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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/P46/102

Note

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

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Table of contents

1. Introduction

On 14 June 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

ROTA-096 is a phase III, observer-blind, randomized, multi-country study to assess the reactogenicity and safety of the Porcine circovirus (PCV) free liquid formulation of GSK's oral live attenuated human rotavirus (HRV) vaccine, Rotarix, as compared to the lyophilised formulation of GSK's HRV vaccine, when administered as a 2-dose vaccination in infants starting at age 6-12 weeks. Note that 'PCV-free' is defined as no detection of PCV-1 and PCV-2 according to the limit of detection of the tests used'.

2.2. Information on the pharmaceutical formulation used in the study

Table 1. Treatments administered (Protocol Table 5)

Study treatment name	HRV Liquid	HRV Lyophilized	
Vaccine/Product name	HRV PCV-free*	HRV Lyo	HRV Diluent
Presentation	Liquid vaccine in a pre-filled oral applicator	Lyophilized vaccine in a monodose glass vial	Diluent for lyophilized vaccine (calcium carbonate liquid antacid) supplied separately in a pre-filled oral applicator.
Vaccine/Product formulation	PCV-free HRV RIX4414 live attenuated $\geq 10^{6.0}CCID_{50}$	HRV RIX4414 live attenuated $\geq 10^{6.0}CCID_{50}$	$CaCO_3$=60mg
Storage condition	-20°C or -4°F	+2 to +8°C or +36 to +46°F	+2 to +8°C or +36 to +46°F
Route of Administration	oral	oral	
– **Location**	Not applicable	Not applicable	
– **Directionality**	Not applicable	Not applicable	
– **Laterality**	Not applicable	Not applicable	
Number of doses to be administered	2	2	
Volume to be administered#	1.5 ml	1 ml	
Manufacturer	GSK	GSK	

*HRV PCV-free: No detection of PCV-1 and PCV-2 according to the limit of detection of the tests used.

Assessor comments

Two formulations of the Rotarix vaccine (liquid PCV-free and lyophilized) are administered in this study.

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 were given.

In EU, both a liquid and lyophilized formulation of the Rotarix vaccine are approved for use in infants from 6 to 24 weeks to protect against gastroenteritis (diarrhoea and vomiting) caused by rotavirus

infections. However, the HRV liquid formulation used in the ROTA-096 study is PCV free (no detection of PCV-1 and PCV-2 according to the limit of detection of the test used).

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- study ROTA-096 entitled ' A phase III, observer-blind, randomized, multi-country study to assess the reactogenicity and safety of the Porcine circovirus (PCV) free liquid formulation of GSK's oral live attenuated human rotavirus (HRV) vaccine as compared to the lyophilized formulation of the GSK's HRV vaccine, when administered as a 2-dose vaccination in infants starting at age 6-12 weeks.'

Rotarix is a live attenuated HRV vaccine (strain G1P[8], RIX4414) for oral administration that is manufactured by GlaxoSmithKline Biologicals SA (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. the 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-096 study report is being submitted to comply with the requirements of Article 46 of the pediatric regulation 1901/2006.

Study ROTA-096 has not been conducted in accordance with an agreed pediatric investigation plan.

On 15-16 March 2010, GSK informed the Health Authorities worldwide (including the European Medicines Agency [EMA], WHO, and the United States (US) Food and Drug Administration [FDA]) of the unexpected presence of a non-pathogenic viral strain of porcine circovirus type 1 (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 authorisation 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 6 May 2021).

GSK conducted a clinical study to evaluate the reactogenicity and safety of a PCV-free HRV liquid vaccine.

2.3.2. Clinical study ROTA-096

2.3.2.1. Description

2.3.2.2. Methods

2.3.2.2.1. Objective(s)

Objectives	Endpoints
Primary	
To evaluate the reactogenicity of the liquid HRV vaccine and lyophilized HRV vaccine in terms of solicited adverse events (AEs) during the 8-day (Day 1-Day 8) follow-up period after each vaccination.	• Occurrence of each solicited general AE within 8 days (Day 1–Day 8) after each vaccination.
To assess the safety of the liquid HRV vaccine and lyophilized HRV 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.	• Occurrence of unsolicited AEs within 31 days (Day 1–Day 31) after any vaccination, according to the medical dictionary for regulatory activities (MedDRA) classification. • Occurrence of SAEs throughout the study period (i.e. from Dose 1 of the HRV vaccine to study conclusion at the end of the follow-up period).

Assessor comments

This trial has two primary safety objectives. There are no immunogenicity or efficacy objectives in this trial.

The first primary 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 liquid PCV free and HRV lyophilized vaccines.

The second primary objective is to assess unsolicited AEs during the 31-day (Day 1 – Day 31) follow-up period after each vaccination and SAEs during the entire study period, meaning up to 6 months after the last dose.

The follow up period for solicited/unsolicited AEs and SAEs are in line with previous HRV vaccine trials. Overall, the objectives and endpoints are considered appropriate.

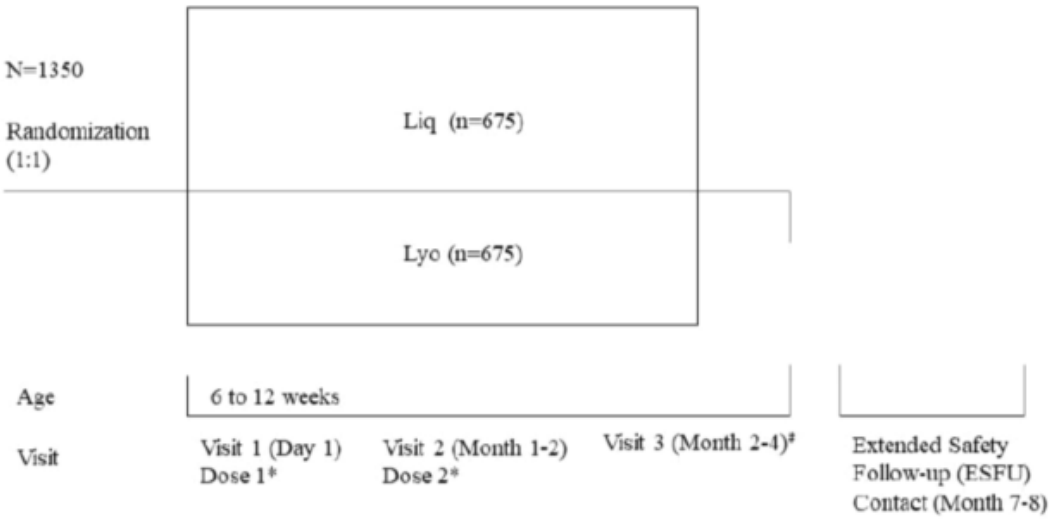
The HRV lyophilized vaccine is used as a control in this study because the liquid formulation is not licensed in the US. Therefore, the company used the lyophilized vaccine as a control in all phase III studies as part of the PCV-free development program. This is considered acceptable as a comparable safety profile of both formulations was shown in clinical trials with approximately 1900 infants.

2.3.2.2.2. Study design

Two oral doses of the study vaccines were administered at 1-month or 2-months interval to subjects, according to the immunization schedule for RV vaccine administration in participating countries.

Due to the difference in the appearance and volume between lyophilized HRV vaccine and PCV-free liquid HRV vaccine, the study was observer-blinded.

The total duration of the study, per subject, was approximately 7-8 months including the 6 months of extended safety follow-up (ESFU) period after the last dose of HRV vaccine.



The Extended safety follow-up (ESFU) contact (by telephone call or any other convenient procedure) will take place 6 months after the last dose of the study vaccines.
N=Target number of subjects, n=Target number of subjects in each study group.
*Two doses of the study vaccines will be administered to subjects at 1-month or 2-months interval.
#For authorized sites in Canada only, with approved site level standard operating procedures (SOP): Safety assessments scheduled at Visit 3 (Month 2-4) may take place at the subject's home or at the investigator's clinical facility as appropriate to the circumstances in the judgment of the investigator.

Figure 1. Study design overview (CSR Figure 1)

Assessor comments

The study ROTA-096 is a Phase III, observer-blind, randomized (1:1), controlled, multi-country study with 2 parallel groups: HRV liquid PCV-free and HRV lyophilized.

The study is observer-blind because double blinding was not possible due to a difference in appearance and volume of the HRV liquid (1.5 ml, clear and colourless liquid) and HRV lyophilized (1.0 ml, turbid liquid after reconstitution) formulation. This approach is acceptable.

Each subject received 2 doses of the vaccine with an interval of 1 to 2 months. The first dose was administered at an age between 6 and 12 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.

2.3.2.2.3. Study population /Sample size

The target sample size is 1350 subjects, 675 subjects per group.

Inclusion criteria

- Subjects' parent(s)/LAR(s) who, in the opinion of the investigator, can and will comply, with the requirements of the protocol (e.g. completion of the diary cards, return for follow-up visits).
- Written or witnessed/thumb printed informed consent obtained from the parent(s)/LAR(s) of the subject prior to performance of any study specific procedure.

- Healthy subjects as established by medical history and clinical examination before entering into the study.
- A male or female between, and including, 6 and 12 weeks (42-90 days) of age at the time of the first vaccination.

