Amsterdam, 24 July 2025
EMADOC-1700519818-2079193
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

Rotarix

Common name: rotavirus vaccine, live

Procedure no.: EMA/PAM/0000267192

Marketing authorisation holder (MAH): GlaxoSmithKline Biologicals S.A.

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Status of this report and steps taken for the assessment			
Current step	**Description**	**Planned date**	**Actual Date**
☐	CHMP Rapporteur AR	30 June 2025	26 June 2025
☐	CHMP comments	14 July 2025	14 July 2025
☐	Updated CHMP Rapporteur AR	17 July 2025	N/A
☒	CHMP outcome	24 July 2025	24 July 2025

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1. Introduction

On 16 April 2025, the MAH submitted a completed paediatric study for Rotarix, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

These data are also submitted as part of the post-authorisation measures.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that ROTA-097 (212692), entitled: "A Phase III, observer-blind, randomized, multicenter study to evaluate immunogenicity, reactogenicity and safety of GlaxoSmithKline (GSK) Biologicals' Rotarix Porcine circovirus (PCV)-free liquid as compared to GSK's Rotarix liquid, given in 2 doses in healthy Chinese infants starting at age 6-16 weeks." is a stand-alone study.

The ROTA-097 study report is being submitted to comply with the requirements of Article 46 of the pediatric regulation 1901/2006.

Study ROTA-097 has not been conducted according to an agreed pediatric investigation plan (PIP).

2.2. Information on the pharmaceutical formulation used in the study

On 15-16 March 2010, GSK informed the Health Authorities worldwide (including the European Medicines Agency [EMA], WHO, and the US Food and Drug Administration [FDA]) of the unexpected presence of a non-pathogenic viral strain of PCV-1 deoxyribonucleic acid (DNA) in its Rotarix vaccine. Further investigations confirmed the presence of PCV-1 DNA fragments in Rotarix and in its starting materials as well as low levels of PCV-1 viral particles during the production process and in the final container.

EMA initiated an Art 20 procedure (EMEA/H/C/639/A-20/0024) and concluded that:

1- The benefit outweighed the risk in the authorized therapeutic indication of *Rotarix*,

2- A PCV-1 free vaccine should be developed, and

3- The marketing authorization for *Rotarix* should contain information regarding the development of a PCV-1 free vaccine and therefore recommended the amendment of Annex II of the EU Product Information (European Public Assessment Report available at https://www.ema.europa.eu/en/documents/variation-report/rotarix-h-c-639-a20-0024-epar-assessment-report-article-20_en.pdf , document dated 30 September 2010, last accessed 3 March 2025).

The Rotarix PCV-free license variation (covering all presentations) is now approved in most countries where Rotarix is licensed. The Committee for Medicinal Products for Human Use (CHMP)/EMA was the first regulatory authority to approve the use of the PCV-free starting materials (Vero cell banks and HRV seeds) for the manufacturing of Rotarix in Europe (on 13 February 2020). It was then approved by WHO (on 16 December 2020), Japan (19 January 2022) and US (on 4 November 2022). Rotarix PCV-free vaccine is already marketed in EU, US, Japan and many additional countries and is planned to be distributed worldwide during the course of 2025; it is progressively replacing the initial Rotarix.

Study ROTA-097 was designed to support licensure of the Rotarix PCV-free vaccine in China. The objective of the study was to evaluate, in healthy Chinese infants starting at age 6-16 weeks, the immunogenicity, reactogenicity and safety of GSK's Rotarix PCV-free, compared to initial Rotarix, for which vaccine efficacy was demonstrated in the ROTA-075 study conducted in China.

Table 1. Study interventions administered (Source: Protocol Table 5)

Study intervention name	HRV (*Rotarix*)	HRV PCV-free (*Rotarix* PCV-free)
Presentation	Oral applicator.	Squeezable tubes.
Study interventions formulation	Human Rotavirus, Live Attenuated, RIX4414 strain (≥ $10^{6.0}$ $CCID_{50}$); Sucrose (1.073 g); Di-sodium adipate; DMEM; Sterile water q.s. 1.5 mL	Human Rotavirus, Live Attenuated, RIX4414 strain (≥ $10^{6.0}$ $CCID_{50}$); Sucrose (1.073 g); Di-sodium adipate; DMEM; Sterile water q.s. 1.5 mL
Type	Control	Study
Product category	Combination Product*	Combination Product*
Route of administration	Oral use	Oral use
Number of doses to be administered	2	2
Volume to be administered	1.5 mL	1.5 mL
Packaging, labelling and TM	Refer to SPM for more details	Refer to SPM for more details
Manufacturer	GSK	GSK

Refer to Section 4.1 for schedule of study intervention administration; mL: milliliter; qs: quantum satis
*Combining a biological product and device

Rapporteur's assessment

The unexpected detection of a non-pathogenic viral strain of PCV-1 deoxyribonucleic acid (DNA) in Rotarix in 2010 triggered the development of a PCV-1 free Rotarix vaccine.

PCV-free Rotarix is authorized by EMA since 13 February 2020 based on data of study Rota-081 in procedure EMEA/H/C/000639/P46/095. Based on these study data, it was concluded that the PCV-free Rotarix formulation had a similar immunogenicity and safety profile to the initial Rotarix, and no update to the SmPC was required. In the meantime, it is also approved by WHO, Japan and the US. Furthermore, it is marketed in EU, US, Japan and other countries are planned this year.

Study ROTA-097 was designed to support licensure of the Rotarix PCV-free vaccine in China.

Two formulations of the vaccine are administered in this study; HRV (initial Rotarix), administered in an oral applicator; and HRV PCR-free (Rotarix PCV-free, i.e. no detection of PCV-1 and PCV-2 according to the limit of detection of the tests used), administered in a squeezable tube. The volume to be administered is 1.5 ml for each formulation.

In Europe, Rotarix (PCV free) is indicated for the active immunization of infants aged 6 to 24 weeks for prevention of gastroenteritis due to rotavirus infection. The vaccination course consists of two doses. The first dose may be administered from the age of 6 weeks. There should be an interval of at least 4 weeks between doses. The vaccination course should preferably be given before 16 weeks of age, but must be completed by the age of 24 weeks.

