with available results in the Staggered and Co-administration groups for seroconversion rates for anti-RV IgA antibody titers 1 month post Dose 2 (per Protocol Set for immunogenicity for Rotarix PCV-free) was 130 participants and 146 participants respectively.

Assessor's comment

The proportions of randomised participants that were not evaluable and eliminated for the analysis of the immunogenicity to inactivated poliovirus vaccine (PP set for IPV), i.e., the primary analysis addressing the confirmatory objective, were unexpectedly high with 26% (1-143/193) and 37.2% (1-125/199) for the Co-administration group and Staggered group, respectively. These percentages were above the assumption of percentage of non-evaluable enrolled participants for sample size calculation (20%). Comparable proportions of participants were excluded from the PP set for Rotarix-PCV free vaccination.

This high rate of protocol deviations is essentially due to non-compliance of "out of window treatment administration" and "out of window visits". The intervals between administration of dose 1 and dose 2 and of dose 2 and dose 3 were 30 days, with an allowed interval (during special circumstances) of 28 to 60 days which is considered as a wide/quite flexible interval. The interval between administration of dose 3 and blood sampling was to respect a 30-day timing, with an allowed interval of 30-36 days. Furthermore, a higher proportion of protocol deviations was observed in the Staggered group compared to the Co-administration group.

The reasons for these high rates of protocol deviations, particularly of "out of window treatment administration" although not very stringent, and for this difference in proportions between groups, were not discussed by the MAH.

Because of this high rate of protocol deviations, the sample size of 160 evaluable participants defined to reach the 90% statistical power for the non-inferiority null hypothesis was not reached. This constitutes a major limitation regarding interpretation of the primary endpoint. The findings will present a relatively low strength of evidence to demonstrate the non-inferiority of co-administration versus staggered administration of IPV-Rotarix dosing in healthy Chinese infants receiving 1st dose between 6-10 weeks of age.

The primary analysis was also performed on the ES. This is because, as defined in the protocol, sensitivity analyses were to be performed if more than 5% of the ES participants with immunogenicity results after study intervention are excluded from the PPS.

Recruitment

The first subject was enrolled on 22 March 2024 (first participant first visit) and the last subject completed on 22 October 2024 (last participant last visit). The analyses presented in this report are based on a database lock date of 29 April 2025. The study was conducted in 5 different sites in China.

Conduct of the Study

Changes in planned analyses prior to unblinding or database lock

Changes made after the final SAP and before the database lock are described below:

The percentage of doses and participants reporting at least 1 AE (solicited or unsolicited) during the 14-day follow-up period were to be computed as described in SAP Section 4.5. The same calculations were planned for Grade 3 AEs and AEs leading to medically attended visits. However, the combination of solicited and unsolicited events within the same summary table was not deemed to be clinically

meaningful and therefore these analyses were not performed. All solicited and unsolicited events are summarized in separate tables.

Changes following study unblinding/database lock and post-hoc analyses

No changes were made following database lock.

Baseline data

Demographic and baseline characteristics were similar between both groups. Overall, the mean (standard deviation) age at first dose was 8.1 (1.3) weeks. The number of female and male participants were comparable in both the Co-administration (92 females [47.7%] and 101 males [52.3%]) and Staggered (96 females [48.2%] and 103 males [51.8%]) groups. The demographic characteristics for the PPS populations were similar to those of the ES population (see Table 8.1.4, 8.1.5 and 8.1.6).