Exclusion criteria

- Medical conditions
    - Uncorrected congenital malformation (such as Meckel's diverticulum) of the gastrointestinal tract that would predispose for IS.
    - Very prematurely born infants (born ≤28 weeks of gestation).
    - History of IS.
    - Family history of congenital or hereditary immunodeficiency.
    - Any confirmed or suspected immunosuppressive or immunodeficient condition, based on medical history and physical examination (no laboratory testing required).
    - Hypersensitivity to latex.
    - Major congenital defects or serious chronic illness, as assessed by the investigator.
    - Previous confirmed occurrence of RV GE.
    - History of any reaction or hypersensitivity likely to be exacerbated by any component of the vaccines.
    - History of SCID.
- Prior/Concomitant therapy
    - Use of any investigational or non-registered product (drug, vaccine or medical device) other than the study vaccines during the period starting 30 days before the first dose of study vaccines (Day -29 to Day 1), or planned use during the study period.
    - Planned administration/administration of a vaccine not foreseen by the study protocol in the period starting 30 days before the first dose and ending 30 days after the last dose of study vaccine administration, with the exception of the inactivated influenza vaccine, which is allowed at any time during the study, and other licensed routine childhood vaccinations.
    - Administration of long-acting immune-modifying drugs at any time during the study period (e.g. infliximab).
    - Administration of immunoglobulins and/or any blood products from birth or planned administration during the study period.
    - Chronic administration (defined as more than 14 days in total) of immunosuppressants or other immune-modifying drugs since birth. For corticosteroids, this will mean prednisone ≥0.5 mg/kg/day, or equivalent. Inhaled and topical steroids are allowed.
    - Previous vaccination against RV.
- Other

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

Assessor Comments

The study targets to enrol 1350 subjects, 675 subjects per group.

The main criteria for inclusion are male or female infants of 6 to 12 weeks of age at the time of first vaccination.

Criteria for exclusion from participation in the trial are several medical conditions related to immunological conditions or intussusception, which is a known risk associated with rotavirus vaccination. In addition, prematurely born infants (born =<28 weeks of gestation) could not participate. No weight limit was applied to qualify for participation.

Concomitant use of another vaccine was not allowed from 30 days before until 30 days after study vaccination. However, an exception are inactivation influenza vaccine and other licensed routine childhood vaccines, which can all be administered without restriction. Clinical studies have shown that the immune response and the safety profiles of routine childhood vaccines are unaffected when given concomitantly with Rotarix. Only concomitant administration of an oral polio vaccine may slightly reduce the immune response of Rotarix. 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.

2.3.2.2.4. Treatments

The doses used in this study were based on previous preclinical and clinical studies that demonstrated acceptable toxicological, safety and immunogenicity profiles.

Assessor comments

The study treatments are discussed in section 2.2.

2.3.2.2.5. Outcomes/endpoints

Assessor comments

The endpoints of this trials are considered appropriate. Refer to section '2.3.2.2.1 Objectives' for more details.

2.3.2.2.6. Statistical Methods

Analysis sets defined in the study

Analysis set	Description
Enrolled	All subjects who were randomised or vaccinated
Exposed	All subjects who received at least 1 dose of the study treatment. For the sake of analysis, the study group is defined by the treatment administered at Dose 1.

Analysis of Demographics and baseline characteristics

The median, mean, range and standard deviation of age (in weeks) at each study vaccine dose and of the gestational age at birth was computed by study group. The median, mean and standard deviation of length (in centimetres) and weight (in kilograms) at Visit 1 will be computed by study group. The distribution of racial and sex composition of the study population will be presented.

Analysis of safety and reactogenicity

The primary safety analysis will be performed on the Exposed set.
The percentage of doses and of subjects reporting at least 1 AE (solicited or unsolicited) during the 8 day (Day 1-Day 8) solicited follow-up period post-vaccination was computed, along with exact 95% CI. The same calculations were done for AEs (solicited or unsolicited) rated as grade 3 in intensity, those assessed as causally related to vaccination, those rated as grade 3 in intensity with causal relationship to vaccination and those that resulted in a medically attended visit.

The percentage of doses and of subjects reporting each individual solicited general AE was computed, over the 8-day (Day 1-Day 8) solicited follow-up period post- vaccination, along with exact 95% CI. The same calculations were done for each individual general solicited AE rated as grade 3 in intensity, those assessed as causally related to vaccination, those rated as grade 3 in intensity with causal relationship to vaccination and those that resulted in a medically attended visit. For fever, additional analyses will be performed by 0.5°C increments. These calculations were also performed by country, sex and frequent race.

The verbatim reports of unsolicited AEs were reviewed by a physician and the signs and symptoms were coded according to MedDRA. Every verbatim term were matched with the appropriate preferred term. The percentage of subjects with unsolicited AEs occurring within 31-day (Day 1-Day 31) follow-up period after any dose with its exact 95% CI were tabulated by group, and by preferred term. Similar tabulation was done for unsolicited AEs rated as grade 3, for unsolicited AEs with causal relationship to vaccination, for unsolicited AEs rated as grade 3 with causal relationship to vaccination and those that resulted in a medically attended visit. These calculations were also performed by country.

For each study group, the percentage of subjects who started taking at least 1 concomitant medication, antipyretic medication and prophylactic antipyretic medication during the 8-day (Day 1 Day 8) and 31-day (Day 1-Day 31) follow-up periods post-vaccination was tabulated by dose, by subject for each dose and across the 2 doses.

Subjects who experienced at least 1 SAE during the entire study period (from Dose 1 till ESFU contact at Month 7-8) were summarised by study group and all SAEs were tabulated.

Assessor Comments

The exposed set (ES) consist of all subjects who received at least 1 dose of a study vaccine. All safety analyses are based on the exposed set.

The proposed analysis methods for reactogenicity and safety are considered appropriate.

2.3.2.3. Results

2.3.2.3.1. Recruitment/ Number analysed

The study enrolled 1351 subjects, all of which were vaccinated and included in the exposed set (ES), and of which 1310 subjects completed the study (Table 2).

None of the withdrawals was due to COVID-19.

One subject in the HRV Liq group was withdrawn due to an unsolicited non-serious AE (Hematochezia) assessed by the investigator as related to study vaccine.

Table 2. Number (%) of subjects vaccinated, completed and withdrawn from the study with reason for study withdrawal - Exposed Set (CSR Table 10.1)

	HRV Liq N=677		HRV Lyo N=674		Total N=1351	
	n	%	n	%	n	%
Number of subjects vaccinated	677	100.0	674	100.0	1351	100.0
End of study status:						
Completed	653	96.5	657	97.5	1310	97.0
Withdrawn	24	3.5	17	2.5	41	3.0
Reasons for withdrawal:						
Unsolicited non-serious adverse event	1	0.1	0	0.0	1	0.1
Protocol deviation	1	0.1	0	0.0	1	0.1
Consent withdrawal, not due to an adverse event	13	1.9	12	1.8	25	1.9
Migrated / moved from the study area	3	0.4	1	0.1	4	0.3
Lost to follow-up	6	0.9	4	0.6	10	0.7

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
Vaccinated=number/percentage of subjects who were vaccinated in the study
Completed=number/percentage of subjects who completed last study visit
Withdrawn=number/percentage of subjects who did not come for the last visit
Source: Table 14.1.2 (27MAY2021 7:24 GMT)

Assessor Comments

In total 1351 subjects were enrolled in the study, 677 in the HRV liquid PCV-free group and 674 in the HRV lyophilized group, which approximately meets the enrolment target of 675 subjects per group. All subjects enrolled in the trial were vaccinated and included in the ES. The study was completed by the majority of the subjects enrolled (653 subjects in the HRV Liquid group and 657 subjects in the HRV Lyophilized group). One subject in the HRV liquid group was withdrawn due to a non-serious adverse event of Hematochezia which the investigator considered related to the vaccine (further discussed in Section 2.3.2.3.4. Safety results – unsolicited adverse events). The most common reason for not completing the study was due to consent withdrawal, not due to an AE (N=25 subjects) and lost to follow-up (N=10 subjects).

2.3.2.3.2. Baseline data

The mean age of subjects was 9.0 ± 1.5 weeks at Dose 1 of HRV vaccine; 51.3% of the subjects were female. White (50.7%) was the predominant race followed by Asian (44.6%) (Table 3).

Among all subjects of the exposed set (ES), 26.9% were enrolled in Hong Kong, 20.4% in Turkey, 19.1% in the US, 17.7% in Canada and 15.9% in Taiwan.

The demographic characteristics were comparable across the groups in each country.