Resulting questions: none

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report(s) for:

ROTA-097 (212692), entitled: "A Phase III, observer-blind, randomized, multicenter study to evaluate immunogenicity, reactogenicity and safety of GlaxoSmithKline (GSK) Biologicals' Rotarix Porcine circovirus (PCV)-free liquid as compared to GSK's Rotarix liquid, given in 2 doses in healthy Chinese infants starting at age 6-16 weeks.

2.3.2. Clinical study

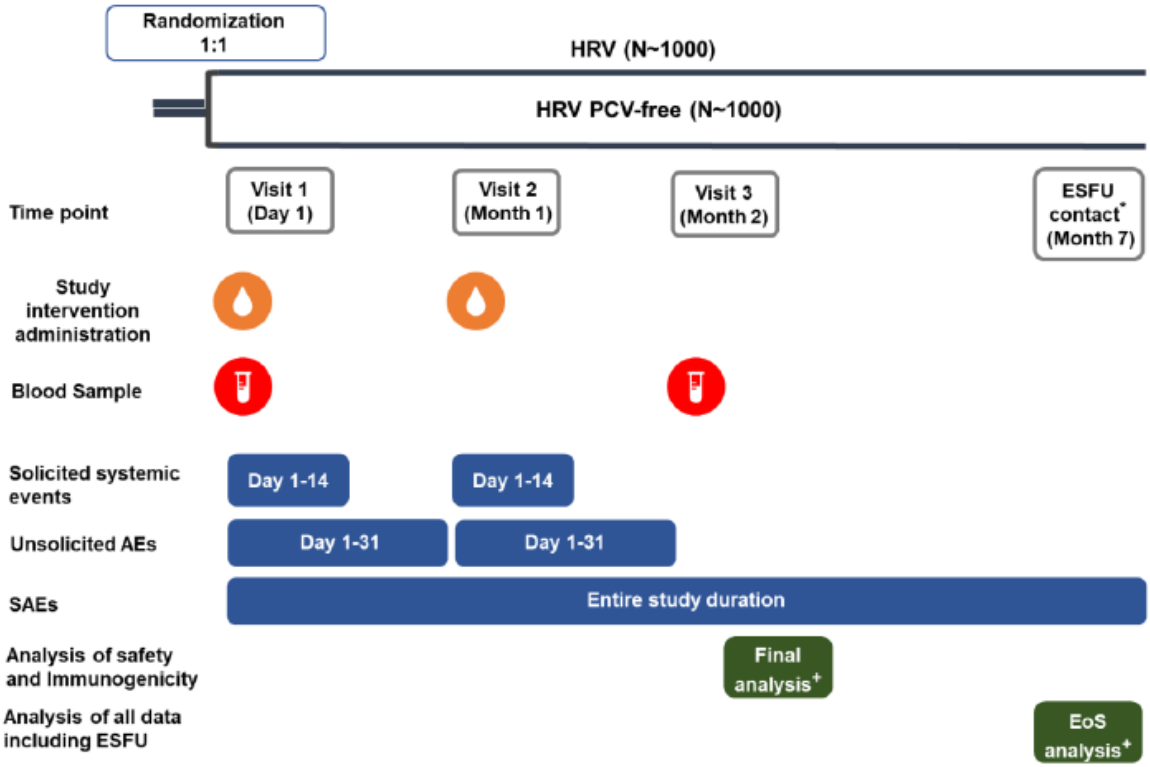
ROTA-097 (212692), entitled: "A Phase III, observer-blind, randomized, multicenter study to evaluate immunogenicity, reactogenicity and safety of GlaxoSmithKline (GSK) Biologicals' Rotarix Porcine circovirus PCV)-free liquid as compared to GSK's Rotarix liquid, given in 2 doses in healthy Chinese infants starting at age 6-16 weeks.

Description

Study ROTA-097 was a Phase III, self-contained, observer-blind, randomized, multicenter study with 2 parallel groups of *Rotarix* PCV-free and *Rotarix.*

The *Rotarix* PCV-free vaccine and *Rotarix* were orally administered at Day 1 (Visit 1) and Month 1 (Visit 2). Blood samples were collected at Visit 1 (pre-study vaccination) and at Visit 3 (1 month post Dose 2) for antibody determination. The total duration of the study, per participant, was approximately 7 months including the 6 months of extended safety follow-up period after the last dose of study vaccination.

The study was conducted at 12 centers that enrolled participants in China.



N = number of participants; AE = adverse event; SAE = serious adverse event; EoS: end of study; ESFU: extended safety follow-up; HRV: Human Rotavirus; PCV-free = No detection of PCV-1 and PCV-2 according to the limit of detection of the tests used.
* An ESFU contact (by telephone call or any convenient procedure) 6 months post Dose 2.
+ Refer to Section 9.5.1 for detailed information about sequence of analysis.

Figure 1. Study design overview (Source: Protocol Figure 1)

- Experimental design: Phase III, self-contained, observer-blind, randomized, multicenter study with 2 parallel groups (see Figure 1).
- Duration of the study: The total duration of the study, per participant, will be approximately 7 months including the 6 months of extended safety follow-up (ESFU) period after the last dose of study intervention.
- Primary completion date: Visit 3 (Month 2).
- Control: Active control, GSK's HRV liquid vaccine (Rotarix).
- Blinding: Observer-blind. Refer to Section 6.3.4 for details.
- 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 2 for an overview of the study groups.

Table 2. Study groups, intervention and blinding foreseen in the study (Source: Protocol Table 4)

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

*Observer-blind except for a limited number of GSK personnel. For unblinding after Visit 3, refer to Section 4.2.1.
ESFU: extended safety follow-up

Rapporteur's assessment

ROTA-097 is a phase 3, observer-blind, randomized, multicenter study conducted in China, with the aim to evaluate immunogenicity, reactogenicity and safety of the Rotarix PCV-free vaccine as compared to initial Rotarix. Two doses, given 1 month apart, were administered orally to healthy infants of 6-16 weeks of age at time of first administration. This is in line with the posology of Rotarix in Europe. The goal was to enroll 1000 participants in each group.

The study has an observer-blinded design, meaning that parents/LARs, clinical evaluators and laboratory in charge of sample testing were blinded for the study intervention, while other study personnel may know the treatment assignment. The study was unblinded for a limited number of people of the MAH at the final analysis (Visit 3), while all other remained blinded.

