22 April 2021
EMA/267200/2021
Human Medicines Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Rotarix

rotavirus vaccine, live

Procedure no: EMEA/H/C/000639/P46/101

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

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1. Introduction

On 27 January 2021, the MAH submitted a completed paediatric study for Rotarix, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

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

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

ROTARIX ART46 Rota-083 (e-track 116566_Eudra CT 2012-001875-35) clinical study report: Rota-083 is a phase III, randomized, open study to assess the immunogenicity, reactogenicity and safety of two different formulations (liquid and lyophilised) of GlaxoSmithKline (GSK) Biologicals' oral live attenuated human rotavirus (HRV) vaccine, Rotarix, when given as a two-dose primary vaccination, in healthy infants with no previous history of rotavirus illness or vaccination. The study was conducted in India.

2.2. Information on the pharmaceutical formulation used in the study

Table 1. Study vaccine (CSR table 9.5)

Treatment name	Vaccine name	Formulation	Presentation	Volume to be administered orally	Number of doses	Lot numbers
HRV Liquid	HRV Liquid vaccine	**Active substance**: HRV RIX4414 live attenuated $\geq 10^{6.0}$ $CCID_{50}$ **Excipients:** Sucrose; Di-sodium Adipate; DMEM; water for injection=1.5 mL	Liquid vaccine in a pre-filled oral applicator	1.5 mL	2	AROLB993AZ/487495 AROLC101AH/498768
HRV Lyophilized	HRV Lyophilized vaccine	HRV RIX4414 live attenuated $\geq 10^{6.0}$ $CCID_{50}$	Lyophilized vaccine in a monodose glass vial. Diluent supplied separately	1 mL	2	AROTA356BZ/487549
	HRV Diluent	$CaCO_3$	Diluent for lyophilized vaccine supplied separately in a pre-filled oral applicator			AD05B208AZ/491079 AD05B219AY/491079

HRV: Human rotavirus; $CCID_{50}$: Median Cell Culture Infective Dose; $CaCO_3$: calcium carbonate DMEM: Dulbecco's Modified Eagle Medium

***CHMP comments*:**

Two formulations of the Rotarix vaccine are compared in this study. Both formulations contain $\geq 10^{6.0}$ $CCID_{50}$ of the active substance HRV RIX4414 live attenuated. The HRV liquid formulation is administered as a 1.5 ml oral dose while the HRV lyophilized formulation is administered as a 1 ml oral dose. For each formulation, two doses of the vaccine are needed.

Both formulations are approved for use in infants from 6 to 24 weeks to protect against gastroenteritis (diarrhoea and vomiting) caused by rotavirus infections.

Both formulations are authorized in EU.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report(s) for the study 116566 (ROTA-083) entitled "A phase III, randomized, open study to assess the immunogenicity, reactogenicity and safety of two different formulations of GlaxoSmithKline (GSK) Biologicals' oral live attenuated human rotavirus (HRV) vaccine, Rotarix, when given as a two-dose primary vaccination, in healthy infants with no previous history of rotavirus illness or vaccination."

Rotarix is a live attenuated HRV vaccine (strain G1P[8], RIX4414) for oral administration that is manufactured by GlaxoSmithKline Biologicals, s.a. (referred to as GSK). Two pharmaceutical forms of Rotarix are available: the lyophilized formulation to be reconstituted with a liquid diluent and the liquid formulation ready to use. The active ingredient (rotavirus strain RIX4414) is the same for both formulations; only the excipients differ, which is linked to manufacturing and vaccine stability constraints. The lyophilized formulation was approved in the European Union (EU) via the centralized procedure on 21 February 2006 and the liquid formulation was approved as a line extension on 1 September 2008. Rotarix liquid formulation is prequalified by the World Health Organization (WHO). The current indication in the EU summary of product characteristics (SmPC) is active immunization of infants aged 6 to 24 weeks for prevention of gastroenteritis due to rotavirus infection.

The ROTA-083 study report is being submitted to comply with the requirements of Article 46 of the paediatric regulation 1901/2006.

Study ROTA-083 has not been conducted in accordance with an agreed paediatric investigation plan.

In this study, the immunogenicity, reactogenicity and safety of GSK's HRV liquid vaccine compared to GSK's HRV lyophilized vaccine were evaluated.

2.3.2. Clinical study

2.3.2.1. Description

Study 116566 (ROTA-083) entitled "A phase III, randomized, open study to assess the immunogenicity, reactogenicity and safety of two different formulations of GlaxoSmithKline (GSK) Biologicals' oral live attenuated human rotavirus (HRV) vaccine, Rotarix, when given as a two-dose primary vaccination, in healthy infants with no previous history of rotavirus illness or vaccination

2.3.2.2. Methods

2.3.2.2.1. Objective(s)

Primary objective

- To evaluate non-inferiority of GSK's HRV liquid vaccine compared to GSK's HRV lyophilized vaccine in terms of geometric mean concentrations (GMCs) for anti-RV antibodies, 1 month post-Dose 2 of HRV liquid vaccine and HRV lyophilized vaccine.
  - *Non-inferiority was stated if the lower limit of the 2-sided 95% confidence interval (CI) for the ratio of anti-RV IgA antibody GMCs between HRV liquid vaccine over the HRV lyophilized vaccine, 1 month after Dose 2 was greater than or equal to 0.5.*

Secondary objectives

Immunogenicity

- To assess the immunogenicity of the HRV liquid vaccine and HRV lyophilized vaccine, in terms of seroconversion* rates, 1 month post-Dose 2 of HRV vaccine.
  *Definition:
  - for subjects with a pre-vaccination anti-RV IgA antibody concentration <20 U/mL, seroconversion was achieved when the post-vaccination concentration was ≥20 U/mL.
  - for subjects with a pre-vaccination anti-RV IgA antibody concentration ≥20 U/mL, seroconversion was achieved when the post-vaccination concentration was ≥2 times the pre-vaccination concentration.