Table 3. Summary of demographic characteristics – Exposed set (CSR Table 11.1)

	HRV Liq N=677		HRV Lyo N=674		Total N=1351	
	Value or n	%	Value or n	%	Value or n	%
Age at Dose 1 of HRV vaccine (weeks)						
N	677		674		1351	
Mean	9.0		9.0		9.0	
SD	1.5		1.5		1.5	
Median	9.0		9.0		9.0	
Minimum	6		5		5	
Maximum	13		13		13	
Age at Dose 2 of HRV vaccine (weeks)						
N	663		657		1320	
Mean	16.7		16.9		16.8	
SD	2.6		2.7		2.7	
Median	17.0		17.0		17.0	
Minimum	10		10		10	
Maximum	23		29		29	
Gestational Age (weeks)						
N	677		674		1351	
Mean	38.5		38.5		38.5	
SD	1.5		1.5		1.5	
Median	39.0		39.0		39.0	
Minimum	30		31		30	
Maximum	42		42		42	

	HRV Liq N=677		HRV Lyo N=674		Total N=1351	
	Value or n	%	Value or n	%	Value or n	%
Gender						
Male	341	50.4	317	47.0	658	48.7
Female	336	49.6	357	53.0	693	51.3
Race						
American Indian Or Alaska Native	2	0.3	1	0.1	3	0.2
Asian	302	44.6	301	44.7	603	44.6
Black Or African American	14	2.1	10	1.5	24	1.8
Native Hawaiian Or Other Pacific Islander	0	0.0	2	0.3	2	0.1
White	339	50.1	346	51.3	685	50.7
Other	20	3.0	14	2.1	34	2.5
Country						
Canada	122	18.0	117	17.4	239	17.7
Hong Kong	182	26.9	182	27.0	364	26.9
Taiwan	107	15.8	108	16.0	215	15.9
Turkey	137	20.2	138	20.5	275	20.4
United States	129	19.1	129	19.1	258	19.1
Height at visit 1 (cm)						
N With Data	677		674		1351	
Mean	58.1		58.2		58.1	
SD	2.8		2.9		2.8	
Median	58.0		58.0		58.0	
Weight at visit 1 (kg)						
N With Data	677		674		1351	
Mean	5.4		5.4		5.4	
SD	0.8		0.7		0.8	
Median	5.4		5.3		5.4	
BMI at visit 1 (kg/m²)						
N With Data	677		674		1351	
Mean	15.8		15.8		15.8	
SD	1.6		1.6		1.6	
Median	15.8		15.7		15.8	

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
Source: Table 14.1.6 (27MAY2021 7:24 GMT)

Assessor Comments

Overall, the baseline characteristics are well balanced between both groups.

The mean and median age at dose 1 of the HRV vaccine was 9.0 weeks in both groups. The youngest participant was 5 weeks old in the HRV lyophilized group and 6 weeks in the HRV liquid group. In both groups the maximum age was 13 weeks at the first dose. The median age at the second dose was 17.0 weeks in both groups, ranging from 10 to 23 weeks in the HRV liquid group and from 10 to 29 weeks in the HRV lyophilized group. As Rotarix was administered at young age, it is expected that most subjects have not been infected yet with rotavirus before. The majority of the subjects in the ROTA-096 study received Rotarix according to the EU label, meaning at an age of 6 to 24 weeks old.

The median gestational age of participants in the trial was 39 weeks, with a minimum of 30 weeks.

Overall the number of females and males is well balanced (693 vs. 658, respectively). While in the HRV liquid group the gender distribution is almost equal (49.6% females and 50.4% males), there are slightly more females in the HRV lyophilized group compared to males (53.0% vs. 47.0%, respectively).

The majority of the subjects originate from Hong Kong (26.9%), followed by Turkey (20.4%), United States (19.1%), Canada (17.7%) and Taiwan (15.9%). The race of most participants was White (50.7%) or Asian (44.6%) and similar in both groups.

Co-administration (= on the same day) or concomitant administration (=on any other day in the trial) of routine childhood vaccines was allowed in the ROTA-096 trial and not expected to impact the safety data. In total, co-administration occurred in 43.7% of subjects at Dose 1 and 43.0% of subjects at Dose 2. Most frequently co-administered vaccines were Streptococcus pneumoniae vaccine (43.1% with Dose 1, 39.3% with Dose 2), Haemophilus influenzae type b vaccine (40.6% with Dose 1, 42.4% with Dose 2), diphtheria-tetanus-pertussis vaccine (40.5% with Dose 1, 42.3% with Dose 2) and inactivated poliovirus vaccine (40.5% with Dose 1 and 42.3% with Dose 2). A concomitant vaccine was administered to 39.2% of the subjects between Dose 1 and 2 and to 50.8% of the subjects between Dose 2 and the visit at Month 2-4.

2.3.2.3.3. Efficacy results

Efficacy was not analysed in this study.

2.3.2.3.4. Safety results

Adverse events

During the 8 days (Day 1 - Day 8) following HRV vaccination, at least 1 solicited or unsolicited AE was reported in 85.2% and 82.5% of the subjects in the HRV Liq and HRV Lyo groups, respectively (Table 4). In both the vaccine groups, the incidence of the solicited or unsolicited AEs (grade 3, causally related, grade 3 causally related and AEs leading to medically attended visits) was comparable.

Table 4. Percentage of doses and of subjects reporting any solicited or unsolicited adverse events during the 8 days (Day 1 - Day 8) following HRV vaccination - Exposed Set (CSR Table 12.1)

	HRV Liq					HRV Lyo				
				95% CI					95% CI	
Dose	N	n	%	LL	UL	N	n	%	LL	UL
Dose 1	677	513	75.8	72.4	79.0	674	494	73.3	69.8	76.6
Dose 2	663	443	66.8	63.1	70.4	657	425	64.7	60.9	68.3
Overall/dose	1340	956	71.3	68.8	73.8	1331	919	69.0	66.5	71.5
Overall/subject	677	577	85.2	82.3	87.8	674	556	82.5	79.4	85.3

HRV Liq=HRV vaccine liquid formulation; HRV Lyo=HRV vaccine lyophilized formulation
For each dose: N=number of subjects with the corresponding administered dose, n/%=number/percentage of subjects reporting at least one adverse event following the corresponding dose
For overall/dose: N=number of administered doses, n/%=number/percentage of doses followed by at least one adverse event
For overall/subject: N=number of subjects with at least one administered dose, n/%=number/percentage of subjects reporting at least one adverse event
95% CI=exact 95% confidence interval; LL=lower limit; UL=upper limit
Source: Table 14.3.1.4.1 (27MAY2021 7:13 GMT)

Assessor Comments

The analysis of safety was performed on the exposed set (ES), comprising 1351 subjects of which 677 received at least 1 dose of the HRV liquid vaccine and 674 received at least 1 dose of the HRV lyophilized vaccine. The second dose was administered to 663 and 657 subjects, respectively.

The number of subjects who reported at least one solicited or unsolicited AEs during the 8-day period following vaccination (overall/subject) was similar for the HRV Liq group (85.2%) compared to the HRV Lyo group (82.5%).

Solicited Adverse Events during 8 days following vaccination (Day 1-Day 8)

Table 5. Percentage of doses and of subjects reporting solicited general adverse events during the 8 days (Day 1 - Day 8) following HRV vaccination - Exposed Set (CSR Table 12.2)

			HRV Liq					HRV Lyo				
						95% CI					95% CI	
Dose	Adverse event	Type	N	n	%	LL	UL	N	n	%	LL	UL
Dose 1	Cough / Runny Nose	Overall	677	139	20.5	17.5	23.8	674	166	24.6	21.4	28.1
		Grade 3	677	2	0.3	0.0	1.1	674	3	0.4	0.1	1.3
		Related	677	46	6.8	5.0	9.0	674	64	9.5	7.4	12.0
		Grade 3 Related	677	1	0.1	0.0	0.8	674	1	0.1	0.0	0.8
		Medically Attended	677	9	1.3	0.6	2.5	674	10	1.5	0.7	2.7
	Diarrhea	Overall	677	41	6.1	4.4	8.1	674	47	7.0	5.2	9.2
		Grade 3	677	2	0.3	0.0	1.1	674	3	0.4	0.1	1.3
		Related	677	34	5.0	3.5	6.9	674	35	5.2	3.6	7.1
		Grade 3 Related	677	2	0.3	0.0	1.1	674	2	0.3	0.0	1.1
		Medically Attended	677	2	0.3	0.0	1.1	674	0	0.0	0.0	0.5
	Fever (C)	Overall	677	27	4.0	2.6	5.7	674	21	3.1	1.9	4.7
		>= 38	677	27	4.0	2.6	5.7	674	21	3.1	1.9	4.7
		> 38.5	677	4	0.6	0.2	1.5	674	3	0.4	0.1	1.3
		> 39	677	1	0.1	0.0	0.8	674	0	0.0	0.0	0.5
		> 39.5	677	1	0.1	0.0	0.8	674	0	0.0	0.0	0.5
		Related	677	0	0.0	0.0	0.5	674	0	0.0	0.0	0.5
		> 39.5 Related	677	0	0.0	0.0	0.5	674	0	0.0	0.0	0.5
		Medically Attended	677	3	0.4	0.1	1.3	674	2	0.3	0.0	1.1
	Irritability / Fussiness	Overall	677	431	63.7	59.9	67.3	674	428	63.5	59.7	67.1
		Grade 3	677	45	6.6	4.9	8.8	674	26	3.9	2.5	5.6
		Related	677	313	46.2	42.4	50.1	674	310	46.0	42.2	49.8
		Grade 3 Related	677	36	5.3	3.8	7.3	674	22	3.3	2.1	4.9
		Medically Attended	677	3	0.4	0.1	1.3	674	3	0.4	0.1	1.3
	Loss of appetite	Overall	677	201	29.7	26.3	33.3	674	186	27.6	24.3	31.1
		Grade 3	677	2	0.3	0.0	1.1	674	4	0.6	0.2	1.5
		Related	677	128	18.9	16.0	22.1	674	119	17.7	14.8	20.7
		Grade 3 Related	677	1	0.1	0.0	0.8	674	3	0.4	0.1	1.3
		Medically Attended	677	4	0.6	0.2	1.5	674	3	0.4	0.1	1.3
	Vomiting	Overall	677	113	16.7	14.0	19.7	674	122	18.1	15.3	21.2
		Grade 3	677	32	4.7	3.3	6.6	674	23	3.4	2.2	5.1
		Related	677	68	10.0	7.9	12.6	674	70	10.4	8.2	12.9
		Grade 3 Related	677	20	3.0	1.8	4.5	674	17	2.5	1.5	4.0