There were 4 visits in total. The vaccine was administered at Visit 1 and Visit 2, one month apart. A blood sample to evaluate immunogenicity was taken at Visit 1 pre-vaccination an at Visit 3, one month after the second dose. The last visit (extended safety follow-up [ESFU]) took place 6 months after the second dose. The total duration of the study, per participant, was approximately 7 months.

Immunogenicity was evaluated using a validated anti-RV IgA ELISA. The assay was performed at

laboratories in China, designated by GSK and using validated GSK procedures. No detailed information is provided on the assay. It is unclear if inter-laboratory validation has been performed.

Solicited AEs were monitored for 14 days after each dose. Unsolicited AEs were monitored for 31 days after each dose. SAEs were monitored throughout the entire study duration.

The final analysis was planned when immunogenicity and safety data up to Visit 3 (1 month after Dose 2) were available. An end of study analysis included all data up to the ESFU.

The design of ROTA-097 is overall similar to ROTA-081, which supported authorization of PCV-free Rotarix by EMA.

Resulting questions: none

Methods

Study participants

The study population consisted of healthy male or female participants of Chinese origin, between, and including, 6 and 16 weeks (42-112 days) of age at the time of the first study intervention administration. Participants were born after a gestation period of 36 to 42 weeks inclusive.

Participants with any confirmed or suspected immunosuppressive or immunodeficient condition, history of severe combined immunodeficiency, seizures or progressive neurological conditions, uncorrected congenital malformations of the gastrointestinal tract that would predispose to intussusception (IS), history of IS, major congenital defects or serious illness, previous confirmed occurrence of rotavirus gastroenteritis (RVGE), confirmed or suspected coronavirus disease 2019 were excluded. Participants using immunoglobulins and/or any blood products or plasma derivatives and long-acting Immune-modifying drugs from birth or those who planned to use them during the study were excluded. Additionally, participants using any investigational or non-registered product within 30 days before the first dose of study interventions and those with 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 second dose of study intervention administration were also excluded.

Rapporteur's assessment:

The study enrolled healthy male and female participants of Chinese origin, aged 6 to 16 weeks, born after 36 to 42 weeks of gestation. Participants with immunosuppressive conditions, expected predisposition to intussusception (IS), severe illnesses, previous rotavirus gastroenteritis, or recent use of certain medications and vaccines were excluded.

Resulting questions: none

Treatments

Refer to Section 2.2.

Objective(s)

Table 3. Study objectives and endpoints (Source: Protocol Table 3)

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

Ab = Antibody; AE = Adverse event; CI = Confidence Interval; IgA = Immunoglobulin A; GMC = Geometric mean Ab concentration; MedDRA = Medical Dictionary for Regulatory Activities; PCV = Porcine circovirus; SAE = Serious adverse event; RV = Rotavirus; U = Unit; mL = milliliter

Rapporteur's assessment:

The co-primary objectives were to demonstrate the immunological non-inferiority of Rotarix PCV-free compared to initial Rotarix in terms of seroconversion rates and serum anti-rotavirus immunoglobulin A antibody concentrations one month after Dose 2. Non-inferiority was confirmed if the lower limit of the 95% confidence interval for the difference in seroconversion rates was ≥ -10%, and for the ratio of antibody concentrations was ≥ 0.67.

Seroconversion was defined as initially seronegative participants (anti-RV IgA Ab < 20 U/mL) who developed anti-RV IgA Ab ≥ 20 U/mL following vaccination. This threshold of 20 U/mL is a standardly used cutoff in other Rotarix studies to determine seroconversion. Although no validated immunological correlate of protection (CoP) exists for rotavirus vaccines, anti-RV serum IgA antibody levels are considered a non-mechanistic indication of protection. Higher antibody levels are known to increase the likelihood of individual protection (refer to WHO's 'Recommendations to assure the quality, safety and efficacy of rotavirus vaccines').

The secondary immunogenicity objective was assessment of the non-inferiority of Rotarix PCV-free compared to initial Rotarix in terms of the percentage of participants with anti-RV IgA antibody concentrations ≥ 90 U/mL one month after Dose 2, with non-inferiority confirmed if the lower limit of the 95% confidence interval for the difference was ≥ -10%. No justification for the cutoff of ≥ 90 U/mL is provided.

A hierarchical testing strategy was employed in this study to control the type 1 error for the primary objectives and first secondary objective.

Additionally, the study aimed to evaluate as secondary objectives the reactogenicity of both vaccines in terms of solicited systemic events and to assess their safety in terms of unsolicited adverse events and serious adverse events.

Resulting questions: none

Outcomes/endpoints

Refer to Table 3.

Rapporteur's assessment:

The primary immunogenicity assessment focuses on anti-RV IgA antibody concentrations. It includes the anti-RV IgA antibody seroconversion rate one month after Dose 2 in both the Rotarix PCV-free and initial Rotarix groups, and the serum anti-RV IgA antibody concentrations expressed as GMCs one month after Dose 2 in both groups. Seroconversion rate is defined as the percentage of participants who were initially seronegative (anti-RV IgA antibody concentration < 20 U/mL before the first dose) and developed an anti-RV IgA antibody concentration ≥ 20 U/mL at Visit 3 (one month after Dose 2). Participants who are seropositive at baseline are excluded from the per-protocol set for immunogenicity analyses (refer to 'Statistical Methods').

As a secondary endpoint, immunogenicity in terms of anti-RV IgA antibody concentrations ≥ 90 U/mL 1 month post Dose 2 are evaluated.

The safety endpoints include the percentage of participants reporting solicited systemic AEs within 14 days after each study intervention administration, the percentage of participants reporting unsolicited

AEs within 31 days after each study intervention administration according to MedDRA classification, and the percentage of participants reporting SAEs from Dose 1 up to the end of the study.

Resulting questions: none

Sample size

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

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

The sample size provides at least 90% power to reach the first primary endpoint and at least 80.7% power to reach the second primary endpoint. Using the same approach, the power to meet the first secondary objectives will be at least 67% power.

Rapporteur's assessment:

A maximum of 2000 participants were planned to be randomized to ensure approximately 1500 evaluable participants to complete the study. A hierarchical procedure is used to control type 1 error, providing at least 90% power for the first primary endpoint and at least 80.7% for the second primary endpoint.