Table 14. Summary of demography and baseline characteristics – Exposed Set (CSR, Table 5)

	Staggered N=199		Co-administration N=193		Total N=392	
	Value or n	%	Value or n	%	Value or n	%
Age (weeks) at informed consent						
n	199		193		392	
Mean	8.1		8.2		8.1	
Standard Deviation	1.2		1.3		1.3	
Median	8.0		8.1		8.0	
Minimum	6.0		6.0		6.0	
Maximum	10.9		10.7		10.9	
Age (weeks) at first dose						
n	199		193		392	
Mean	8.1		10.5		9.3	
Standard Deviation	1.3		1.3		1.8	
Median	8.0		10.4		9.3	
Minimum	6.0		8.6		6.0	
Maximum	10.9		14.9		14.9	
Country						
China	199	100	193	100	392	100
Center ID						
257119	27	13.6	26	13.5	53	13.5
261074	37	18.6	37	19.2	74	18.9
262708	34	17.1	33	17.1	67	17.1
268131	51	25.6	49	25.4	100	25.5
268291	50	25.1	48	24.9	98	25.0
Sex						
Male	103	51.8	101	52.3	204	52.0
Female	96	48.2	92	47.7	188	48.0
Ethnicity						
Not Hispanic or Latino	199	100	193	100	392	100
Race						
Asian	199	100	193	100	392	100
Length (cm)						
n	199		193		392	
Mean	57.6		57.5		57.6	
Standard Deviation	2.4		2.4		2.4	
Median	58.0		57.0		58.0	
Minimum	51		52		51	
Maximum	63		64		64	
Weight (gr)						
n	199		193		392	
Mean	5315.6		5423.4		5368.7	
Standard Deviation	666.4		741.2		705.4	
Median	5275.0		5390.0		5300.0	
Minimum	3700		3800		3700	
Maximum	7200		7980		7980	

N = number of participants
n/% = number / percentage of participants in a given category
Source: Table 8.1.4

The percentage of participants (per participant) in ES who received concomitant medication (including anti-pyretic drugs) during the 14-day period (Day 1-Day 14) was lower in the Co-administration group (26.4% [15.0%]) compared to the Staggered group (45.2% [23.1%]) (see Table 8.1.7 of the CSR).

The incidence of concomitant medication use during the 31-day period (Day 1-Day 31) following each dose was mostly similar between both groups (see Table 8.1.8 of the CSR).

Immunogenicity results

Analyses on the immunogenicity endpoint were conducted primarily on the PPS. Immunogenicity summaries were also generated by sex and study sites. More than 5% of the ES participants with immunogenicity results after study intervention were excluded from the PPS and hence, the confirmatory analysis was repeated on the ES.

Primary objective

The primary objective (confirmatory) was met. In terms of anti-poliovirus serotypes neutralizing antibody seroconversion rates at 1 month post Dose 3 of the IPV study intervention, the Co-administration group was shown to be non-inferior to the Staggered group, as the LL of the 2-sided 95% CI for the group difference (Co-administration group minus Staggered group) in seroconversion rate was greater than or equal to -10% for each of the anti-poliovirus types 1, 2 and 3 antibodies.

- At 1 month post Dose 3, the difference in seroconversion rate between the Co-administration group and the Staggered group for anti-poliovirus type 1 neutralizing antibody was 0.10 (LL: -3.14; UL: 3.76).
- At 1 month post Dose 3, the difference in seroconversion rate between the Co-administration group and the Staggered group for anti-poliovirus type 2 neutralizing antibody was -0.70 (LL: -3.86; UL: 2.30).
- At 1 month post Dose 3, the difference in seroconversion rate between the Co-administration group and the Staggered group for anti-poliovirus type 3 neutralizing antibody was 0 (LL: -2.63; UL: 2.99).

The immunological response for IPV in ES was comparable to PPS.

Assessor's comment

The primary objective was the demonstration of non-inferior neutralising antibody responses (seroconversion rates) specific to polioviruses 1, 2 and 3 following administration of IPV with Rotarix PCV-free versus IPV alone. In the Co-administration group, participants received Rotarix PCV-free co-administered with IPV at Month 0.5 and Month 1.5, and the third dose of IPV at Month 2.5. In the Staggered group, participants received Rotarix PCV-free at Day 1 and Month 1, and IPV at Month 0.5, Month 1.5, and Month 2.5.