			HRV Liq					HRV Lyo				
						95% CI					95% CI	
Dose	Adverse event	Type	N	n	%	LL	UL	N	n	%	LL	UL
		Medically Attended	677	8	1.2	0.5	2.3	674	3	0.4	0.1	1.3
Dose 2	Cough / Runny Nose	Overall	663	147	22.2	19.1	25.5	657	145	22.1	19.0	25.4
		Grade 3	663	2	0.3	0.0	1.1	657	3	0.5	0.1	1.3
		Related	663	69	10.4	8.2	13.0	657	72	11.0	8.7	13.6
		Grade 3 Related	663	1	0.2	0.0	0.8	657	3	0.5	0.1	1.3
		Medically Attended	663	12	1.8	0.9	3.1	657	8	1.2	0.5	2.4
	Diarrhea	Overall	663	28	4.2	2.8	6.0	657	36	5.5	3.9	7.5
		Grade 3	663	4	0.6	0.2	1.5	657	6	0.9	0.3	2.0
		Related	663	18	2.7	1.6	4.3	657	31	4.7	3.2	6.6
		Grade 3 Related	663	2	0.3	0.0	1.1	657	6	0.9	0.3	2.0
		Medically Attended	663	2	0.3	0.0	1.1	657	1	0.2	0.0	0.8
	Fever (C)	Overall	663	46	6.9	5.1	9.1	657	40	6.1	4.4	8.2
		>= 38	663	46	6.9	5.1	9.1	657	40	6.1	4.4	8.2
		> 38.5	663	16	2.4	1.4	3.9	657	7	1.1	0.4	2.2
		> 39	663	4	0.6	0.2	1.5	657	3	0.5	0.1	1.3
		> 39.5	663	1	0.2	0.0	0.8	657	0	0.0	0.0	0.6
		Related	663	0	0.0	0.0	0.6	657	0	0.0	0.0	0.6
		> 39.5 Related	663	0	0.0	0.0	0.6	657	0	0.0	0.0	0.6
		Medically Attended	663	4	0.6	0.2	1.5	657	4	0.6	0.2	1.6
	Irritability / Fussiness	Overall	663	368	55.5	51.6	59.3	657	362	55.1	51.2	58.9
		Grade 3	663	35	5.3	3.7	7.3	657	27	4.1	2.7	5.9
		Related	663	274	41.3	37.5	45.2	657	285	43.4	39.6	47.3
		Grade 3 Related	663	25	3.8	2.5	5.5	657	25	3.8	2.5	5.6
		Medically Attended	663	4	0.6	0.2	1.5	657	1	0.2	0.0	0.8
	Loss of appetite	Overall	663	170	25.6	22.4	29.1	657	168	25.6	22.3	29.1
		Grade 3	663	7	1.1	0.4	2.2	657	4	0.6	0.2	1.6
		Related	663	126	19.0	16.1	22.2	657	123	18.7	15.8	21.9
		Grade 3 Related	663	5	0.8	0.2	1.8	657	4	0.6	0.2	1.6
		Medically Attended	663	3	0.5	0.1	1.3	657	2	0.3	0.0	1.1
	Vomiting	Overall	663	82	12.4	10.0	15.1	657	88	13.4	10.9	16.2
		Grade 3	663	24	3.6	2.3	5.3	657	24	3.7	2.4	5.4
		Related	663	55	8.3	6.3	10.7	657	63	9.6	7.4	12.1
		Grade 3 Related	663	14	2.1	1.2	3.5	657	18	2.7	1.6	4.3
		Medically Attended	663	1	0.2	0.0	0.8	657	1	0.2	0.0	0.8

			HRV Liq					HRV Lyo				
						95% CI					95% CI	
Dose	Adverse event	Type	N	n	%	LL	UL	N	n	%	LL	UL
Overall/Dose	Cough / Runny Nose	Overall	1340	286	21.3	19.2	23.6	1331	311	23.4	21.1	25.7
		Grade 3	1340	4	0.3	0.1	0.8	1331	6	0.5	0.2	1.0
		Related	1340	115	8.6	7.1	10.2	1331	136	10.2	8.6	12.0
		Grade 3 Related	1340	2	0.1	0.0	0.5	1331	4	0.3	0.1	0.8
		Medically Attended	1340	21	1.6	1.0	2.4	1331	18	1.4	0.8	2.1
	Diarrhea	Overall	1340	69	5.1	4.0	6.5	1331	83	6.2	5.0	7.7
		Grade 3	1340	6	0.4	0.2	1.0	1331	9	0.7	0.3	1.3
		Related	1340	52	3.9	2.9	5.1	1331	66	5.0	3.9	6.3
		Grade 3 Related	1340	4	0.3	0.1	0.8	1331	8	0.6	0.3	1.2
		Medically Attended	1340	4	0.3	0.1	0.8	1331	1	0.1	0.0	0.4
	Fever (C)	Overall	1340	73	5.4	4.3	6.8	1331	61	4.6	3.5	5.8
		>= 38	1340	73	5.4	4.3	6.8	1331	61	4.6	3.5	5.8
		> 38.5	1340	20	1.5	0.9	2.3	1331	10	0.8	0.4	1.4
		> 39	1340	5	0.4	0.1	0.9	1331	3	0.2	0.0	0.7
		> 39.5	1340	2	0.1	0.0	0.5	1331	0	0.0	0.0	0.3
		Related	1340	0	0.0	0.0	0.3	1331	0	0.0	0.0	0.3
		> 39.5 Related	1340	0	0.0	0.0	0.3	1331	0	0.0	0.0	0.3
		Medically Attended	1340	7	0.5	0.2	1.1	1331	6	0.5	0.2	1.0
	Irritability / Fussiness	Overall	1340	799	59.6	56.9	62.3	1331	790	59.4	56.7	62.0
		Grade 3	1340	80	6.0	4.8	7.4	1331	53	4.0	3.0	5.2
		Related	1340	587	43.8	41.1	46.5	1331	595	44.7	42.0	47.4
		Grade 3 Related	1340	61	4.6	3.5	5.8	1331	47	3.5	2.6	4.7
		Medically Attended	1340	7	0.5	0.2	1.1	1331	4	0.3	0.1	0.8
	Loss of appetite	Overall	1340	371	27.7	25.3	30.2	1331	354	26.6	24.2	29.1
		Grade 3	1340	9	0.7	0.3	1.3	1331	8	0.6	0.3	1.2
		Related	1340	254	19.0	16.9	21.2	1331	242	18.2	16.1	20.4
		Grade 3 Related	1340	6	0.4	0.2	1.0	1331	7	0.5	0.2	1.1
		Medically Attended	1340	7	0.5	0.2	1.1	1331	5	0.4	0.1	0.9
	Vomiting	Overall	1340	195	14.6	12.7	16.6	1331	210	15.8	13.9	17.8
		Grade 3	1340	56	4.2	3.2	5.4	1331	47	3.5	2.6	4.7
		Related	1340	123	9.2	7.7	10.9	1331	133	10.0	8.4	11.7
		Grade 3 Related	1340	34	2.5	1.8	3.5	1331	35	2.6	1.8	3.6
		Medically Attended	1340	9	0.7	0.3	1.3	1331	4	0.3	0.1	0.8

			HRV Liq					HRV Lyo				
						95% CI					95% CI	
Dose	Adverse event	Type	N	n	%	LL	UL	N	n	%	LL	UL
Overall/Subject	Cough / Runny Nose	Overall	677	237	35.0	31.4	38.7	674	235	34.9	31.3	38.6
		Grade 3	677	4	0.6	0.2	1.5	674	6	0.9	0.3	1.9
		Related	677	106	15.7	13.0	18.6	674	112	16.6	13.9	19.6
		Grade 3 Related	677	2	0.3	0.0	1.1	674	4	0.6	0.2	1.5
		Medically Attended	677	20	3.0	1.8	4.5	674	18	2.7	1.6	4.2
	Diarrhea	Overall	677	58	8.6	6.6	10.9	674	71	10.5	8.3	13.1
		Grade 3	677	5	0.7	0.2	1.7	674	9	1.3	0.6	2.5
		Related	677	45	6.6	4.9	8.8	674	57	8.5	6.5	10.8
		Grade 3 Related	677	4	0.6	0.2	1.5	674	8	1.2	0.5	2.3
		Medically Attended	677	4	0.6	0.2	1.5	674	1	0.1	0.0	0.8
	Fever (C)	Overall	677	66	9.7	7.6	12.2	674	56	8.3	6.3	10.7
		>= 38	677	66	9.7	7.6	12.2	674	56	8.3	6.3	10.7
		> 38.5	677	20	3.0	1.8	4.5	674	10	1.5	0.7	2.7
		> 39	677	5	0.7	0.2	1.7	674	3	0.4	0.1	1.3
		> 39.5	677	2	0.3	0.0	1.1	674	0	0.0	0.0	0.5
		Related	677	0	0.0	0.0	0.5	674	0	0.0	0.0	0.5
		> 39.5 Related	677	0	0.0	0.0	0.5	674	0	0.0	0.0	0.5
		Medically Attended	677	7	1.0	0.4	2.1	674	6	0.9	0.3	1.9
	Irritability / Fussiness	Overall	677	507	74.9	71.4	78.1	674	486	72.1	68.6	75.5
		Grade 3	677	66	9.7	7.6	12.2	674	48	7.1	5.3	9.3
		Related	677	403	59.5	55.7	63.3	674	389	57.7	53.9	61.5
		Grade 3 Related	677	51	7.5	5.7	9.8	674	42	6.2	4.5	8.3
		Medically Attended	677	7	1.0	0.4	2.1	674	4	0.6	0.2	1.5
	Loss of appetite	Overall	677	290	42.8	39.1	46.7	674	259	38.4	34.7	42.2
		Grade 3	677	8	1.2	0.5	2.3	674	8	1.2	0.5	2.3
		Related	677	208	30.7	27.3	34.4	674	191	28.3	25.0	31.9
		Grade 3 Related	677	6	0.9	0.3	1.9	674	7	1.0	0.4	2.1
		Medically Attended	677	7	1.0	0.4	2.1	674	5	0.7	0.2	1.7
	Vomiting	Overall	677	151	22.3	19.2	25.6	674	162	24.0	20.9	27.4
		Grade 3	677	41	6.1	4.4	8.1	674	39	5.8	4.1	7.8
		Related	677	101	14.9	12.3	17.8	674	108	16.0	13.3	19.0
		Grade 3 Related	677	28	4.1	2.8	5.9	674	30	4.5	3.0	6.3
		Medically Attended	677	9	1.3	0.6	2.5	674	4	0.6	0.2	1.5