Statistical Methods

Populations for analysis

Table 4. Populations for analyses (Source: Protocol Table 16)

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 Analysis set as they did not enter the study.
Exposed Set (ES)	All participants with at least 1 dose of the study intervention documented. The allocation in a group is done in function of the administered intervention. The ES analysis will be performed per treatment actually administered at Dose 1.
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 2). Note that in case regurgitation or vomiting occurs within 30 minutes after study intervention administration and impairs up-take of the intervention, a single replacement dose should be used for the participant to be part of the PPS, • who were not unblinded, • who did not receive a vaccine not specified or forbidden in the protocol up to Visit 3 blood sampling, • who did not receive medication forbidden by the protocol up to Visit 3 blood sampling, • who had anti-RV concentration below 20 U/mL before study intervention administration and who had anti-RV results from the Visit 3 blood sampling, • who complied with the blood sampling schedule for Visit 3 (see Table 2), • who had no concomitant infection up to Visit 3 blood sample, which may influence the immune system.

Immunogenicity Analyses

The analyses of immunogenicity were primarily conducted on the per protocol set (PPS). To control the type 1 error for the immunogenicity endpoints (first and second primary endpoints and first secondary endpoint; see Table 1 for order of endpoints) a hierarchical procedure was used for analyses as follows:

- The first primary endpoint had to be met before the second primary endpoint could be interpreted.
- Both primary endpoints had to be met before the first secondary endpoint could be interpreted.

Within group assessments

The following calculations were performed for each group at Visit 1 and Visit 3 timepoints:

- Seropositivity (at Visit 1 and Visit 3) and Seroconversion rates (at Visit 3) and their exact 95% confidence interval (CI) were computed using the method of Clopper and Pearson.
- Geometric mean antibody concentration (GMCs) and their exact 95% CIs were computed.
- The percentage of participants with anti-rotavirus (RV) immunoglobulin A (IgA) antibody concentrations ≥ 90 U/mL and their exact 95% CI was computed.
- The distribution of anti-RV IgA Ab concentrations at Visit 3 was displayed using reverse cumulative curves for the PPS.

Between group assessments

- The asymptotic standardized 95% CI for the difference in the percentage of participants with anti-RV IgA antibody concentrations ≥20 U/mL and ≥ 90 U/mL at Visit 3 between *Rotarix* PCV-free minus *Rotarix* were computed.
- The 95% CI for the ratio of anti-RV IgA Ab GMCs at Visit 3 between *Rotarix* PCV-free over *Rotarix* were computed.

Safety Analyses

The analyses of safety were descriptive and conducted on the Exposed Set (ES).

The following calculations were performed for each group:

- The percentage of doses and participants reporting at least 1 adverse event (AE) (solicited or unsolicited) during the 14-day (Day 1 to Day 14) solicited follow-up period were computed, along with exact 95% CI. The same calculations were 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 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 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 was also summarized with threshold defined by half degree increment.

Note: Intensity of fever was assessed by considering the grading scales recommended by the Chinese authorities.

- The percentage of participants with unsolicited AEs occurring within 31-day (Day 1 to Day 31) follow-up period after any dose with its exact 95% CI was tabulated by preferred term [PT]. The same calculations were 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 serious adverse events (SAEs) (any, related, fatal, fatal related) from Dose 1 of the study intervention up to study end with its exact 95% CI were tabulated by study group and by PT.
- 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 were tabulated by study group and by PT.
- SAEs and AEs leading to withdrawal from study are described in detail.

Rapporteur's assessment:

The enrolled set included all participants who were randomized to receive study intervention or underwent a post-screening study procedure.

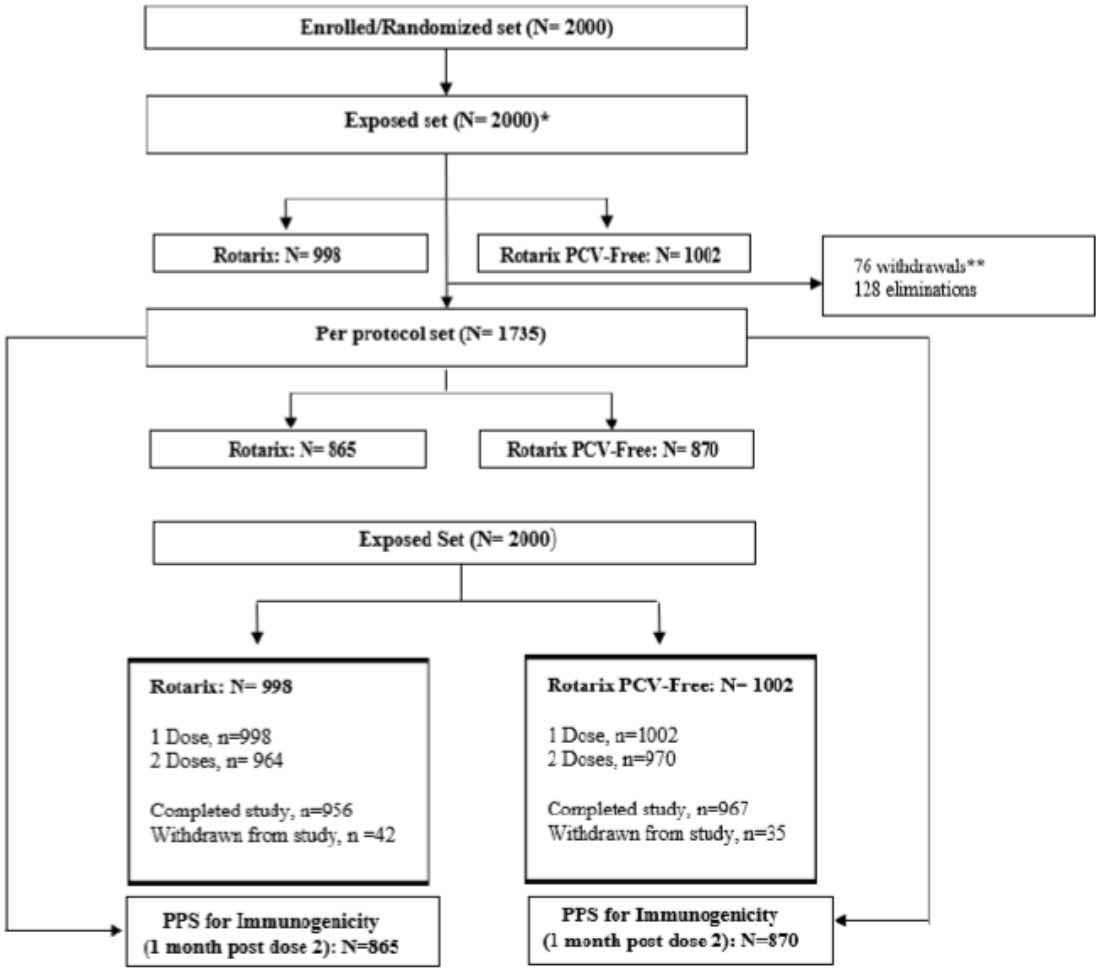
The Exposed set (ES) includes all participants who received at least one dose of study intervention. Analyses of safety were descriptive and conducted on the ES.