Reactogenicity and safety

- To assess the reactogenicity of the HRV liquid vaccine and the HRV lyophilized vaccine in terms of solicited adverse events (AEs), during the 8-day (Day 1–Day 8) follow-up period after each vaccination.
- To assess the safety of the HRV liquid vaccine and the HRV lyophilized vaccine in terms of unsolicited AEs, during the 31-day (Day 1–Day 31) follow-up period after each vaccination and serious adverse events (SAEs), during the entire study period.

***CHMP comments*:**

This trial has a primary and secondary immunogenicity objective, while the reactogenicity and safety objective is secondary. There is no efficacy objective in this trial.

The primary objective of this trial is to evaluate non-inferiority of the HRV liq compared to the HRV lyo formulation in terms of geometric mean concentrations (GMCs) for anti-RV antibodies, 1 month post-Dose 2. Non-inferiority is defined as: if the lower limit of the 2-sided 95% confidence interval (CI) for the ratio of anti-RV IgA antibody GMCs between HRV liquid vaccine over the HRV lyophilized vaccine, 1 month after Dose 2 is greater than or equal to 0.5.

The secondary immunogenicity objective is to assess seroconversion rates of the HRV liq and HRV lyo vaccine 1 month post-Dose 2. In the absence of an immunological correlate of protection, two definitions of seroconversion were used:

- for subjects with a pre-vaccination anti-RV IgA antibody concentration <20 U/mL, seroconversion was achieved when the post-vaccination concentration was ≥20 U/mL.

- for subjects with a pre-vaccination anti-RV IgA antibody concentration ≥20 U/mL, seroconversion was achieved when the post-vaccination concentration was ≥2 times the pre-vaccination concentration.

A study by Cheuvart et al., in 2014 showed that a post-vaccination antibody concentration ≥ 20 U/mL may serve as a useful correlate of vaccine efficacy in clinical trials with Rotarix. An independent analysis [Baker, 2020] confirmed the GSK analysis by Cheuvart et al, 2014. The definition of seroconversion for subjects with a pre-vaccination anti-RV IgA antibody concentration ≥20 U/mL was already used in another study with Rotarix in India.

The secondary reactogenicity objective is to assess solicited AEs during the 8-day (Day 1 – Day 8) follow-up period after dose 1 and dose 2 of the HRV liq and HRV lyo vaccines**.**

The secondary safety objective is to assess unsolicited AEs during the 31-day (Day 1 – Day 31) follow-up period after dose 1 and dose 2 of the HRV liq and HRV lyo vaccines vaccination and SAEs, during the entire study period**.**

Overall, the objectives are considered appropriate. As there is currently no immune correlate of protection, the relation to protection against disease is still poorly understood.

2.3.2.2.2. Study design

This was a phase III, open-label, active-controlled, randomized (1:1), multi-center, single-country study with 2 parallel groups:

- HRV Liquid vaccine group (also referred to as HRV Liq)
- HRV Lyophilized vaccine group (also referred to as HRV Lyo)

Two oral doses of the HRV vaccine were given according to a 0, 1 month schedule.

All subjects were allowed to receive routine childhood vaccinations according to the local immunization practice. Administration of all routine childhood vaccinations given since birth was to be recorded in the electronic Case Report Form (eCRF).

Blood samples (approximately 2 mL) were collected from all subjects at Visit 1 and Visit 3 to measure serum anti-RV Immunoglobulin A (IgA) antibody concentrations using enzyme-linked immunosorbent assay (ELISA).

***CHMP comments*:**

This is a phase III, open-label, active-controlled, randomized (1:1), multi-center, single-country study in India with 2 parallel groups: HRV liq and HRV lyo. Each subject received 2 doses of the vaccine with an interval of 1 month.

The first dose was administered at an age between 6 and 10 weeks. Although Rotarix is indicated for immunization of infants from 6 to 24 weeks, a lower age limit is preferred as it is known that the first infection with a rotavirus is more severe than the subsequent infections which can be either mild or asymptomatic. Therefore, it is most important to prevent the first rotavirus infection in infants.

All subjects were allowed to receive routine childhood vaccinations according to the local immunization practice.

Blood samples for immunogenicity analysis were collected pre-dose 1 and 1 month post-dose 2.

2.3.2.2.3. Study population /Sample size

Number of subjects
The target enrolment was 450 subjects (225 subjects in each study group) to obtain at least 292 evaluable subjects (146 subjects in each study group) for the evaluation of the primary and secondary objectives.

A total of 451 subjects were enrolled in the study. Of these subjects, 449 subjects (224 subjects in HRV Liq group, 225 subjects in HRV Lyo group) were included in the Exposed Set (ES).

Inclusion/exclusion criteria

The study was conducted in healthy male or female infants, who were between, and including 6 and 10 weeks of age at the time of first vaccination and with a birth weight >2000 grams. Written informed consent was obtained from the parents/ legally acceptable representatives (LARs) of the subjects prior to performing any study specific procedure. Exclusion criteria essentially consisted of very prematurely born infants (born ≤28 weeks of gestation), administration of vaccines not foreseen by the study protocol, history of confirmed RV gastroenteritis (GE), previous vaccination against RV, administration of immunoglobulins, long-acting immune-modifying drugs, immunosuppressant medications or any chronic drug therapy, a potential reaction or hypersensitivity to the HRV vaccine components and significant history of chronic gastrointestinal disease or uncorrected gastrointestinal malformation or intussusception (IS) or any neurological disorders or seizures.

***CHMP comments*:**

In total 451 subjects were enrolled in the study, with in the Exposed set 224 subjects in HRV Liq group and 225 subjects in HRV Lyo group. This number is aligned with the pre-specified target for enrollment.

The main inclusion criteria were male or female infants of 6 to 10 weeks of age at the time of first vaccination with a birth weight > 2000 gram.