Immunogenicity data specific to polioviruses 1, 2, and 3 at 1 month post Dose 3 to address the primary objective were available for n=143 and n=125 participants in the Co-administration group and in the Staggered group respectively (PP set for IPV).

The primary (confirmatory) objective was met but, as mentioned above, without sufficient statistical power. Nevertheless, and consistent with previous findings, immunogenicity data of anti-poliovirus neutralising antibodies (in terms of both SRC and GMTs) suggest overall similar immune responses when co-administrated versus single administration (Staggered administration group). The reverse cumulative distribution curves for anti-poliovirus neutralizing antibody titres 1 month post Dose 3 confirm these findings (see below, secondary objectives and Figures 8.2.6 of the CSR). The humoral responses for IPV in ES was comparable to PPS.

Secondary objectives

Regarding the IPV immunogenicity secondary objective (Table 15),

For anti-poliovirus serotype 1 neutralizing Ab titer at 1 month post Dose 3 of IPV:

- GMTs were 1374.44 (95% CI: 1148.21, 1645.25) in the Co-administration group and 1369.71 (95% CI: 1140.65, 1644.78) in the Staggered group. The GMT ratio (Co-administration/Staggered) was 1.00 (95% CI: 0.78, 1.30).
- The percentage of participants with titer ≥1:8 was 100% in both the Co-administration and Staggered groups.
- The percentage of participants with titer ≥1:64 was 100% in both the Co-administration and Staggered groups.

For anti-poliovirus serotype 2 neutralizing Ab titer at 1 month post Dose 3 of IPV:

- GMTs were 190.44 (95% CI: 164.90, 219.94) in the Co-administration group and 194.95 (95% CI: 168.13, 226.06) in the Staggered group. The GMT ratio (Co-administration/Staggered) was 0.98 (95%CI: 0.79, 1.20).
- The percentage of participants with titer ≥1:8 was 100% in both the Co-administration and Staggered groups.
- The percentage of participants with titer ≥1:64 was 91.6% in the Co-administration group and 91.2% in the Staggered group.

For anti-poliovirus serotype 3 neutralizing Ab titer at 1 month post Dose 3 of IPV:

- GMTs were 450.15 (95% CI: 395.92, 511.79) in the Co-administration group and 451.36 (95% CI: 389.37, 523.23) in the Staggered group. The GMT ratio (Co-administration/Staggered) was 1.00 (95%CI: 0.82, 1.21).
- The percentage of participants with titer ≥1:8 was 100% in both the Co-administration and Staggered groups.
- The percentage of participants with titer ≥1:64 was 99.3% in the Co-administration group and 98.4% in the Staggered group.

The immunological responses for IPV in ES were comparable to PPS (Table 8.2.1.3 in the CSR).

Table 15. Number and percentage of participants with anti-poliovirus types 1, 2 and 3 neutralizing Ab titers equal to or above 1:8, also equal to or above 1:64 and GMT at pre-vaccination, 1 month post Dose 3 - Per Protocol Set (IPV) (CSR, Table 8.2.1)

			Staggered				Co-administration			
					95% CI				95% CI	
Antibody	Time point		n	% or value	LL	UL	n	% or value	LL	UL
anti-poliovirus serotype1	PRE	N	125				143			
		% >= 8	68	54.4	45.3	63.3	59	41.3	33.1	49.8
		% >= 64	19	15.2	9.4	22.7	11	7.7	3.9	13.3
		GMT		12.16	9.60	15.39		8.37	6.96	10.07
	PIII(M3.5)	N	125				143			
		% >= 8	125	100	97.1	100	143	100	97.5	100
		% >= 64	125	100	97.1	100	143	100	97.5	100
		N of seronegative at PRE	57	45.6	36.7	54.7	84	58.7	50.2	66.9
		N of seropositive at PRE	68	54.4	45.3	63.3	59	41.3	33.1	49.8
		N of adjusted seropositive at PRE	68	54.4	45.3	63.3	59	41.3	33.1	49.8
		Seroconversion rate	124	99.2	95.6	100	142	99.3	96.2	100
		GMT		1369.71	1140.65	1644.78		1374.44	1148.21	1645.25