The Per Protocol Set (PPS) includes all participants from the ES who adhered to the protocol requirements and had no important protocol deviations. Also, participants were required to have pre-vaccination an anti-RV concentration below 20 U/mL. The analyses of immunogenicity were primarily conducted on the PPS.

Resulting questions: none

Results

Participant flow



Source: Table 8.1.1, Table 8.1.2, Table 8.1.3, Table 8.1.10, Table 8.1.12; Table 8.1.13
ESFU=extended safety follow-up; PCV= Porcine Circovirus; PPS=per protocol set
*Notes: 1 participant was enrolled to *Rotarix* group but received study intervention in the *Rotarix* PCV-free group. For all analyses, this participant was included in Rotarix PCV-free group.
**Note: A total of 77 participants withdrew from the study, but 1 participant was withdrawn after Visit 3 (i.e., this participant did not complete ESFU). Data from this participant was used for immunogenicity and safety analyses.

Figure 2. Participant Disposition (Source : ROTA-097 final report Figure 2)

Rapporteur's assessment:

The study enrolled 2000 participants (= Enrolled set), as planned. The Exposed set (ES) includes also 2000 participants. In the Rotarix PCV-free group, 1002 participants received at least one dose, with 96.5% completing the study and 3.5% withdrawing, mainly due to migration. In the initial Rotarix group, 998 participants received at least one dose, with 95.8% completing the study and 4.2% withdrawing, also primarily due to migration.

The per protocol set (PPS) includes 1735 participants, of which 870 in the Rotarix PCV-Free group and 865 in the Rotarix group.

Resulting questions: none

Baseline data

Table 5. Summary of demography and baseline characteristics (Exposed Set) (Source: ROTA-097 final report Table 7)

	ROTARIX N=998		ROTARIX PCV-FREE N=1002		Total N=2000	
	Value or n	%	Value or n	%	Value or n	%
Age (weeks) at first dose						
n	998		1002		2000	
Mean	10.1		10.2		10.1	
Standard Deviation	2.9		2.9		2.9	
Median	10.0		10.0		10.0	
Minimum	6		6		6	
Maximum	17		16		17	
Country						
China	998	100	1002	100	2000	100
Center ID						
252228	3	0.3	3	0.3	6	0.3
257116	7	0.7	6	0.6	13	0.7
257118	113	11.3	112	11.2	225	11.3
260498	215	21.5	218	21.8	433	21.7
260504	148	14.8	150	15.0	298	14.9
261075	62	6.2	61	6.1	123	6.2
261338	180	18.0	181	18.1	361	18.1
262815	41	4.1	41	4.1	82	4.1
266364	60	6.0	61	6.1	121	6.1
266374	68	6.8	67	6.7	135	6.8
266376	45	4.5	46	4.6	91	4.6
266379	56	5.6	56	5.6	112	5.6
Sex						
MALE	543	54.4	490	48.9	1033	51.7
FEMALE	455	45.6	512	51.1	967	48.4

	ROTARIX N=998		ROTARIX PCV-FREE N=1002		Total N=2000	
	Value or n	%	Value or n	%	Value or n	%
Height/Length (cm)						
n	998		1002		2000	
Mean	58.5		58.4		58.4	
Standard Deviation	3.4		3.2		3.3	
Median	58.3		58.0		58.1	
Minimum	47		47		47	
Maximum	71		70		71	
Weight (kg)						
n	998		1002		2000	
Mean	5.9		5.9		5.9	
Standard Deviation	0.9		0.9		0.9	
Median	5.9		5.9		5.9	
Minimum	3.5		3.1		3.1	
Maximum	8.9		9.0		9.0	
BMI (kg/m²)						
n	998		1002		2000	
Mean	17.2		17.3		17.3	
Standard Deviation	2.0		2.0		2.0	
Median	17.0		17.1		17.1	
Minimum	12.4		13.0		12.4	
Maximum	27.9		29.0		29.0	

N = number of participants
n/% = number / percentage of participants in a given category
Source: Table 8.1.4 (17JAN2025 13:32 GMT)

Rapporteur's assessment:

In the ES, demographic and baseline characteristics were similar between both groups. All participants were Chinese, with a mean age of 10.1 weeks and a mean BMI of 17.3 kg/m². The Rotarix PCV-free group had a nearly equal number of female (51.1%) and male (48.9%) participants, while the initial Rotarix group had slightly fewer females (45.6%) compared to males (54.4%). This difference is considered not significant.

The demographic characteristics for the PPS population were similar to those of the ES population

Resulting questions: none

Exposure

Table 6. Exposure to study interventions – Exposed Set (Source: ROTA-097 Final Report Table 8)

Study intervention administered	Number of participants receiving	ROTARIX N=998		ROTARIX PCV-FREE N=1002	
		n	%	n	%
ROTARIX	No doses	0	0.0	1002	100
	Exactly 1 dose	34	3.4	0	0.0
	Exactly 2 doses	964	96.6	0	0.0
	At least 1 dose	998	100	0	0.0
ROTARIX PCV-FREE	No doses	997	99.9	0	0.0
	Exactly 1 dose	1	0.1	32	3.2
	Exactly 2 doses	0	0.0	970	96.8
	At least 1 dose	1	0.1	1002	100

N = number of participants in each group included in the considered analysis set
n = number of participants in the given category
% = percentage of participants in the given category
Exactly x dose(s) categories are mutually exclusive
Source: Table 8.1.10 (17JAN2025 13:31 GMT)

Rapporteur's assessment:

Of 1002 participants in the ES of the Rotarix PCV-free group, 970 participants (96.8%) received both doses of the study intervention.

Of 998 participants in the ES of the initial Rotarix group, 964 participants (96.6%) received both doses of study the intervention.