Main exclusion criteria include very prematurely born infants (born ≤28 weeks of gestation), administration of vaccines not foreseen by the study protocol (routine childhood vaccinations were accepted), history of confirmed RV gastroenteritis (GE), previous vaccination against RV, administration of immunoglobulins, long-acting immune-modifying drugs, immunosuppressant medications or any chronic drug therapy, a potential reaction or hypersensitivity to the HRV vaccine components and significant history of chronic gastrointestinal disease or uncorrected gastrointestinal malformation or intussusception (IS) or any neurological disorders or seizures.

2.3.2.2.4. Treatments

Table 2. Test Vaccine

Treatment name	Vaccine name	Formulation	Presentation	Volume to be administered orally	Number of doses	Lot numbers
HRV Liquid	HRV Liquid vaccine	**Active substance**: HRV RIX4414 live attenuated $\geq 10^{6.0} CCID_{50}$ **Excipients:** Sucrose; Di-sodium Adipate; DMEM; water for injection=1.5 mL	Liquid vaccine in a pre-filled oral applicator	1.5 mL	2	AROLB993AZ/487495 AROLC101AH/498768

HRV: Human rotavirus; $CCID_{50}$: Median Cell Culture Infective Dose; DMEM: Dulbecco's Modified Eagle Medium

Table 3. Other vaccine

Treatment name	Vaccine name	Formulation	Presentation	Volume to be administered orally	Number of doses	Lot numbers
HRV Lyophilized	HRV Lyophilized vaccine	HRV RIX4414 live attenuated $\geq 10^{6.0} CCID_{50}$	Lyophilized vaccine in a monodose glass vial. Diluent supplied separately	1 mL	2	AROTA356BZ/487549
	HRV Diluent	$CaCO_3$	Diluent for lyophilized vaccine supplied separately in a pre-filled oral applicator			AD05B208AZ/491079 AD05B219AY/491079

HRV: Human rotavirus; $CCID_{50}$: Median Cell Culture Infective Dose; $CaCO_3$: calcium carbonate DMEM: Dulbecco's Modified Eagle Medium

***CHMP comments*:**

Refer to section '2.2. Information on the pharmaceutical formulation used in the study'

2.3.2.2.5. Outcomes/endpoints

Primary Endpoint

- Anti-RV IgA antibody concentrations
    - Serum anti-RV IgA antibody concentrations, expressed as GMCs, 1 month post-Dose 2 of HRV vaccine.

Secondary Endpoints

- Anti-RV IgA antibody concentrations

- Anti-RV IgA antibody seroconversion* rate, 1 month post-Dose 2 of HRV vaccine.

  *Definition:

  - for subjects with a pre-vaccination anti-RV IgA antibody concentration <20 U/mL, seroconversion was achieved when the post-vaccination concentration was ≥20 U/mL.
  - for subjects with a pre-vaccination anti-RV IgA antibody concentration ≥20 U/mL, seroconversion was achieved when the post-vaccination concentration was ≥2 times the pre-vaccination concentration.
- Solicited general symptoms
  - Occurrence of each type of solicited general symptom within the 8-day (Day1-Day 8) solicited follow-up period, after each dose of HRV vaccine.
- Unsolicited adverse events
  - Occurrence of unsolicited AEs within 31 days (Day 1-Day 31) after any dose of HRV vaccine according to Medical Dictionary for Regulatory Activities (MedDRA) classification.
- Serious adverse events
  - Occurrence of SAEs from Dose 1 of HRV vaccine up to study end.

CHMP comments

Refer to section '2.3.2.2.1 Objectives'.

2.3.2.2.6. Statistical Methods

The analyses were conducted as per protocol amendment 3 (primary objective and secondary immunogenicity objective) dated 31 October 2017, protocol amendment 4 dated 30 October 2019 and Statistical Analysis Plan (SAP) amendment 2 dated 23 June 2020.

Analysis sets

- ES
- Per-protocol set (PPS)

Analysis of Immunogenicity

The primary analysis was based on the PPS for analysis of immunogenicity. As the percentage of vaccinated subjects with serological results excluded from the PPS for analysis of immunogenicity was more than 5%, a second within-group analysis based on the ES was performed to complement the PPS analysis.

Within group assessment

The following calculations were performed for each group

- For each group, at each time point that anti-RV IgA was measured,

- GMCs and their 95% CIs were computed.
- Seropositivity/seroconversion rates and their exact 95% CI were computed.
- The distribution of anti-RV IgA antibody concentrations at Visit 1 and Visit 3 was displayed using Reverse Cumulative Curves (RCCs).

Between groups assessment

- The 95% CI for the ratio of anti-RV IgA antibody GMCs at Visit 3 between the HRV liquid vaccine over the HRV lyophilized vaccine was computed using an analysis of covariance (ANCOVA) model on the logarithm-transformed concentrations. This model included the vaccine group and the logarithm of the baseline concentration as covariables. The GMC ratios and their 95% CI were derived by exponential transformation of the corresponding group contrast in the model (primary objective).
- The asymptotic standardized 95% CI for the difference in seroconversion rate at Visit 3 between the HRV liquid vaccine and HRV lyophilized vaccine was computed (secondary objective).

Complementary to the within group assessment of immunogenicity; fold increase from pre-vaccination to 1 month post-Dose 2 of anti-RV antibody concentrations was computed for each group.

The protocol amendment 3 required an additional condition to be part of the PPS. This condition was to have pre-vaccination anti-RV IgA antibody concentration <20 U/mL. As per request from the Indian Regulatory Authorities (Scientific Expert Committee [SEC], earlier called New Drug Advisory Committee on Vaccines [NDAC] of Drug Controller General of India [DCGI]), the PPS analyses addressing the primary and secondary immunogenicity objectives planned in the protocol amendment 3 were also generated, namely for the PPS limited to subjects with available pre-vaccination anti-RV IgA antibody concentrations <20 U/mL.