HRV Liq=HRV vaccine liquid formulation; HRV Lyo=HRV vaccine lyophilized formulation
For each dose: N=number of subjects with the corresponding administered dose, n/%=number/percentage of subjects reporting the type of adverse event at least once following the corresponding dose
For overall/dose: N=number of administered doses, n/%=number/percentage of doses followed by at least one type of adverse event
For overall/subject: N=number of subjects with at least one administered dose, n/%=number/percentage of subjects reporting the type of adverse event at least once
95% CI=exact 95% confidence interval; LL=lower limit; UL=upper limit
Source: Table 14.3.1.5 (27MAY2021 7:20 GMT)

Assessor Comments

Solicited AEs collected during the 8-day post-vaccination period are Cough/Runny nose; Diarrhea; Fever; Irritability/Fussiness; Loss of appetite and Vomiting.

Similar percentages of subjects reported solicited AEs after administration of the HRV Liquid PCV-free or HRV Lyophilized formulation (overall/subject). The most frequently reported solicited AEs are irritability/Fussiness (74.9% and 72.1%, respectively in the HRV Liquid and HRV Lyophilized group), followed by Loss of appetite (42.8% vs. 38.4%, respectively), cough/Runny nose (35.0% vs. 34.9%, respectively), vomiting (22.3% vs. 24.0%) and Diarrhea (8.6% vs. 10.5%). Fever was only solicited AE reported by less than 10% of the subject and was mainly mild.

The frequency of solicited AEs reported after the first and second dose is similar. Only for Irritability/Fussiness, the frequency is slightly lower after the second dose in both the HRV Liquid PCV-free (Dose 1: 63.7% (95% CI: 59.9-67.3) vs. Dose 2: 55.5% (95% CI: 51.6-59.3)) and HRV Lyophilized group (Dose 1: 63.5% (95% CI: 59.7-67.1) vs. Dose 2: 55.1% (95% CI: 51.2-58.9)).

The most commonly reported Grade 3 solicited AEs were Irritability/Fussiness (9.7% vs. 7.1% in the HRV Liquid and HRV lyophilized group, respectively) and Vomiting (6.1% vs. 5.8%, respectively). For all other solicited AEs, Grade 3 events were reported for less than 1.5% of the subjects. No significant differences in frequency of Grade 3 events are observed between both groups, or between first and second dose.

Clinical investigators considered approximately 70% of all events of Diarrhea, Irritability/Fussiness, Loss of Appetite and Vomiting related to the study vaccine. Relatedness was a bit lower for Cough/Runny

Nose (approximately 40%) and none of the fever episodes were considered related. Overall, relatedness was well balanced between the HRV liquid and HRV lyophilized group and after the first and second dose.

Medically attended solicited AEs were reported for ≤1% of the subjects, except for Cough/Runny nose (3.0% vs. 2.7% in the HRV Liquid and HRV Lyophilized group, respectively) and Vomiting in the HRV Liquid group (1.3%).

In the current SmPC, only diarrhea and irritability are considered common AEs possibly related to vaccination. The severity of all solicited AEs was not found to be significantly different in the group receiving Rotarix compared to placebo, in 3 placebo-controlled trials. In addition, there was also no difference in incidence or severity after the first or second dose.

To conclude, no meaningful differences are observed in the frequency of solicited adverse events between the HRV Liquid and HRV Lyophilized group.

Unsolicited Adverse Events during the 31 days (Day 1 - Day 31) following HRV vaccination

Table 6. Percentage of subjects with unsolicited adverse events classified by MedDRA Primary System Organ Class and Preferred Term with causal relationship to vaccination, during the 31 days (Day 1 - Day 31) following HRV vaccination - Exposed Set (CSR Table 12.3)

		HRV Liq N=677				HRV Lyo N=674			
				95% CI				95% CI	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL
At least one adverse event		17	2.5	1.5	4.0	30	4.5	3.0	6.3
Gastrointestinal disorders (10017947)	At least one PT related to the corresponding SOC	11	1.6	0.8	2.9	11	1.6	0.8	2.9
	Abdominal discomfort (10000059)	0	0.0	0.0	0.5	1	0.1	0.0	0.8
	Abdominal pain (10000081)	1	0.1	0.0	0.8	1	0.1	0.0	0.8
	Abnormal faeces (10000133)	1	0.1	0.0	0.8	0	0.0	0.0	0.5
	Constipation (10010774)	4	0.6	0.2	1.5	0	0.0	0.0	0.5
	Diarrhoea (10012735)	1	0.1	0.0	0.8	4	0.6	0.2	1.5
	Faeces discoloured (10016100)	1	0.1	0.0	0.8	0	0.0	0.0	0.5
	Flatulence (10016766)	1	0.1	0.0	0.8	2	0.3	0.0	1.1
	Gastrointestinal pain (10017999)	0	0.0	0.0	0.5	1	0.1	0.0	0.8
	Haematochezia (10018836)	2	0.3	0.0	1.1	1	0.1	0.0	0.8
	Infrequent bowel movements (10059158)	1	0.1	0.0	0.8	0	0.0	0.0	0.5
	Vomiting (10047700)	0	0.0	0.0	0.5	2	0.3	0.0	1.1
General disorders and administration site conditions (10018065)	At least one PT related to the corresponding SOC	3	0.4	0.1	1.3	5	0.7	0.2	1.7
	Discomfort (10013082)	0	0.0	0.0	0.5	1	0.1	0.0	0.8
	Fatigue (10016256)	1	0.1	0.0	0.8	3	0.4	0.1	1.3
	Ill-defined disorder (10061520)	1	0.1	0.0	0.8	0	0.0	0.0	0.5
	Pain (10033371)	0	0.0	0.0	0.5	1	0.1	0.0	0.8
	Pyrexia (10037660)	1	0.1	0.0	0.8	1	0.1	0.0	0.8
Infections and infestations (10021881)	At least one PT related to the corresponding SOC	0	0.0	0.0	0.5	1	0.1	0.0	0.8
	Bronchiolitis (10006448)	0	0.0	0.0	0.5	1	0.1	0.0	0.8
Investigations (10022891)	At least one PT related to the corresponding SOC	0	0.0	0.0	0.5	1	0.1	0.0	0.8
	Body temperature increased (10005911)	0	0.0	0.0	0.5	1	0.1	0.0	0.8
Metabolism and nutrition disorders (10027433)	At least one PT related to the corresponding SOC	0	0.0	0.0	0.5	1	0.1	0.0	0.8
	Decreased appetite (10061428)	0	0.0	0.0	0.5	1	0.1	0.0	0.8

		HRV Liq N=677				HRV Lyo N=674			
				95% CI				95% CI	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL
Nervous system disorders (10029205)	At least one PT related to the corresponding SOC	1	0.1	0.0	0.8	6	0.9	0.3	1.9
	Lethargy (10024264)	0	0.0	0.0	0.5	1	0.1	0.0	0.8
	Somnolence (10041349)	1	0.1	0.0	0.8	5	0.7	0.2	1.7
Psychiatric disorders (10037175)	At least one PT related to the corresponding SOC	0	0.0	0.0	0.5	3	0.4	0.1	1.3
	Irritability (10022998)	0	0.0	0.0	0.5	3	0.4	0.1	1.3
Respiratory, thoracic and mediastinal disorders (10038738)	At least one PT related to the corresponding SOC	1	0.1	0.0	0.8	1	0.1	0.0	0.8
	Cough (10011224)	0	0.0	0.0	0.5	1	0.1	0.0	0.8
	Nasal congestion (10028735)	1	0.1	0.0	0.8	0	0.0	0.0	0.5
	Rhinorrhoea (10039101)	0	0.0	0.0	0.5	1	0.1	0.0	0.8
Skin and subcutaneous tissue disorders (10040785)	At least one PT related to the corresponding SOC	3	0.4	0.1	1.3	8	1.2	0.5	2.3
	Dermatitis diaper (10012444)	1	0.1	0.0	0.8	0	0.0	0.0	0.5
	Eczema (10014184)	1	0.1	0.0	0.8	1	0.1	0.0	0.8
	Erythema (10015150)	0	0.0	0.0	0.5	1	0.1	0.0	0.8
	Rash (10037844)	1	0.1	0.0	0.8	3	0.4	0.1	1.3
	Rash erythematous (10037855)	0	0.0	0.0	0.5	1	0.1	0.0	0.8
	Rash macular (10037867)	0	0.0	0.0	0.5	2	0.3	0.0	1.1