All participants received at least 1 dose.

Resulting questions: none

Immunogenicity results

Table 7. Difference between groups in the percentage of participants with anti-RV IgA antibody concentrations ≥20 U/mL, ≥ 90 U/mL and ratio of GMC at Visit 3 (Per-Protocol Set) (Source: ROTA-097 final report)

	ROTARIX				ROTARIX PCV-FREE				ROTARIX PCV FREE vs ROTARIX			P-value
			95% CI				95% CI			95% CI		
	n	% or value	LL	UL	n	% or value	LL	UL	value	LL	UL	
N	865				870							
% >= 20 U/mL (a)	767	88.7	86.4	90.7	739	84.9	82.4	87.3	-3.73	-6.93	-0.55	0.0317
% >= 90 U/mL (a)	599	69.2	66.1	72.3	547	62.9	59.6	66.1	-6.37	-10.81	-1.92	0.1240
GMC (b)		222.82	198.03	250.71		157.31	139.31	177.64	0.71	0.60	0.84	<.0001

GMC= geometric mean antibody concentration; N = number of participants with available results; n/% = number / percentage of participants with titer equal to or above specified value; RV=rotavirus

(a) comparison is done by the difference of % between groups

(b) comparison is done using the group ratio of GMC (ROTARIX PCV FREE/ROTARIX) (Anova model - pooled variance)

p-values are computed under the null hypothesis of no difference between treatment groups

Source: Table 8.2.2 (17JAN2025 13:32 GMT)

Rapporteur's assessment:

At baseline, anti-RV IgA GMCs (95% CI) were similar in both groups (6.78 U/mL [6.65; 6.90] in the Rotarix PCV-free group and 6.80 U/mL [6.66; 6.95] in the initial Rotarix group. Fifteen (1.5%) and 17 (1.7%) participants were seropositive at baseline (anti-RV IgA ≥20 U/mL) and were excluded from the per-protocol set for immunogenicity analyses.

At 1-month post-dose 2, 84.9% (95% CI: 82.4; 87.3) of participants in the Rotarix PCV-free group and 88.7% (95% CI: 86.4; 90.7) in the initial Rotarix group reached anti-RV IgA Ab concentrations ≥ 20 U/mL. GMCs (95% CI) were 157.31 U/ml(139.31; 177.64) and 222.82 U/ml (198.03; 250.71), respectively.

The first co-primary objective was evaluation of Rotarix PCV-free non-inferiority to initial Rotarix in terms of seroconversion rates at Visit 3 (1-month post-dose 2)(i.e. percentage of participants with anti-RV IgA Ab concentration <20 U/mL prior the first dose of study intervention and developed anti-RV IgA Ab concentration ≥ 20 U/mL). This was confirmed as the lower limit of the 95% CI for the difference in seroconversion rates between the Rotarix PCV-free and initial Rotarix (-3.73) was greater than the pre-defined non-inferiority margin of -10% (LL: -6.93%; p=0.0317).

The second co-primary objective was evaluation of non-inferiority of anti-RV IgA antibody GMCs at Visit 3 (1-month post-dose 2). The Rotarix PCV-free did not meet the non-inferiority criteria compared with initial Rotarix. The lower limit of the 95% CI for the ratio of anti-RV IgA antibody GMCs between the Rotarix PCV-free and initial Rotarix (0.71) was lower than the pre-defined non-inferiority margin of 0.67 (LL: 0.60; p < 0.0001).

The secondary immunogenicity objective was to assess the non-inferiority in terms of anti-RV IgA antibody concentrations ≥90 U/mL at Visit 3. However, due to the failure to meet the co-primary objective 2, this secondary objective could not be assessed. Anti-RV IgA antibody concentrations ≥90 U/mL were observed in 62.9% (95% CI: 59.6, 66.1) of participants in the Rotarix PCV-free group and 69.2% (95% CI: 66.1, 72.3) in the initial Rotarix group.

Results for anti-RV IgA antibody seroconversion rates, anti-RV IgA antibody concentrations ≥90 U/mL and serum anti-RV IgA antibody GMCs at Visit 3 were analyzed by gender and study sites. The findings

indicated no significant difference in immunological response between males and females in both groups and response was generally consistent across study sites.

Resulting questions: none

Safety results

Solicited Adverse events

Solicited systemic events reported during the 14-day (Day 1-Day 14) follow-up period, after each dose of the study intervention, are presented below (per participant):

- Cough/runny nose was the most frequently reported solicited systemic event in both the Rotarix PCV-free and Rotarix groups (30.6% of participants and 25.4% of participants, respectively).
- Fever was the most frequently reported solicited systemic event that led to medically attended visits in both the Rotarix PCV-free and Rotarix groups (5.5% of participants and 5.2% of participants, respectively).
- The percentage of participants reporting Grade 3 solicited systemic events was low (<3% of participants for any of the solicited systemic events).

Unsolicited Adverse events

Unsolicited AEs were collected during the 31 days (Day 1-Day 31) follow-up period, after each dose of the study intervention, are presented below:

- Unsolicited AEs were reported in 38.9% of participants in Rotarix PCV-free group and 38.8% of participants in the Rotarix group.
- Unsolicited AEs reported in <5% of participants in either Rotarix PCV-free group or in the Rotarix group were cough, rhinorrhea, pneumonia, and pyrexia.
- Pneumonia and cough were the most frequently reported unsolicited AEs that led to medically attended visits (6.6% and 5.4% of participants, respectively, in the Rotarix PCV-free group and 7.5% and 5.8% of participants, respectively, in the Rotarix group).
- Unsolicited AEs considered causally related to study intervention by the investigator were reported in 0.8% of participants in the Rotarix PCV-free group and in 0.6% of participants in the Rotarix group; these included:
    - In the Rotarix PCV-free group, study intervention related AEs of upper respiratory tract infection were reported in 3 participants, and AEs of gastroenteritis, nasopharyngitis, sputum retention, hematochezia, and thrombocytopenia were reported in 1 participant each.
    - In the Rotarix group, study intervention related AEs of upper respiratory tract infection and nasal congestion were reported in 2 participants each, and AEs of dyspepsia and eczema were reported in 1 participant each.

Serious adverse events (SAEs)

SAEs were collected during the entire study period (i.e., beyond the 31-day [Day 1-Day 31] follow-up period as well).