- The 95% CI for the ratio of anti-RV IgA antibody GMCs at Visit 3 between the HRV liquid vaccine over the HRV lyophilized vaccine was computed using an ANOVA model on the logarithm-transformed concentrations. This model included the vaccine group as a covariable. The GMC ratio and its 95% CI were derived by exponential transformation of the corresponding group contrast in the model (primary objective from protocol amendment 3).
- The asymptotic standardized 95% CI for the difference in seroconversion rate at Visit 3 between the HRV liquid vaccine and HRV lyophilized vaccine was computed (secondary immunogenicity objective from protocol amendment 3).

Analysis of safety

The ES was used for the analysis of safety.

Descriptive summaries were generated via the percentage by group and associated exact 95% CI.

Further details of the statistical analyses are provided in the SAP.

CHMP comments

In total 451 subjects were enrolled in the study, of which 449 subjects (224 subjects in the HRV Liq group and 225 subjects in the HRV Lyo group) were included in the exposed set (ES). The ES included all subjects with at least 1 study vaccine administration documented and is used for the safety analyses. The per protocol set (PPS) is used for the immunogenicity analysis. In this study, subjects were eliminated from the PPS because *Rotarix* was not administered as requested per protocol, blood samples were not taken according to the time periods defined in the protocol or the subjects did not have immunogenicity results for the pre and/or the post-vaccination timepoint. The PPS consists of 381 subjects in total, of which 189 subjects in the HRV Liq group and 192 subjects in the HRV Lyo group.

A secondary immunogenicity analysis was done based on the ES to complement the PPS analysis, since more than 5% of the vaccinated subjects with serological results were excluded from the PPS.

Within group assessment was done by calculating GMCs and 95% CI for each timepoint that anti-RV IgA was measured. Seropositivity/seroconversion rates with their exact 95% CI were computed.

For analysis of the primary immunogenicity objective to compare the two vaccine formulations, 95% CI for the ratio of anti-RV IgA antibody GMCs after the second dose were calculated for the HRV liq over the HRV lyo group using an analysis of covariance (ANCOVA) model on the logarithm-transformed concentrations. The asymptotic standardized 95% CI for the difference in seroconversion rate at Visit 3 between the HRV liquid vaccine and HRV lyophilized vaccine was computed (secondary objective).

The protocol amendment 3 required an additional condition to be part of the PPS. This condition was to have pre-vaccination anti-RV IgA antibody concentration <20 U/mL. As per request from the Indian Regulatory Authorities (SEC of DCGI), the PPS analyses addressing the primary and secondary immunogenicity objectives planned in the protocol amendment 3 were also generated, namely for the PPS limited to subjects with available pre-vaccination anti-RV IgA antibody concentrations <20 U/mL.

The PPS as defined in protocol amendment 3 consists of 215 subjects in total, of which 108 subjects in the HRV Liq group and 107 subjects in the HRV Lyo group. However, this analysis is no pre-defined endpoint of the study.

For analysis of the primary objective as described in protocol amendment 3, The 95% CI for the ratio of anti-RV IgA antibody GMCs at Visit 3 between the HRV liquid vaccine over the HRV lyophilized vaccine was computed using an ANOVA model on the logarithm-transformed concentrations instead of the ANCOVA model.

2.3.2.3. Results

2.3.2.3.1. Recruitment/ Number analysed

2.3.2.3.2. Baseline data

Table 4. Study population (Exposed set)

	HRV Liq N=224	HRV Lyo N=225	Total N=449
Number of subjects			
Planned, N	225	225	450
Completed, n (%)	209 (93.3)	210 (93.3)	419 (93.3)
Demographics			
N	224	225	449
Females:Males	100:124	120:105	220:229
Mean Age, weeks (SD)	6.8 (1.0)	6.8 (1.1)	6.8 (1.0)
Median Age, weeks (minimum, maximum)	6.0 (6,10)	6.0 (6,10)	6.0 (6,10)
Race			
Asian	224 (100.0)	225 (100.0)	449 (100.0)

HRV Liq=HRV vaccine liquid formulation; HRV Lyo=HRV vaccine lyophilized formulation
N=total number of subjects in each group
n (%)=number/percentage of subjects in a given category
SD=standard deviation

Table 5. Summary of demographic characteristics (Per-Protocol Set)

	HRV Liq N=189		HRV Lyo N=192		Total N=381	
	Value or n	%	Value or n	%	Value or n	%
Age at Dose 1 of HRV vaccine (weeks)						
N	189		192		381	
Mean	6.8		6.8		6.8	
SD	1.1		1.1		1.1	
Median	6.0		6.0		6.0	
Minimum	6		6		6	
Maximum	10		10		10	
Age at Dose 2 of HRV vaccine (weeks)						
N	189		192		381	
Mean	11.6		11.5		11.5	
SD	1.3		1.2		1.3	
Median	11.0		11.0		11.0	
Minimum	10		10		10	
Maximum	16		15		16	
Gender						
Male	106	56.1	91	47.4	197	51.7
Female	83	43.9	101	52.6	184	48.3
Race						
Asian	189	100.0	192	100.0	381	100.0
Height at visit 1 (cm)						
N With Data	189		192		381	
Mean	55.0		54.8		54.9	
SD	2.6		2.7		2.7	
Median	55.0		55.0		55.0	
Weight at visit 1 (kg)						
N With Data	189		192		381	
Mean	4.3		4.3		4.3	
SD	0.7		0.7		0.7	
Median	4.3		4.3		4.3	
BMI at visit 1 (kg/m²)						
N With Data	189		192		381	
Mean	14.1		14.3		14.2	
SD	2.0		1.9		2.0	
Median	14.2		14.3		14.2	
Gestational age <37 weeks						
Yes	22	11.6	24	12.5	46	12.1
No	167	88.4	168	87.5	335	87.9

HRV Liq=HRV vaccine liquid formulation; HRV Lyo=HRV vaccine lyophilized formulation
N=total number of subjects; n/%=number/percentage of subjects in a given category
Value=value of the considered parameter
N with data=number of subjects with documentation of the corresponding data
SD=standard deviation; BMI=body mass index
Source: Table 14.1.5.2 (08SEP2020 5:19 GMT)

***CHMP comments*:**

Of the 449 subjects in the ES, 224 subjects were in HRV Liq group and 225 subjects in HRV Lyo group. In each group 93.3% of the subjects, or 209 subjects and 210 subjects in the HRV liq and HRV Lyo group, respectively, completed the study.