			Staggered				Co-administration			
					95% CI				95% CI	
Antibody	Time point		n	% or value	LL	UL	n	% or value	LL	UL
anti-poliovirus serotype2	PRE	N	125				143			
		% >= 8	57	45.6	36.7	54.7	58	40.6	32.4	49.1
		% >= 64	6	4.8	1.8	10.2	2	1.4	0.2	5.0
		GMT		8.30	7.01	9.84		6.74	5.93	7.65
	PIII(M3.5)	N	125				143			
		% >= 8	125	100	97.1	100	143	100	97.5	100
		% >= 64	114	91.2	84.8	95.5	131	91.6	85.8	95.6
		N of seronegative at PRE	68	54.4	45.3	63.3	85	59.4	50.9	67.6
		N of seropositive at PRE	57	45.6	36.7	54.7	58	40.6	32.4	49.1
		N of adjusted seropositive at PRE	57	45.6	36.7	54.7	58	40.6	32.4	49.1
		Seroconversion rate	125	100	97.1	100	142	99.3	96.2	100
		GMT		194.95	168.13	226.06		190.44	164.90	219.94

			Staggered				Co-administration			
					95% CI				95% CI	
Antibody	Time point		n	% or value	LL	UL	n	% or value	LL	UL
anti-poliovirus serotype3	PRE	N	125				143			
		% >= 8	21	16.8	10.7	24.5	14	9.8	5.5	15.9
		% >= 64	4	3.2	0.9	8.0	1	0.7	0.0	3.8
		GMT		5.22	4.61	5.91		4.62	4.26	5.01
	PIII(M3.5)	N	125				143			
		% >= 8	125	100	97.1	100	143	100	97.5	100
		% >= 64	123	98.4	94.3	99.8	142	99.3	96.2	100
		N of seronegative at PRE	104	83.2	75.5	89.3	129	90.2	84.1	94.5
		N of seropositive at PRE	21	16.8	10.7	24.5	14	9.8	5.5	15.9
		N of adjusted seropositive at PRE	21	16.8	10.7	24.5	14	9.8	5.5	15.9
		Seroconversion rate	125	100	97.1	100	143	100	97.5	100
		GMT		451.36	389.37	523.23		450.15	395.92	511.79

GMT = geometric mean titer
N = Number of participants with available results
n/% = number / percentage of participants with concentration within the specified range
95% CI = 95% confidence interval. LL = Lower Limit , UL = Upper Limit
Seroconversion rate = percentage of participants who are considered seroconverted at visit 7 as per SAP section 4.1.1 and 4.2.1 (PRE seronegative (IPV Ab titer < 8) and developed IPV Ab titer >= 8 at Visit 7, or adjusted for maternal antibody decay PRE seropositive who developed >= 4 fold increase of titer at visit 7)
PRE= Day 1 for Staggered group and Month 0.5 for Co-administration group
PIII(M3.5) = 1 month post dose 3 of IPV (anti-poliovirus)

Assessor's comment

At 1 month post Dose 3 of IPV administration, an increase in the immune response in terms of anti-poliovirus serotypes 1, 2, and 3 neutralizing antibody titers compared to baseline was observed for IPV both in the Co-administration group and Staggered group. Anti-poliovirus types 1, 2 and 3 neutralizing antibody GMTs at 1 month post Dose 3 of IPV in the Co-administration and Staggered groups were within similar ranges. The humoral responses for IPV in ES was comparable to PPS.