- The percentage of participants who had at least 1 SAE during the study was 26.1% in the *Rotarix* PCV-free group and 25.2% in the *Rotarix* group.
- Pneumonia and bronchitis were the most frequently reported SAEs in both the *Rotarix* PCV-free group (13.8% and 3.6%, respectively) and the *Rotarix* group (14% and 3.9%, respectively).
    - One participant (8-month-old male) in the *Rotarix* PCV-free group had an SAE of intussusception (BCWG Level 4), 169 days after receiving the second dose of study intervention. The SAE was considered as causally not related to study intervention by the investigator and resolved 4 days after its onset
- No SAEs reported during the study were considered causally related to study intervention by the investigator. The majority of these SAEs were of moderate intensity and had resolved by the end of study

Discontinuation of study intervention/withdrawal from study due to AEs

A total of 5 participants in Rotarix PCV-free group and 2 participants in the Rotarix group were withdrawn from the study due to solicited systemic events.

- One participant in the Rotarix PCV-free group and 3 participants in the Rotarix group were withdrawn from the study due to unsolicited AEs; and 1 participant in the Rotarix group was withdrawn from the study due to an SAE of craniocerebral injury (reported above in this section).

None of these events (unsolicited AEs and SAE) were considered as causally related to the study intervention by the investigator.

One participant in the Rotarix PCV-free group discontinued the study intervention due to 2 SAEs. Both these events were considered as causally not related to study intervention by the investigator.

Rapporteur's assessment:

The reactogenicity (solicited AEs follow-up period of 14 days) was comparable between the 2 formulations. Fever was the most frequently reported solicited systemic event that led to medically attended visits in both the Rotarix PCV-free and initial Rotarix groups (5.5% of participants and 5.2% of participants, respectively). Only a small percentage of participants (≤ 2.6%) reported Grade 3 solicited adverse events AEs.

Unsolicited AEs (followed up to day 31 post any dose) were reported by approximately 39% of participants in each group of which ≤ 1.3% reported a grade 3 event. Pneumonia and cough were the most frequently reported AEs that led to medically attended visits (6.6% and 5.4%, respectively, in the Rotarix PCV-free group and 7.5% and 5.8%, respectively, in the initial Rotarix group). Unsolicited AEs considered causally related to study intervention by the investigator were reported in 0.8% (n=8) of participants in the Rotarix PCV-free group and in 0.6% (n=6) of participants in the Rotarix group. All related events resolved during the study and were mild or moderate in severity.

The SAEs occurrences and severity were comparable between the 2 formulations. The percentage of participants who had at least 1 SAE during the entire study duration was 26.1% in the *Rotarix* PCV-free group and 25.2% in the *Rotarix* group. None of the SAEs were considered related to either vaccine.

However, one participant (8-month-old male) in the *Rotarix* PCV-free group had an SAE of intussusception (BCWG Level 4), 169 days after receiving the second dose of study intervention. The SAE was considered as causally not related to study intervention by the investigator and resolved 4 days after its onset.

Overall, the data collected in the study ROTA-097 in China has shown that safety profile of Rotarix PCV-free was comparable to the initial Rotarix formulation when administered as a 2-dose vaccination in infants starting at age 6-16 weeks (mean age of 10 weeks). The administration of Rotarix PCV-free and initial Rotarix formulations did not raise safety concern.

Resulting questions: none

2.3.3. Discussion on clinical aspects

This report assesses the final Clinical Study Report (CSR) of study ROTA-097 (212692), which is being submitted to comply with the requirements of Article 46 of the pediatric regulation 1901/2006.

On 15-16 March 2010, GSK informed the Health Authorities worldwide (including EMA, WHO, and FDA) of the unexpected presence of a non-pathogenic viral strain of PCV-1 DNA in its Rotarix vaccine. This triggered the development of a PCV-free (i.e. no detection of PCV-1 and PCV-2 according to the limit of detection of the tests used) Rotarix vaccine. PCV-free Rotarix is authorized by EMA since 13 February 2020 based on data of study ROTA-081 in procedure EMEA/H/C/000639/P46/095. Based on these study data, it was concluded that the PCV-free Rotarix formulation had a similar immunogenicity and safety profile to the initial Rotarix formulation, and no update to the SmPC was required. In the meantime, PCV-free Rotarix is also approved by WHO, Japan and the US. Furthermore, it is marketed in EU, US, Japan and other countries are planned this year. Study ROTA-097 was designed to support licensure of the Rotarix PCV-free vaccine in China.

In Europe, Rotarix (PCV free) is indicated for the active immunization of infants aged 6 to 24 weeks for prevention of gastroenteritis due to rotavirus infection. The vaccination course consists of two doses. The first dose may be administered from the age of 6 weeks. There should be an interval of at least 4 weeks between doses. The vaccination course should preferably be given before 16 weeks of age, but must be completed by the age of 24 weeks.

STUDY DESIGN

ROTA-097 was a phase 3, observer-blind, randomized, multicenter study conducted in China. The study aimed to evaluate the immunogenicity, reactogenicity, and safety of the Rotarix PCV-free vaccine compared to the initial Rotarix formulation. Two doses, given 1 month apart, were administered orally to healthy infants of 6-16 weeks of age at time of first administration. The study intended to enroll 1000 participants in each group. The last visit took place 6 months after the second dose.

The design is overall similar to ROTA-081, which supported authorization of PCV-free Rotarix by EMA.

METHODS

ROTA-097 enrolled healthy male and female participants of Chinese origin, aged 6 to 16 weeks, born after 36 to 42 weeks of gestation. Participants with immunosuppressive conditions, expected predisposition to intussusception (IS), severe illnesses, previous rotavirus gastroenteritis, or recent use of certain medications and vaccines were excluded.

The co-primary objectives were to demonstrate immunological non-inferiority of Rotarix PCV-free compared to initial Rotarix in terms of seroconversion rates (frequency of individuals reaching anti-RV IgA Ab ≥ 20 U/mL after vaccination when initially seronegative) and serum anti-RV IgA antibody concentrations, one month after Dose 2. Non-inferiority was confirmed if the lower limit of the 95% CI ≥ -was 10% for the difference in seroconversion rates, and was ≥ 0.67 for the ratio of antibody concentrations. As a secondary immunogenicity objective, non-inferiority of Rotarix PCV-free in terms of the percentage of participants with anti-RV IgA antibody concentrations ≥ 90 U/mL one month after Dose 2 was assessed.