Overall, the number of females and males is well balanced (220 vs 229, respectively). However, there is a small imbalance in each group with more males in the HRV Liq group (44.6% vs 55.4% females and males, respectively) and more females in the HRV Lyo group (53.3% vs 46.7% females and males, respectively). This is not considered an issue as comparable immune responses were observed in the HRV liq and HRV lyo groups in females and males in previous studies (Public assessment report Rotarix).

The age was well balanced across the HRV Liq and HRV Lyo group, with a mean age of 6.8 weeks and a median age of 6.0 weeks (min: 6 weeks; max: 10 weeks) at the time of first vaccination. At this age, it is expected that most subjects have not been infected yet with rotavirus. Rotarix is approved in EU for use in infants from 6 to 24 weeks old.

All participating subjects are Asian as the study was done in India.

There are 381 subjects in total in the PPS, of which 189 subjects were in HRV Liq group and 192 subjects in HRV Lyo group. This is well above the target to obtain at least 292 evaluable subjects (146 subjects in each study group) for the evaluation of the primary and secondary objectives.

Overall, the baseline characteristics form the PPS is similar to the ES set. There is a small imbalance in gender between the HRV Lig and HRV Lyo group (43.9% females and 56.1% males vs 52.6% females and 47.4% males in each group, respectively). Mean and median age at dose 1 are 6.8 weeks and 6.0 weeks, respectively, in both groups.

In the ES, 52 subjects had a gestational age of <37 weeks, with an even distribution in the HRV Liq group (25 subjects) and the HRV Lyo group (27 subjects). The majority of these subjects (78.8%) had a gestational age of 36 weeks.

Co-administration of routine vaccines was allowed in this study. A total of 85.1% of subjects at Dose 1 and 82.4% of subjects at Dose 2 were co-administered with routine vaccines (most frequently with hepatitis B vaccine, diphtheria-tetanus-pertussis vaccine, Haemophilus influenzae type b vaccine and inactivated/oral poliovirus vaccine). Clinical studies have demonstrated that the immune responses and the safety profiles of the administered vaccines were unaffected. Although concomitant administration of OPV may slightly reduce the immune response to rotavirus vaccine, clinical protection against severe rotavirus gastro-enteritis was shown to be maintained in a clinical trial involving more than 4,200 subjects who received Rotarix concomitantly with OPV (SmPC Rotarix).

2.3.2.3.3. Efficacy/Immunogenicity results

Primary objective

The primary objective was met.

In terms of anti-RV IgA antibody GMCs, GSK's HRV liquid vaccine was shown to be non-inferior to GSK's HRV lyophilized vaccine as the lower limit (LL) of the 2-sided 95% CI for the ratio of anti-RV IgA antibody GMCs, between HRV liquid vaccine over the HRV lyophilized vaccine was greater than 0.5 (LL: 0.65).

Table 6. Confirmatory comparison: Ratio of anti-RV IgA GMCs between the HRV liquid vaccine and (over) the HRV lyophilized vaccine group, 1 month post-Dose 2 of HRV vaccine (Per-Protocol Set)

					GMC ratio (HRV Liq / HRV Lyo)		
	HRV Liq		HRV Lyo			95% CI	
Antibody	N	GMC	N	GMC	Value	LL	UL
Anti-RV IgA (U/mL)	189	88.8	192	95.6	0.93	0.65	1.34

HRV Liq=HRV vaccine liquid formulation; HRV Lyo=HRV vaccine lyophilized formulation
N=number of subjects with both pre- and post-vaccination results available
GMC=geometric mean concentration estimated from the ANCOVA model
95% CI=95% confidence interval for the adjusted GMC ratio (ANCOVA model including the vaccine group (HRV Liq and HRV Lyo) and the logarithm of baseline concentration as fixed effects).
LL=lower limit, UL=upper limit
Success criterion: the lower limit of the 2-sided 95% CI for the group GMC ratio (HRV Liq /HRV Lyo) is greater than or equal to 0.5

Secondary immunogenicity objective and analyses as per protocol amendment 3

The results of the secondary immunogenicity objective and the analyses as per protocol amendment 3 are supportive of the primary objective analysis result that the immune response to HRV liquid vaccine is comparable to HRV lyophilized vaccine.

Table 7. Exploratory comparison: Difference in seroconversion rate between the HRV liquid vaccine and (minus) the HRV lyophilized vaccine group, 1 month post-Dose 2 of HRV vaccine (Per-Protocol Set)

							Difference in seroconversion rate (HRV Liq - HRV Lyo)		
	HRV Liq			HRV Lyo				95% CI	
Antibody	N	n	%	N	n	%	%	LL	UL
Anti-RV IgA (U/mL)	189	103	54.5	192	96	50.0	4.50	-5.53	14.44

HRV Liq=HRV vaccine liquid formulation; HRV Lyo=HRV vaccine lyophilized formulation
N=number of subjects with both pre- and post-vaccination results available
n=number of subjects who seroconverted at 1 month post-Dose 2
%=percentage of subjects who seroconverted at 1 month post-Dose 2
95% CI=asymptotic standardized 95% confidence interval; LL=lower limit, UL=upper limit

Table 8. Comparison as planned in protocol amendment 3: Ratio of anti-RV IgA GMCs between the HRV liquid vaccine and (over) the HRV lyophilized vaccine group in seronegative subjects at pre-Dose 1, 1 month post-Dose 2 of HRV vaccine (Per-Protocol Set)

					GMC ratio (HRV Liq / HRV Lyo)		
	HRV Liq		HRV Lyo			95% CI	
Antibody	N	GMC	N	GMC	Value	LL	UL
Anti-RV IgA (U/mL)	108	43.05	107	48.97	0.88	0.52	1.49