Regarding the secondary objective Rotarix PCV-free immunogenicity (Table 16),

- The seroconversion rate (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), was 90.4% (95% CI: 84.4, 94.7) in the Co-administration group and 78.5% (95% CI: 70.4, 85.2) in the Staggered group.
- Anti-RV IgA Ab GMCs at 1 month post Dose 2, anti-RV IgA Ab GMC was 222.15 (95% CI: 165.98, 297.34) in the Co-administration group and 160.59 (95% CI: 114.49, 225.25) in the Staggered group.
- Percentage of participants with anti-RV IgA Ab concentrations ≥90 U/mL at 1 month post Dose 2 was 68.5% (95% CI: 60.3, 75.9) in the Co-administration group and 63.8% (95% CI: 55.0, 72.1) in the Staggered group.

The immunological response for Rotarix PCV-free in ES was comparable to PPS (Table 8.2.2.3 of CSR).

Table 16. Number and percentage of participants with anti-RV IgA antibody concentrations equal to or above 20 U/mL, also equal to or above 90 U/mL and GMC at 1 month post Dose 2 - Per Protocol Set (CSR, Table 8.2.2)

			Staggered				Co-administration			
					95% CI				95% CI	
Antibody	Time point		n	% or value	LL	UL	n	% or value	LL	UL
Rotavirus IgA Antibody	PII(M2)	N	130				146			
		% >= 20 U/mL	102	78.5	70.4	85.2	132	90.4	84.4	94.7
		% >= 90 U/mL	83	63.8	55.0	72.1	100	68.5	60.3	75.9
		GMC		160.59	114.49	225.25		222.15	165.98	297.34

GMC = geometric mean concentration
N = Number of participants with available results who were seronegative at baseline (pre-dose 1)
n/% = number / percentage of participants with concentration within the specified range
95% CI = 95% confidence interval. LL = Lower Limit , UL = Upper Limit
PII(M2) = 1 month post dose 2 of HRV

Assessor's comment

At 1 month post Dose 2 of Rotarix PCV-free administration, an increase in the immune response in terms of anti-RV IgA antibody concentration compared to baseline was observed for Rotarix PCV-free both in the Co-administration group and Staggered group.

A trend for higher seroconversion rate was observed in the Co-administration group (90.4% [95% CI: 84.4, 94.7]) as compared to in the Staggered group (78.5% [95% CI: 70.4, 85.2]). This trend was less pronounced in terms of anti-RV IgA antibody GMC, with overlapping 95% CI (GMC of 222.15 [95% CI: 165.98, 297.3] in the Co-administration group and of 160.59 [95% CI: 114.49, 225.2] in the Staggered group). The humoral response for Rotarix PCV-free in ES was comparable to PPS.

Safety results

The analysis of safety was performed on the ES. Compliance in completing the solicited systemic AE information following Dose 1 and Dose 2 administration in the Co-administration group was 100%. Compliance in completing the solicited systemic AE information following Dose 1, Dose 2, Dose 3, and Dose 4 administration in the Staggered group was 99.0%, 100%, 99.5%, and 99.5%, respectively.

Solicited systemic events

During the 14-day (Day 1-Day 14) follow-up period, the solicited systemic events reported (per participant) after dose 1 and dose 2 of the study interventions (both Rotarix PCV-free and IPV), are presented below:

- Fever was the most frequently reported solicited systemic event in both the Co-administration and Staggered groups (21.8% of participants and 48.2% of participants, respectively). Majority of the participants had fever <38.5°C.
- Cough/runny nose was the most frequently reported solicited systemic event that led to medically attended visits in both the Co-administration and Staggered groups (10.9% of participants and 18.8% of participants, respectively).
- Grade 3 solicited systemic events were reported in a small percentage of participants in both the Co-administration group (ranging between 0.0% of participants to 3.6% of participants) and the Staggered group (ranging between 0.0% of participants to 3.0% of participants). The duration of each solicited systemic event was mostly similar between the Co-administration and Staggered groups. The median duration (per dose) for solicited systemic events ranged between 1.0 day to 5.0 days in both groups. Per dose, the median duration was highest for cough/runny nose (5.0 days) in Co-administration group, and loss of appetite (3.5 days) in Staggered group.