The threshold of 20 U/mL is standardly used as cutoff in other Rotarix studies to determine seroconversion. Although no validated immunological correlate of protection (CoP) exists for rotavirus vaccines, anti-RV serum IgA antibody levels are considered a non-mechanistic indication of protection. Higher antibody levels are known to increase the likelihood of individual protection (refer to WHO's 'Recommendations to assure the quality, safety and efficacy of rotavirus vaccines').

Safety was evaluated as secondary objectives, including solicited systemic adverse events within 14 days post-vaccination, unsolicited adverse events within 31 days post-vaccination, and serious adverse events from the first dose to the end of the study.

Safety analyses were conducted on the exposed set (ES), including all participants who received at least one dose. Immunogenicity analyses were conducted on the per-protocol set (PPS), which includes participants from the ES who adhered to protocol requirements, had no significant deviations, and had pre-vaccination anti-RV concentrations below 20 U/mL.

RESULTS

Study population

The ES included 2000 participants in total, with 1002 participants in the Rotarix PCV-free group and 998 participants in the Rotarix group. The PPS comprised 1735 participants, with 870 in the Rotarix PCV-free group and 865 in the Rotarix group.

In the ES, demographic and baseline characteristics were similar between both groups. All participants were Chinese with a mean age of 10.1 weeks and a mean BMI of 17.3 kg/m². The Rotarix PCV-free group had a nearly equal number of female (51.1%) and male (48.9%) participants, while the initial Rotarix group had slightly fewer females (45.6%) compared to males (54.4%). This difference is considered not significant. The demographic characteristics for the PPS population were similar to those of the ES population.

Immunogenicity results

At baseline, anti-RV IgA GMCs (95% CI) were similar in both groups (6.78 U/mL [6.65; 6.90] in the Rotarix PCV-free group and 6.80 U/mL [6.66; 6.95] in the initial Rotarix group.

At 1 month post-dose 2, 84.9% (95% CI: 82.4; 87.3) of baseline seronegative participants in the Rotarix PCV-free group and 88.7% (95% CI: 86.4; 90.7) in the initial Rotarix group reached anti-RV

IgA Ab concentrations ≥ 20 U/mL. Anti-RV IgA Ab GMCs (95% CI) were 157.31 U/ml (139.31; 177.64) and 222.82 U/ml (198.03; 250.71), respectively.

The first co-primary objective was met, demonstrating that Rotarix PCV-free was non-inferior to initial Rotarix in terms of seroconversion rates at 1 month post-dose 2. The lower limit of the 95% CI for the difference in seroconversion rates between Rotarix PCV-free and initial Rotarix was greater than the non-inferiority margin of -10% (LL: -6.93%; p=0.0317).

However, the second co-primary objective was not met. The lower limit of the 95% CI for the ratio of anti-RV IgA antibody GMCs between the Rotarix PCV-free and initial Rotarix at 1 month post-dose 2 was lower than the non-inferiority margin of 0.67 (LL: 0.60; p < 0.0001).

The secondary objective to evaluate non-inferiority in terms of anti-RV IgA antibody concentrations ≥90 U/mL was not assessed due to failure to meet the second primary objective.

Safety results

Reactogenicity, evaluated by solicited systemic adverse events occurring within 14-day following vaccination, was comparable between the two formulations. Fever was the most frequently reported solicited systemic event that led to medically attended visits in both the Rotarix PCV-free and initial Rotarix groups (5.5% of participants and 5.2% of participants, respectively). Only a small percentage of participants (≤ 2.6%) reported Grade 3 solicited adverse events AEs.

Unsolicited AEs, which were monitored up to 31 days after vaccination, were reported by approximately 39% of participants in each group, of which ≤ 1.3% reported a grade 3 event. Pneumonia and cough were the most frequently reported AEs that led to medically attended visits (6.6% and 5.4%, respectively, in the Rotarix PCV-free group and 7.5% and 5.8%, respectively, in the Rotarix group). Unsolicited AEs considered causally related to study intervention by the investigator were reported in 0.8% of participants in the Rotarix PCV-free group and in 0.6% of participants in the Rotarix group. All related events resolved during the study and were mild or moderate in severity.

SAE occurrences and severity were also comparable between the 2 formulations. The percentage of participants who had at least 1 SAE during the entire study duration was 26.1% in the Rotarix PCV-free group and 25.2% in the Rotarix group. This high frequency of SAEs could potentially be affected by various factors, including environmental conditions, overall health, and healthcare-seeking behavior. None of the SAEs were considered related to either vaccine.

CONCLUSION

ROTA-097 was a phase 3, observer-blind, randomized, multicenter study conducted in China. The study aimed to evaluate the immunogenicity, reactogenicity, and safety of the Rotarix PCV-free vaccine compared to the initial Rotarix formulation. Two doses, given 1 month apart, were administered orally to healthy infants of 6-16 weeks of age (mean age of 10 weeks) at time of first administration.

Immunological non-inferiority of the PCV-free Rotarix compared to the initial Rotarix formulation was not confirmed in this study. Although non-inferiority was demonstrated for the first co-primary objective (seroconversion rates), the second co-primary objective (serum anti-RV IgA antibody concentrations) was not achieved. This outcome is not in line with the results of study ROTA-081, which supported authorization of PCV-free Rotarix by EMA. ROTA-081, conducted in 1313 individuals (PPS, ratio 3:1 in Rotarix PCV-free and initial Rotarix group) with a similar design and objectives, demonstrated non-inferiority in terms of anti-RV IgA seroconversion rates and GMC using the same criteria. Nevertheless, the anti-RV IgA GMCs after vaccination with PCV-free Rotarix were in the same

range in ROTA-097 and ROTA-081 (159.5 U/mL). The reasons for these conflicting results remain unclear and may be attributed to several factors, including potential differences in demographic characteristics. In addition, given the limited details provided about the ELISA assay performed in China, it cannot be ruled out that the differences in results may be attributed to no/insufficient inter-laboratory validation.

Safety data of ROTA-097 showed that the reactogenicity and safety profile of Rotarix PCV-free was comparable to the initial Rotarix formulation. No safety concerns were raised.

It is agreed that no changes to the SmPC are required.

3. CHMP overall conclusion and recommendation

☒ **Fulfilled:**

No regulatory action required.