HRV Liq=HRV vaccine liquid formulation; HRV Lyo=HRV vaccine lyophilized formulation
N=number of subjects with both pre- and post-vaccination results available
GMC=geometric mean concentration estimated from the ANOVA model
95% CI=95% confidence interval for the adjusted GMC ratio (ANOVA model including the vaccine group (HRV Liq and HRV Lyo) as fixed effects).
LL=lower limit, UL=upper limit

Table 9. Comparison as planned in protocol amendment 3: Difference in seroconversion rate between the HRV liquid vaccine and (minus) the HRV lyophilized vaccine group in seronegative subjects at pre-Dose 1, 1 month post-Dose 2 of HRV vaccine (Per-Protocol Set)

							Difference in seroconversion rate (HRV Liq - HRV Lyo)		
	HRV Liq			HRV Lyo				95% CI	
Antibody	N	N	%	N	n	%	%	LL	UL
Anti-RV IgA (U/mL)	108	63	58.3	107	59	55.1	3.19	-10.02	16.30

HRV Liq=HRV vaccine liquid formulation; HRV Lyo=HRV vaccine lyophilized formulation
N=number of subjects with both pre- and post-vaccination results available
n=number of subjects who seroconverted at 1 month post-Dose 2
%=percentage of subjects who seroconverted at 1 month post-Dose 2
95% CI=asymptotic standardized 95% confidence interval; LL=lower limit, UL=upper limit

***CHMP comments*:**

Efficacy was not assessed in this study.

Immunogenicity assessment was based on measuring serological anti-rotavirus IgA antibody levels by ELISA. All serological assays were performed by GSK using standardized and validated procedures.

Blood samples for antibody measurement were collected on Day 1 (pre-dose 1) and on Month 2 (21-48 days after dose 2).

At 1 month post-dose 2, 71.4% and 73.4% of the subjects were seropositive (≥20 U/mL) in both groups and the GMCs increased from 25.06 (95% CI: 19.41-32.35) to 90.25 (95% CI: 67.28-121.06) and from 23.74 (95% CI: 18.96-29.73) to 94.16 (95% CI: 70.29-126.13) in both groups, respectively.

One month post-dose 2, anti-RV seroconversion was 54.5% in the HRV liq group and 50.0% in the HRV lyo group. Seroconversion was defined as anti-RV IgA ≥20 U/mL post-Dose 2 for initially seronegative subjects and as anti-RV IgA post-Dose 2 ≥2 fold the pre-Dose 1 for initially seropositive subjects.

A significant number of subjects already had pre-dose 1 anti-RV IgA concentrations ≥20 U/mL (42.9% and 44.3% in the HRV Liq and HRV Lyo group, respectively) in the PPS. These subjects were excluded from the analysis as planned in protocol amendment 3 (81 subjects form the HRV liq group and 85 subjects form the HRV lyo group). One month post-dose 2, 58.3% and 55.1% of the subjects with baseline anti-RV IgA <20 U/mL seroconverted in the HRV Liq and HRV Lyo groups, respectively.

Seroconversion rates were approximately 10% higher in the baseline seronegative subjects compared to baseline seropositive subjects.

Primary objective

The primary objective of this study was showing non-inferiority between the HRV Liq and HRV Lyo formulation of the Rotarix vaccine, by means of anti-RV IgA antibody levels one month after dose 2. In the absence of an immune correlate of protection, non-inferiority was defined as the lower limit (LL) of the 2-sided 95% CI for the ratio of anti-RV IgA antibody GMCs, between HRV liq over HRV lyo vaccine being greater than 0.5.

Analysis in the PPS showed that the anti-RV IgA GMC in the HRV Liq and HRV Lyo groups was 88.8 and 95.6, respectively. The GMC ratio of HRV Liq/HRV Lyo is 0.93 with a 95% CI of 0.65-1.34. As the LL is

greater than 0.5, non-inferiority of HRV Liq compared to HRV Lyo is shown and the primary objective of the trial is met.

Secondary objective

The secondary immunogenicity objective of this study is to assess seroconversion rates in the HRV liq and HRV lyo group, one month post-dose 2 in the PPS. The difference in seroconversion rates one month post-dose 2 between the HRV liq and HRV lyo group is 4.50% (95% CI : -5.53 – 14.44), which is supportive of the primary objective analysis result that the immune responses in both groups are comparable.

Analyses per protocol amendment 3

The primary and secondary objectives as described in protocol amendment 3 included only baseline seronegative subjects (with anti-RV IgA antibody concentrations <20 U/mL) in the PPS. Although this is not a pre-defined endpoint of the current study, the analyses are used as supportive data.

The ratio of anti-RV IgA GMCs between the HRV liq over the HRV lyo vaccine group in baseline seronegative subjects in the PPS is 0.88 (95% IC: 0.52-1.49). The difference in seroconversion rates one month post-dose 2 between the HRV liq and HRV lyo group in baseline seronegative subjects in the PPS is 3.19 % (95% CI: -10.02-16.30). These data further support the primary objective result that the immune responses in both groups are comparable.

To conclude, this data shows non-inferiority of the immune response elicited by the HRV liq compared to HRV lyo formulation of the Rotarix vaccine, measured by means of anti-RV IgA concentrations 1 month after the second dose.

2.3.2.3.4. Safety results

The safety profile of the HRV liquid vaccine was comparable to the HRV lyophilized vaccine.

Overall incidence of AEs (solicited and unsolicited) during the 8-day period (Day 1- Day 8) following HRV vaccination:

At least 1 solicited or unsolicited AE was reported in 62.5% and 66.2% of the subjects in the HRV Liq and HRV Lyo groups, respectively. In both the vaccine groups, the incidence of the solicited or unsolicited AEs (grade 3, causally related and AEs leading to medically attended visits) was comparable.