A total of 16 solicited systemic events (8%) in the Co-administration group and 9 solicited systemic events (2%) in the Staggered group were ongoing after the 14-days solicited period (see Table 8.3.4 of the CSR). Most of these events were cough/runny nose (9 events in the Co-administration group and 7 events in the Staggered group) with the median duration of 25.0 days in the Co-administration group and 21.0 days in the Staggered group. As of EoS, all these events were resolved.

Unsolicited AEs

During the 31 days (Day 1-Day 31) follow-up period, the unsolicited AEs collected after each dose of Rotarix PCV-free study intervention, are presented below:

- Unsolicited AEs were reported in 38.3% of participants in the Co-administration group and 33.2% of participants in the Staggered group.
- Unsolicited AEs reported in ≥5% of participants in either Co-administration group or Staggered group were pyrexia, pneumonia, upper respiratory tract infection and cough.
- Pneumonia and cough were the most frequently reported unsolicited AEs that led to medically attended visits (6.2% and 5.2% of participants, respectively, in the Co-administration group, and 6.0% and 0.0% of participants, respectively, in the Staggered group).
- Grade 3 unsolicited AEs were reported in 2 participants (1.0%) of the Co-administration group and 1 participant (0.5%) of the Staggered group. The Grade 3 unsolicited AEs reported among

participants of Co-administration group were diarrhoea, pertussis, and pneumonia. The Grade 3 unsolicited AEs reported among participants of Staggered group were bronchitis, and myocardial injury.

- None of the reported non-serious unsolicited AEs were considered causally related to Rotarix PCV-free study intervention by the investigator in participants of Co-administration groups. Nine non-serious unsolicited AEs reported in 8 participants (4.0%) were considered causally related to Rotarix PCV-free study intervention by the investigator in participants of Staggered group.

Serious adverse events

An overview of safety of Rotarix PCV-free and IPV in terms of SAEs reported during the entire study period is provided below:

- SAEs were reported in 15.5% of participants in the Co-administration group and 15.1% of participants in the Staggered group. Pneumonia and febrile infection were the most frequently reported SAEs in both the Co-administration group (8.3% and 2.6%, respectively) and the Staggered group (8.5% and 2.0%, respectively).
- One SAE of diarrhoea reported in the Co-administration group was considered causally related to study intervention by the investigator. None of the SAEs reported among participants of Staggered group during the study were considered causally related to study intervention by the investigator.

Deaths

There were no fatal AEs reported among participants of both Co-administration and Staggered groups.

Discontinuation of study intervention/withdrawal from study due to AEs

An overview of events leading to discontinuation of study intervention or withdrawal from the study is provided below:

One participant from Co-administration group was withdrawn from the study due to an SAE (sepsis). The same participant also experienced unsolicited AE of upper respiratory tract infection. Both the SAE and the other unsolicited AEs were assessed as not related to study intervention by the investigator. One participant from Staggered group experienced a solicited systemic event of vomiting that led to withdrawal from study.

Assessor's comment

Safety analysis was performed on the ES and included n=193 participants in the Co-administration group and n=199 participants in the Staggered group, respectively. The demographic characteristics between the two study groups were overall comparable.
Follow-up for AEs was limited to approximatively 1 month for each of the 3 doses of IPV and Rotarix-PCV free in both study groups.

Solicited systemic AEs and unsolicited AEs frequencies in the Co-administration group were overall comparable to the Staggered group. Duration and severity were overall comparable between the 2 groups and no unexpected safety events were collected. No related SAEs were observed in both groups. No fatal AEs were reported.

Based on the data collected and the descriptive analysis, the tolerability and reactogenicity data from the ROTA-098 study indicated that Rotarix PCV-free vaccine has an acceptable safety and reactogenicity profile in both Co-administration and Staggered groups. The Co-administration of Rotarix PCV-free and IPV did not raise any safety concerns. These findings confirm other the previous studies regarding the Co-administration of Rotarix PCV-free with hexavalent vaccines which contain the similar IPV, and for which the results are already reflected in the current SmPC.