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=number of subjects in each group
n/%=number/percentage of subjects reporting the adverse event at least once
95% CI=exact 95% confidence interval; LL=lower limit; UL=upper limit
Source: Table 14.3.1.6.3 (27MAY2021 7:15 GMT)

Table 7. Percentage of subjects with grade 3 unsolicited adverse events classified by MedDRA Primary System Organ Class and Preferred Term during the 31 days (Day 1 - Day 31) following HRV vaccination Exposed Set (CSR Table 14.3.1.6.2)

		HRV Liq N=677				HRV Lyo N=674			
				95% CI				95% CI	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL
At least one adverse event		8	1.2	0.5	2.3	11	1.6	0.8	2.9
Gastrointestinal disorders (10017947)	At least one PT related to the corresponding SOC	2	0.3	0.0	1.1	4	0.6	0.2	1.5
	Abdominal discomfort (10000059)	0	0.0	0.0	0.5	1	0.1	0.0	0.8
	Abdominal pain (10000081)	1	0.1	0.0	0.8	0	0.0	0.0	0.5
	Diarrhoea (10012735)	0	0.0	0.0	0.5	2	0.3	0.0	1.1
	Gastrooesophageal reflux disease (10017885)	1	0.1	0.0	0.8	0	0.0	0.0	0.5
	Vomiting (10047700)	0	0.0	0.0	0.5	1	0.1	0.0	0.8
General disorders and administration site conditions (10018065)	At least one PT related to the corresponding SOC	3	0.4	0.1	1.3	1	0.1	0.0	0.8
	Ill-defined disorder (10061520)	1	0.1	0.0	0.8	0	0.0	0.0	0.5
	Pyrexia (10037660)	2	0.3	0.0	1.1	1	0.1	0.0	0.8
Infections and infestations (10021881)	At least one PT related to the corresponding SOC	3	0.4	0.1	1.3	4	0.6	0.2	1.5
	Bronchiolitis (10006448)	0	0.0	0.0	0.5	1	0.1	0.0	0.8
	Gastroenteritis viral (10017918)	0	0.0	0.0	0.5	1	0.1	0.0	0.8
	Otitis media acute (10033079)	1	0.1	0.0	0.8	1	0.1	0.0	0.8
	Pyelonephritis acute (10037597)	1	0.1	0.0	0.8	0	0.0	0.0	0.5

		HRV Liq N=677				HRV Lyo N=674			
				95% CI				95% CI	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL
Infections and infestations (10021881)	Respiratory syncytial virus bronchiolitis (10038718)	1	0.1	0.0	0.8	0	0.0	0.0	0.5
	Upper respiratory tract infection (10046306)	0	0.0	0.0	0.5	1	0.1	0.0	0.8
	Viral upper respiratory tract infection (10047482)	1	0.1	0.0	0.8	0	0.0	0.0	0.5
Nervous system disorders (10029205)	At least one PT related to the corresponding SOC	0	0.0	0.0	0.5	1	0.1	0.0	0.8
	Somnolence (10041349)	0	0.0	0.0	0.5	1	0.1	0.0	0.8
Psychiatric disorders (10037175)	At least one PT related to the corresponding SOC	0	0.0	0.0	0.5	1	0.1	0.0	0.8
	Irritability (10022998)	0	0.0	0.0	0.5	1	0.1	0.0	0.8
Skin and subcutaneous tissue disorders (10040785)	At least one PT related to the corresponding SOC	1	0.1	0.0	0.8	0	0.0	0.0	0.5
	Eczema (10014184)	1	0.1	0.0	0.8	0	0.0	0.0	0.5

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=number of subjects in each group
n/%=number/percentage of subjects reporting the adverse event at least once
95% CI=exact 95% confidence interval; LL=lower limit,UL=upper limit

Assessor Comments

During the 31-day post-vaccination period, unsolicited AEs were reported by 29.7% and 30.6% of subjects in the HRV Liquid group and HRV Lyophilized group, respectively.

Unsolicited AEs considered causally related to vaccination by the investigator were reported in 2.5% and 4.5% of subjects in the HRV Liquid group and HRV Lyophilized group, respectively. Most frequently reported was constipation in the HRV Liquid group (4 subjects, vs. 0 subjects in HRV Lyophilized) and somnolence in the HRV Lyophilized group (5 subjects, vs. 1 subject in HRV Liquid). The incidence rates of constipation and somnolence observed in Rota-096 are line with the observations in two other studies where subjects were vaccinated with HRV Liquid and HRV Lyophilized (Rota-081 and Rota-090). In addition, it is acknowledged that sleep disorders and constipation are common and not unexpected in infants (Rajindrajith S et al.; Mindell JA et al.). In the HRV Liquid group, one subject was diagnosed with Hematochezia. This non-serious adverse event was assessed as related to the study vaccine by the clinical investigator. The subject's parents/legally acceptable representatives decided to withdraw the subject from the study. Hematochezia is a known adverse reaction with unknown frequency after vaccination with Rotarix. However, the information provided for this AE is limited.

At least one Grade 3 unsolicited AE was reported by 1.2% (8 subjects) and 1.6% (11 subjects) of the subjects in both groups respectively. Each individual Medra PT was reported by only 2 subjects or less in each group.

Grade 3 unsolicited AEs considered as causally related were reported for 2 subjects in the HRV Liquid group (including Abdominal Pain; Ill-defined disorder) and by 3 subjects in the HRV Lyophilized group (including abdominal discomfort; Bronchiolitis; Somnolence). Of note: intussusception is a known very rare adverse reaction associated with rotavirus vaccine.

Medical attention following an unsolicited AE was needed for 16.1% of the subjects in the HRV Liquid group and for 20.3% of the subjects in the HRV Lyophilized group. Upper respiratory tract infection was the most commonly reported unsolicited AE requiring medical attention in both groups (3.0% and 4.7% of the subjects in HRV Liq and HRV Lyo groups, respectively). These frequencies are overall in line with the observations in the Rota-081 study (6.5% and 6.2% in HRV Liquid vs HRV Lyophilized group, respectively) and Rota-090 study (9.0% and 9.5% in HRV Liquid vs HRV Lyophilized group, respectively). Although it is known that upper respiratory tract infections are common in young children (Cinaroglu, S ; Weintraub B.), there is no data on the incidence of medically attended upper respiratory tract infection in the general population to compare with.

No meaningful differences were observed between countries in the frequency and type of unsolicited AEs.

It is unclear which adverse events occurred after the first or the second dose of the HRV vaccine as this is not discussed in the CSR.

Overall, unsolicited AEs, including Grade 3, medically attended and causally related AEs, are comparable after administration of the HRV Liquid or HRV Lyophilized formulation.

References:

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Rajindrajith S, Devanarayana NM. Constipation in children: novel insight into epidemiology, pathophysiology and management. J Neurogastroenterol Motil. 2011 ;17(1):35-47. doi: 10.5056/jnm.2011.17.1.35.

Weintraub B. Upper Respiratory Tract Infections. Pediatr Rev. 2015;36(12):554-556. doi: 10.1542/pir.36-12-554.

Deaths and Serious Adverse Events

There was no death reported in this study.

SAEs were collected during the entire study period.

- A total of 62 SAEs were reported in 39 subjects in the HRV Liq group (5.8% of subjects) and 59 SAEs were reported in 38 subjects in the HRV Lyo group (5.6% of subjects) (Table 8).
- In the HRV Liq group, 1 SAE (constipation) reported in 1 subject was assessed by the investigator as possibly causally related to the study vaccine.
  – One subject developed constipation on Day 7 of the first dose of the HRV liquid vaccine administration. The event was reported as resolved within 14 days from the onset day.
- None of the SAEs in the HRV Lyo group were assessed by the investigator as related to the study vaccine (Table 8).