Solicited general AEs during the 8-day period (Day 1-Day 8) following HRV vaccination:

In both the vaccine groups, the solicited general AEs were reported in similar percentages of subjects. Irritability/fussiness was the most frequently reported solicited general AE (38.4% and 45.3% of subjects in the HRV Liq and HRV Lyo groups, respectively). Cough/runny nose was the most frequently reported solicited general AE leading to medically attended visits (2.7% and 1.3% of the subjects in HRV Liq and HRV Lyo groups, respectively).

***CHMP comments*:**

The analysis of safety was performed on the exposed set (ES), comprising 449 subjects of which 224 received at least 1 dose of the HRV liquid vaccine and 225 received at least 1 dose of the HRV lyophilized vaccine.

The number of subjects who reported at least one solicited or unsolicited AEs during the 8-day period following vaccination was similar for the HRV Liq group (62.5%) compared to the HRV Lyo group (66.2%).

Solicited AEs collected during the 8-day period are Cough/Runny nose; Diarrhea; Fever; Irritability/Fussiness; Loss of appetite and Vomiting. Overall similar percentages of subjects reported solicited AEs in both groups. The most frequently reported solicited AEs are 'irritability/Fussiness' (38.4% and 45.3%, respectively in the HRV liq and HRV Lyo group) and Fever (35.7% vs 36.9%, respectively in the HRV liq and HRV Lyo group). The majority of subjects reported mild fever, with a temperature >38.5°C reported by 8.5% and 8.4% of the subjects in the HRV liq and HRV Lyo group respectively and a temperature >39°C reported by only 1.3% and 0.9%, in both groups respectively.

In addition, Loss of appetite was reported in 19.6% and 23.6% of the subjects; Cough/Runny nose was reported in 14.3% and 17.3% of the subjects; Vomiting was reported in 14.7% and 13.3% of the subjects and Diarrhea was reported in 2.7 and 2.2% of the subjects, in the HRV Liq and lyo group, respectively.

In the current SmPC, only diarrhea and irritability are considered common AEs possibly related to vaccination. The severity of the solicited AEs, including diarrhea and irritability, was not found to be significantly different in the group receiving Rotarix compared to placebo, in 3 placebo-controlled trials

Relatedness to the study vaccine was most often considered by a clinical investigator for diarrhea (approximately 83% and 60% of the cases in the HRV liq and HRV lyo group). Around 30-50% of the cases of Fever, Irritability/Fussiness and vomiting were considered to be related. Fewer than 20% of cases of cough/runny nose and loss of appetite were considered related to vaccination. Overall relatedness was well balanced between the HRV liq and HRV lyo group and after the first and second dose.

Cough/runny nose was the most frequently reported solicited general AE leading to medically attended visits (2.7% and 1.3% of the subjects in HRV Liq and HRV Lyo groups, respectively)

For grade 3 related AEs, irritability/fussiness was the most commonly reported in HRV Liq group (1.8% of subjects) (defined as: Crying that cannot be comforted/prevents normal activity) and vomiting was the most commonly reported in HRV Lyo group (2.2% of subjects) (defined as: ≥3 episodes of vomiting/day).

Overall the number of AEs reported after the first or second dose is similar in both groups.

Unsolicited AEs during the 31-day period (Day 1-Day 31) following HRV vaccination:

- At least 1 unsolicited AE was reported in 24.1% and 25.8% of subjects in the HRV Liq group and HRV Lyo group, respectively.
- At least 1 grade 3 unsolicited AE was reported in 2.7% of the subjects in the HRV Liq group and 1.3% of the subjects in the HRV Lyo group. The most commonly reported grade 3 unsolicited AE was bronchiolitis in HRV Liq group (1.3% of subjects) and vomiting in HRV Lyo group (0.9% of subjects).

- There was no unsolicited AE considered causally related to vaccination by the investigator reported in this study.
- At least 1 unsolicited AE leading to medical attention following vaccination was reported in 10.7% and 12.9% of subjects in HRV Liq group and in HRV Lyo group, respectively. Upper respiratory tract infection was the most commonly reported AE in HRV Liq group (3.1% of subjects) and cough was the most commonly reported AE in HRV Lyo group (4.9% of subjects).

***CHMP comments*:**

During the 31-day period, unsolicited AEs were reported by 24.1% and 25.8% of subjects in the HRV Liq group and HRV Lyo group in the ES, respectively. At least one Grade 3 unsolicited AE was reported by 2.7% (6 subjects) and 1.3% (3 subjects) of the subjects in both groups respectively. The most commonly reported grade 3 unsolicited AE was bronchiolitis in HRV Liq group (3 subjects) and vomiting in HRV Lyo group (2 subjects).

None of the unsolicited AEs was considered related to the vaccine by the clinical investigator.

Deaths and SAEs during the entire study period:

Deaths:

No deaths were reported in this study.

SAEs:

- A total of 9 SAEs were reported in 7 subjects in the HRV Liq group (3.1% of subjects) and 3 SAEs were reported in 2 subjects in the HRV Lyo group (0.9% of subjects).
- None of the SAEs were assessed by the investigator as related to study vaccination.

Withdrawals due to AE/SAE:

A total of 93.3% of the vaccinated subjects of the ES completed the study. There were no withdrawals due to AE/SAE.