Discussion on clinical aspects

Study ROTA-098 was a PAM, open label, randomised, controlled, Phase 3 conducted in 5 different sites in China 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 vaccine (Rotarix PCV-free) in Chinese healthy infants 6-10 weeks of age. The active control group – "Staggered group" – did receive sequential administrations of Rotarix PCV-free followed by IPV vaccines. The targeted sample size was 200 participants in each group. The total duration of the study, per participant, would be approximately 3.5 months.

The primary objective was the demonstration of non-inferior neutralising antibody responses (in terms of seroconversion rates) specific to polioviruses 1, 2 and 3 following administration of IPV with Rotarix PCV-free versus IPV alone, at 1 month post Dose 3 (Per protocol Set [PPS]). To be achieved, the lower limit of the 2-sided 95% CI for the group difference (Co-administration group minus Staggered group) in seroconversion rate had to be greater than or equal to -10% for each of the anti-poliovirus types 1, 2 and 3 antibodies. Secondary objectives included further characterization of humoral responses to IPV and Rotarix PCV-free vaccinations.

In the Co-administration group, participants received Rotarix PCV-free co-administered with IPV at Month 0.5 and Month 1.5, and the third dose of IPV at Month 2.5. In the Staggered group, participants received Rotarix PCV-free at Day 1 and Month 1, and IPV at Month 0.5, Month 1.5, and Month 2.5.

Immunogenicity data specific to polioviruses 1, 2, and 3 at 1 month post Dose 3 to address the primary objective were available for n=143 (74.1% of the randomised participants) and n=125 (62.8% of the randomised participants) participants in the Co-administration group and in the Staggered group respectively (PP set for IPV). The conservative sample size determination for 90% statistical power (assuming 20% of exposed participants would not be evaluable) was not reached. Indeed, insufficient participant compliances in respecting predefined acceptable scheduled timepoints/time-windows for immunisation and/or visits did impact the statistical power and precision of estimates. The reasons for these high rates of protocol deviations, particularly of "out of window treatment administration" (although not very stringent), and for this difference in proportions between groups, were not discussed by the MAH. Because more than 5% of the ES participants with immunogenicity results after study intervention were excluded from the PPS, the primary analysis was also performed on the ES.

The primary (confirmatory) objective was met but, as mentioned above, without sufficient statistical power. Nevertheless, and consistent with previous findings, immunogenicity data of anti-poliovirus neutralising antibodies (in terms of both SRC and GMTs) suggest overall similar immune responses when co-administrated versus single administration (Staggered group). Regarding humoral response to Rotarix PCV-free, a trend for higher seroconversion rate was observed in the Co-administration group (90.4% [95% CI: 84.4, 94.7]) as compared to in the Staggered group (78.5% [95% CI: 70.4, 85.2]). This trend was less pronounced in terms of anti-RV IgA antibody GMC, with overlapping 95% CI (GMC

of 222.15 [95% CI: 165.98, 297.3] in the Co-administration group and of 160.59 [95% CI: 114.49, 225.2] in the Staggered group).

The safety/reactogenicity data were collected in n=193 and n=199 participants of the Coadministration group and the Staggered group respectively and indicated that Rotarix PCV-free vaccine has an acceptable safety and reactogenicity profile in both Co-administration and Staggered groups. The co-administration of Rotarix PCV-free and IPV did not raise any safety concerns. The safety profile is in line with the frequencies reported in current section 4.8.

3. CHMP overall conclusion and recommendation

In light of the study findings and their limited strength of evidence, there is no request to update section 4.5 of the SmPC as the Co-administration of IPV (included in tetra/hexavalent vaccines) with Rotarix is already described. The results of this study can be considered in line with the wording of the current SmPC.

☒ **Fulfilled:** No regulatory action required.