Table 8. Percentage of subjects reporting SAEs classified by MedDRA Primary System Organ Class and Preferred Term from first study vaccination up to study end - Exposed Set (CSR Table 12.4)

			HRV Liq N=677			HRV Lyo N=674		
Type of Event	Primary System Organ Class (CODE)	Preferred Term (CODE)	n*	n	%	n*	n	%
SAE	At least one adverse event		62	39	5.8	59	38	5.6
	Congenital, familial and genetic disorders (10010331)	Osteogenesis imperfecta (10031243)	0	0	0.0	1	1	0.1
		Scaphocephaly (10049426)	0	0	0.0	1	1	0.1
	Gastrointestinal disorders (10017947)	Constipation (10010774)	1	1	0.1	1	1	0.1
		Vomiting (10047700)	1	1	0.1	0	0	0.0
	General disorders and administration site conditions (10018065)	Pyrexia (10037660)	1	1	0.1	3	3	0.4
	Infections and infestations (10021881)	Adenovirus infection (10060931)	1	1	0.1	1	1	0.1
		Bronchiolitis (10006448)	3	3	0.4	2	2	0.3
		Bronchitis (10006451)	1	1	0.1	0	0	0.0
		Cellulitis (10007882)	1	1	0.1	0	0	0.0
		Citrobacter infection (10051904)	1	1	0.1	0	0	0.0
		Croup infectious (10011416)	0	0	0.0	1	1	0.1
		Enterovirus infection (10014909)	2	2	0.3	1	1	0.1
		Escherichia infection (10061126)	0	0	0.0	1	1	0.1
		Escherichia urinary tract infection (10052238)	1	1	0.1	1	1	0.1
		Exanthema subitum (10015586)	3	3	0.4	3	3	0.4
		Gastroenteritis (10017888)	2	2	0.3	5	4	0.6
		Gastroenteritis enteroviral (10017901)	0	0	0.0	1	1	0.1
		Gastroenteritis norovirus (10068189)	0	0	0.0	1	1	0.1
		Gastroenteritis salmonella (10017914)	3	3	0.4	0	0	0.0
		Gastroenteritis viral (10017918)	1	1	0.1	0	0	0.0
		Human bocavirus infection (10077391)	0	0	0.0	1	1	0.1
		Influenza (10022000)	3	3	0.4	2	2	0.3
		Meningitis (10027199)	0	0	0.0	1	1	0.1
		Meningitis streptococcal (10027256)	1	1	0.1	0	0	0.0
		Metapneumovirus infection (10066226)	1	1	0.1	0	0	0.0
		Parainfluenzae virus infection (10061907)	1	1	0.1	2	2	0.3
		Picornavirus infection (10076233)	0	0	0.0	1	1	0.1
		Pneumonia (10035664)	3	3	0.4	3	3	0.4

			HRV Liq N=677			HRV Lyo N=674		
Type of Event	Primary System Organ Class (CODE)	Preferred Term (CODE)	n*	n	%	n*	n	%
		Pneumonia respiratory syncytial viral (10035732)	0	0	0.0	1	1	0.1
		Pyelonephritis acute (10037597)	1	1	0.1	0	0	0.0
		Respiratory syncytial virus bronchiolitis (10038718)	5	5	0.7	2	2	0.3
		Rhinovirus infection (10061494)	1	1	0.1	2	2	0.3
		Roseola (10039222)	1	1	0.1	0	0	0.0
		Streptococcal sepsis (10048960)	1	1	0.1	0	0	0.0
		Upper respiratory tract infection (10046306)	5	5	0.7	6	6	0.9
		Urinary tract infection (10046571)	6	6	0.9	4	4	0.6
		Urosepsis (10048709)	0	0	0.0	1	1	0.1
		Viral infection (10047461)	2	2	0.3	1	1	0.1
		Viral rash (10047476)	0	0	0.0	1	1	0.1
	Injury, poisoning and procedural complications (10022117)	Craniocerebral injury (10070976)	0	0	0.0	1	1	0.1
		Ear canal abrasion (10052434)	0	0	0.0	1	1	0.1
		Head injury (10019196)	1	1	0.1	1	1	0.1
	Metabolism and nutrition disorders (10027433)	Lactose intolerance (10023681)	1	1	0.1	0	0	0.0
	Nervous system disorders (10029205)	Febrile convulsion (10016284)	1	1	0.1	0	0	0.0
		Haemorrhage intracranial (10018985)	0	0	0.0	1	1	0.1
	Respiratory, thoracic and mediastinal disorders (10038738)	Acute respiratory failure (10001053)	0	0	0.0	1	1	0.1
	Skin and subcutaneous tissue disorders (10040785)	Eczema (10014184)	6	2	0.3	2	1	0.1
	Vascular disorders (10047065)	Kawasaki's disease (10023320)	0	0	0.0	1	1	0.1
Related SAE	At least one adverse event		1	1	0.1	0	0	0.0
	Gastrointestinal disorders (10017947)	Constipation (10010774)	1	1	0.1	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
N=number of subjects with administered dose
n/%=number/percentage of subjects reporting the adverse event at least once
n*=Number of events reported
Related=assessed by the investigator as related
Source: Table 14.3.1.8 (27MAY2021 7:14 GMT)

Assessor Comments

At least one SAE was reported by 39 subjects (62 events) in the HRV Liquid group and by 38 subjects (59 events) in the HRV Lyophilized group. All subjects with an SAE were hospitalized, except for one subject with Exanthema Subitum.

The most frequently reported SAEs were upper respiratory tract infection (5 vs. 6 events in the HRV Liquid and HRV Lyophilized group, respectively), Urinary tract infection (6 vs. 4, respectively), Eczema (6 vs. 2, respectively), Respiratory Syncytial Virus bronchiolitis (5 vs. 2, respectively) and gastroenteritis (2 vs. 5, respectively).

One SAE of constipation was considered as possibly related to the vaccine in the HRV Liquid group. A 8-weeks old male infant developed mild constipation 6 days after the first vaccination and was hospitalized due to no bowel output for 4 days and reduced oral intake. An abdominal X-ray was performed 3 days after onset and revealed no dilated bowels. The event resolved after 14 days. The subject had no symptoms after the second dose of the vaccine.

None of the SAEs in the HRV Lyophilized group were considered related to the study vaccine by the clinical investigator.

Intussusception, a known very rare adverse reaction associated with rotavirus vaccines was not reported in this trial.

The majority of the SAEs were mild or moderate in intensity and 14 SAEs were severe.

No deaths were reported in this trial.

2.3.3. Discussion on clinical aspects

In the phase III randomized Rotarix trial ROTA-096, the safety profile of a HRV Liquid PCV-free formulation was compared with the HRV Lyophilized formulation in 675 infants per group (target sample size) of 6-12 weeks old at time of first vaccination.

The study was performed in Hong Kong, Turkey, United States, Canada and Taiwan. The race of most participants was White (50.7%) or Asian (44.6%) and baseline characteristics are well balanced between both groups.

The number of subjects who reported at least one solicited or unsolicited AEs during the 8-day period following vaccination (overall/subject) was similar for the HRV Liquid group (85.2%) compared to the HRV Lyophilized group (82.5%).

The most frequently reported solicited AEs during 8 days following vaccination are irritability/Fussiness (74.9% and 72.1%, respectively in the HRV liquid and HRV Lyophilized group), followed by Loss of appetite (42.8% vs. 38.4%, respectively), cough/Runny nose (35.0% vs. 34.9%, respectively). Grade 3 events were reported for approximately 5-10% of Irritability/Fussiness and Vomiting events, while for all other solicited AEs Grade 3 events were reported for less than 1.5% of the subjects. In the current SmPC, only diarrhea and irritability are considered common AEs possibly related to vaccination. The severity of the all solicited AEs was not found to be significantly different in the group receiving Rotarix compared to placebo, in 3 placebo-controlled trials.

During the 31-day post-vaccination period, unsolicited AEs were reported by 29.7% and 30.6% of subjects in the HRV Liquid group and HRV Lyophilized group, respectively. Grade 3 unsolicited AEs considered as causally related were reported for 2 subjects in the HRV Liquid group (including Abdominal Pain; Ill-defined disorder) and by 3 subjects in the HRV Lyophilized group (including abdominal discomfort; Bronchiolitis; Somnolence).

In total 121 SAEs were reported by 77 subjects. One SAE of constipation, starting 6 days after vaccination, was considered as possibly related to the HRV Liquid vaccine. The SAE was resolved after 14 days. Intussusception, a known very rare adverse reaction associated with rotavirus vaccines was not reported in this trial.

No deaths were reported in the trial.

Overall, the reactogenicity and safety profile of the PCV-free liquid vaccine, was comparable to the HRV lyophilized vaccine when administered as a 2-dose vaccination. No safety concerns were raised and the data are in line with the current version of the SmPC.

3. Rapporteur's overall conclusion and recommendation

The reactogenicity and safety profile of the HRV Liquid PCV-free and HRV Lyophilized formulation, administered in a 2-dose schedule, is comparable in infants of 6-12 weeks of age at the time of first vaccination. No additional safety concerns have been identified. No update of the SmPC is needed.

☒ Fulfilled:

4. Additional clarification requested

Based on the data submitted, the MAH should address the following question as part of this procedure:

1) The most frequently reported unsolicited AEs considered causally related to vaccination by the investigator were constipation in the HRV Liquid group (4 subjects, vs. 0 subjects in HRV Lyophilized) and somnolence in the HRV Lyophilized group (5 subjects, vs. 1 subject in HRV

Liquid). Upper respiratory tract infection was the most commonly reported unsolicited AE requiring medical attention in both groups (3.0% and 4.7% of the subjects in HRV Liq and HRV Lyo groups, respectively). As these AEs are currently not listed as adverse reactions in the SmPC, the MAH is required to discuss their incidence in the light of the observation made during previous clinical studies.

The timetable is a 30 day response timetable without clock stop.

MAH responses to Request for supplementary information

Question 1

Studies Rota-081 and Rota-090 were selected for this discussion since these studies compare HRV PCV free Liquid versus HRV Lyophilized formulations as does Rota-096. The age groups in the three studies are similar and the sample size of the analysis sets was comparable.