Table 10. Percentage of subjects with grade 3 unsolicited adverse events classified by MedDRA Primary System Organ Class and Preferred Term during the 31-day period (Days 1-31) following HRV vaccination (Exposed Set)

			HRV Liq N=224			HRV Lyo N=225		
Type of Event	Primary System Organ Class (CODE)	Preferred Term (CODE)	n*	n	%	n*	n	%
SAE	At least one adverse event		9	7	3.1	3	2	0.9
	Blood and lymphatic system disorders (10005329)	Thrombocytopenia (10043554)	0	0	0.0	1	1	0.4
	Gastrointestinal disorders (10017947)	Diarrhea haemorrhagic (10012741)	0	0	0.0	1	1	0.4
		Intestinal obstruction (10022687)	1	1	0.4	0	0	0.0
	Infections and infestations (10021881)	Bronchiolitis (10006448)	3	3	1.3	0	0	0.0
		Dengue fever (10012310)	0	0	0.0	1	1	0.4
		Gastroenteritis (10017888)	2	2	0.9	0	0	0.0
		Pneumonia (10035664)	1	1	0.4	0	0	0.0
		Urinary tract infection (10046571)	1	1	0.4	0	0	0.0
	Respiratory, thoracic and mediastinal disorders (10038738)	Respiratory distress (10038687)	1	1	0.4	0	0	0.0
Related SAE	At least one adverse event		0	0	0.0	0	0	0.0
Fatal SAE	At least one adverse event		0	0	0.0	0	0	0.0
Related Fatal SAE	At least one adverse event		0	0	0.0	0	0	0.0

HRV Liq=HRV vaccine liquid formulation; HRV Lyo=HRV vaccine lyophilized formulation
At least one adverse event=at least one adverse event experienced (regardless of the MedDRA Preferred Term)
N=total number of subjects in each group
n/%=number/percentage of subjects reporting the adverse event at least once
n*=Number of events reported
Related=assessed by the investigator as related to vaccination
Source: Table 14.3.1.7 (08SEP2020 5:17 GMT)

***CHMP comments*:**

At least one SAEs was reported by 7 subjects (9 events) in the HRV Liq group and by 2 subjects (3 events) in the HRV Lyo group in the ES. All 9 subjects were hospitalized.

None of the SAEs was considered related to the study vaccine by the clinical investigator.

The most commonly reported SAEs were bronchiolitis (3 subjects) and Gastroenteritis (2 subjects), both in the HRV Liq group.

Two SAES in the Primary System Organ Class 'gastrointestinal disorders' were reported: 1 case of diarrhea hemorrhagic in the HRV Lyo group and 1 case of Intestinal obstruction in the HRV Liq group. Intussusception, a known very rare serious adverse reaction associated with rotavirus vaccines was not reported in this trial.

In six subjects, the SAEs started after dose 2 while in 3 subjects, SAEs had an onset after dose 1. Of the 3 subjects who reported these 3 SAEs, 1 subject also received dose 2 and the 2 other subjects withdrew from the study before administration of the second dose.

Most SAEs were severe (n=10) in intensity. One SAE was moderate (Gastroenteritis) and one SAE was mild (intestinal obstruction).

No deaths were reported in this trial.

To conclude, in this trial the reactogenicity and safety profile of the HRV liq and HRV lyo formulation of Rotarix are comparable. This is in line with 4 previous clinical trials in which approximately 1900 infants received approximately 3800 doses of HRV liquid formulation (SmPC Rotarix). No additional safety concerns have been identified in this trial compared to the information already available in the SmPC.

2.3.3. Discussion on clinical aspects

This phase III, randomized, open study demonstrated non-inferiority of GSK's HRV liquid vaccine compared to GSK's HRV lyophilized vaccine, in terms of anti-RV IgA antibody GMCs, when administered in healthy infants 6-10 weeks of age at the time of first vaccination. The results of immunogenicity analyses in terms of seroconversion rates and analyses in subjects seronegative before vaccination (as per protocol amendment 3 as requested by the Indian Regulatory Authorities [SEC of DCGI]) were supportive of the primary objective analysis result that the immune response to HRV liquid vaccine is comparable to HRV lyophilized vaccine. In addition, the administration of GSK's HRV liquid formulation did not raise any safety concerns. The reactogenicity and safety profile of both formulations of the vaccine was comparable.

GSK has reviewed the immunogenicity and safety results of study ROTA-083 and has concluded that they are in line with the approved product information for Rotarix in the EU. Therefore, no additional changes to the SmPC for Rotarix are considered necessary.

The current version of the EU SmPC states:

- Section 5.1 Pharmacodynamic properties: "In three comparative controlled trials, the immune response elicited by Rotarix liquid formulation was comparable to the one elicited by Rotarix lyophilised formulation".
- Section 4.8 Undesirable effects: "In a total of four clinical trials, approximately 3,800 doses of Rotarix liquid formulation were administered to approximately 1,900 infants. Those trials have shown that the safety profile of the liquid formulation is comparable to the lyophilised formulation".

The Company considers the fact that these statements are now confirmed by an additional study, 438 additional doses of Rotarix liquid and 224 additional infants vaccinated to be of limited added value for the Health Care Providers.

***CHMP comments*:**

The immunogenicity results of this trial demonstrate non-inferiority of the HRV liquid compared to the HRV lyophilized formulation of Rotarix in healthy infants 6-10 weeks of age at the time of first vaccination. In addition, the reactogenicity and safety profile of both formulations is comparable and no additional safety concerns have been identified.

The current version of the EU SmPC states:

- Section 5.1 Pharmacodynamic properties: "In three comparative controlled trials, the immune response elicited by Rotarix liquid formulation was comparable to the one elicited by Rotarix lyophilised formulation".

- Section 4.8 Undesirable effects: "In a total of four clinical trials, approximately 3,800 doses of Rotarix liquid formulation were administered to approximately 1,900 infants. Those trials have shown that the safety profile of the liquid formulation is comparable to the lyophilised formulation".

These results are now confirmed in an additional 224 infants vaccinated with 438 additional doses of Rotarix liquid. The applicant considers an update of the SmPC not needed as the additional information is of limited added value for healthcare providers. We agree with the proposal of the applicant.

3. Rapporteur's overall conclusion and recommendation

The immunogenicity results of this trial demonstrate non-inferiority of the HRV liquid compared to HRV lyophilized formulation of Rotarix in healthy infants 6-10 weeks of age at the time of first vaccination. In addition, the reactogenicity and safety profile of both formulations is comparable and no additional safety concerns have been identified.

No update of the SmPC is required.

☒ Fulfilled:

No regulatory action required.