- **Rota-081**: A phase IIIA, randomised, observer-blind, multi-centre study to evaluate the clinical consistency of 3 production lots of the PCV-free liquid formulation of GSK's oral live attenuated HRV vaccine and to evaluate the PCV-free liquid formulation of GSK's HRV vaccine as compared to the currently licensed lyophilised formulation of the HRV vaccine in terms of immunogenicity, reactogenicity and safety when administered as a 2-dose vaccination in healthy infants starting at age 6-12 weeks.
- **Rota-090**: A phase IIIA, randomised, single-blind, multi-centric study to evaluate the immunogenicity, reactogenicity and safety of 3 doses of Pediarix, Hiberix and Prevenar 13 when co-administered with 2 doses of the PCV-free liquid formulation of GSK's oral live attenuated HRV vaccine as compared to the currently licensed lyophilised formulation of the HRV vaccine in healthy infants 6-12 weeks of age.

In the Rota-096 study, causally related adverse events following immunisation (AEFI) were collected up to 31 days following vaccination. In order to discuss the incidence of constipation and somnolence in the Rota-096 study, we used the tables presenting the percentage of subjects reporting unsolicited adverse events classified by MedDRA Primary System Organ Class and Preferred Term with causal relationship to vaccination, during the 31 days following HRV vaccination.

In the Rota-096 study, medically attended AEFI were collected up to 31 days following vaccination. In order to discuss the incidence of upper respiratory tract infection in the Rota-096 study, we used the table presenting the percentage of subjects with unsolicited adverse events leading to medical attention classified by MedDRA Primary System Organ Class and Preferred Term during the 31 days following HRV vaccination.

Incidence of constipation and somnolence with causal relationship to vaccination in Rota-096 and other clinical studies:

A summary of the data from the different studies is presented in Table 9 and Table 10.

Given the low number of reported constipation cases in the studies, data should be interpreted with caution. Based on the data presented in Table 9 and Table 10 no trend of increased incidence of constipation or somnolence with causal relationship to vaccination was observed in Rota-096 compared to Rota-081 and Rota-090.

Table 9. Summary table of percentage of subjects reporting the occurrence of constipation with causal relationship to vaccination within the 31-days post-vaccination period

Study	HRV Liquid					HRV Lyophilized				
				95% CI					95% CI	
	N	n	%	LL	UL	N	n	%	LL	UL
Rota-081	1198	2	0.2	0.0	0.6	402	2	0.5	0.1	1.8
Rota-090	632	0	0.0	0.0	0.6	640	2	0.3	0.0	1.1
Rota-096	677	4	0.6	0.2	1.5	674	0	0.0	0.0	0.5

Source: Data based on, Rota-081, Rota-090 and Rota-096 individual clinical study reports.
Notes: N=number of subjects having received at least one dose
n/ (%) = number/ (percentage) of subjects reporting at least one unsolicited adverse event within 31 days after any doses
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Table 10. Summary table of percentage of subjects reporting the occurrence of somnolence with causal relationship to vaccination within the 31-days post-vaccination period

Study	HRV Liquid					HRV Lyophilized				
				95% CI					95% CI	
	N	N	%	LL	UL	N	n	%	LL	UL
Rota-081	1198	3	0.3	0.1	0.7	402	0	0.0	0.0	0.9
Rota-090	632	5	0.8	0.3	1.8	640	4	0.6	0.2	1.6
Rota-096	677	1	0.1	0.0	0.8	674	5	0.7	0.2	1.7

Source: Data based on Rota-081, Rota-090 and Rota-096 individual clinical study reports.
Notes: N=number of subjects having received at least one dose
n/ (%) = number/ (percentage) of subjects reporting at least one unsolicited adverse event within 31 days after any doses
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Incidence of upper respiratory tract infection requiring medical attention in ROTA-096 and other clinical studies:

A summary of the data from the different studies is presented in Table 11.

Based on the data presented in Table 11 no trend of increased incidence of upper respiratory tract infection requiring medical attention was observed in the Rota-096 study compared to Rota-081 and Rota-090.

Table 11. Summary table of percentage of subjects reporting the occurrence of upper respiratory tract infection requiring medical attention within the 31-days post-vaccination period

Study	HRV Liquid					HRV Lyophilized				
				95% CI					95% CI	
	N	n	%	LL	UL	N	n	%	LL	UL
Rota-081	1198	78	6.5	5.2	8.1	402	25	6.2	4.1	9.0
Rota-090	632	57	9.0	6.9	11.5	640	61	9.5	7.4	12.1
Rota-096	677	20	3.0	1.8	4.5	674	32	4.7	3.3	6.6

Source: Data based on Rota-081, Rota-090 and Rota-096 individual clinical study reports.
Notes: N=number of subjects having received at least one dose
n/ (%) = number/ (percentage) of subjects reporting at least one unsolicited adverse event within 31 days after any doses
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Conclusion

Table 9, Table 10 and Table 11 show that the observed incidence of constipation and somnolence related to vaccination and upper respiratory tract infection requiring medical attention in Rota-096 study is in line with the incidence observed in studies Rota-081 and Rota-090.

Childhood constipation is a common problem worldwide. Constipation could be caused by underlying functional or organic causes. Because only a minority of patients suffering from constipation seek health care, it is difficult to capture the exact burden (Mugie SM et al). The prevalence of childhood constipation in the general population ranged from 0.7% to 29.6% in children from 0 to 18-year-old (Rajindrajith S et al.).

Sleep disorders are common problems for children and adolescents, with estimates indicating that approximately 20% to 25% of the paediatric population experience some type of sleep disturbance (Mindell JA et al.). Sleep patterns develop rapidly during the first few years of life and this development is a highly dynamic process. At birth, infants lack an established circadian rhythm and hence sleep across multiple intervals throughout the day and night (Tham EK. et al.). Because of these sleep disorders, somnolence is not unexpected in the paediatric population.

Respiratory tract infections (RTI) are a major public health issue in both developed and developing countries (Ge X et al.). In Turkey, one of the countries in which study Rota-096 was conducted, upper respiratory tract infections (URIs) were the most common diseases in children aged 0–6 years with a prevalence of 41.9% (Cinaroglu, S). Children get two to eight URIs annually in the first 2 years after birth; those who attend day care may have as many as 14 annually (Weintraub B.). URIs are more common in children compared to adults because their immune systems are still developing. Functional immune immaturity, anatomical immaturity of respiratory system, seasonality and frequent contact with the family members are the main causes of URIs.

The observed incidence of constipation and somnolence related to vaccination and upper respiratory tract infection requiring medical attention in Rota-096 study is therefore in line with the prevalence in similar age group irrespective of Rotarix administration.

Based on the above information and evaluation, no concern is raised regarding incidence of AEs of constipation and somnolence related to vaccination and upper respiratory tract infection requiring medical attention in Rota-096 study.

Assessor Comments

The MAH compared the incidence of constipation and somnolence with causal relationship to vaccination, and upper respiratory tract infection requiring medical attention in the Rota-096 study with the incidence

in two other studies, Rota-081 and Rota-090. In all three studies, healthy infants of 6-12 weeks old received a 2-dose vaccination with the PCV-free liquid formulation or the lyophilised HRV vaccine formulation.

In all 3 studies, related AEs and medically attended AEs were collected up to 31 days following vaccination.

For constipation, overall the number of cases reported in all 3 studies was low. Although taking this into consideration, there was a small imbalance in number of subjects reporting this related AE between the HRV liquid group (4 subjects out of 677) and the HRV Lyophilized group (0 subjects out of 674) in the Rota-096 study. There was no indication for a difference between the HRV liquid group and HRV Lyophilized group in the Rota-081 (2 subjects out of 1198 and 2 subjects out of 402 reported related constipation in both groups, respectively) and Rota-090 study (0 subjects out of 632 and 2 subjects out of 640 reported related constipation in both groups, respectively). The MAH refers to a publication describing that childhood constipation in the general population ranges from 0.7% to 29.6% in children 0-18 yoa (Rajindrajith S et al.).

The incidence of somnolence in the study Rota-096 was higher in the HRV Lyophilized group (5 subjects out of 674) compared to the HRV liquid group (1 subject out of 677). This data is in line with the Rota-081 (3 subjects out of 1198 and 0 subjects out of 402 reported related constipation in HRV Liquid vs HRV Lyophilized group, respectively) and Rota-090 study (5 subjects out of 632 and 4 subjects out of 640 reported related constipation in both groups, respectively), with the overall incidence being similar in both groups. The MAH indicates that approximately 20% to 25% of the paediatric population experience some type of sleep disturbance (Mindell JA et al.).

Although not possible to compare incidence rates of constipation and somnolence within 31 days after vaccination in the Rota-studies, with the incidences reported in referred publications, it is acknowledged that sleep disorders and constipation are common and not unexpected in infants. We agree that the incidences of constipation and somnolence observed in Rota-096 are line with the observations form Rota-081 and Rota-090.

In the Rota-096 study, upper respiratory tract infection was the most commonly reported unsolicited AE requiring medical attention in both groups (3.0% and 4.7% of the subjects in HRV Liquid and HRV Lyophilized groups, respectively). However, the incidence was similar or even higher in the Rota-081 study (6.5% and 6.2% in HRV Liquid vs HRV Lyophilized group, respectively) and Rota-090 study (9.0% and 9.5% in HRV Liquid vs HRV Lyophilized group, respectively). The MAH indicates that the prevalence of upper respiratory tract infections in 0-6 yoa children in Turkey (were 20.4% of subjects in Rota-096 were enrolled) is 41.9% (Cinaroglu, S). In addition, Children get two to eight URIs annually in the first 2 years after birth; those who attend day care may have as many as 14 annually (Weintraub B.).

We acknowledge that upper respiratory tract infections are common in children, although the incidence of medically attended upper respiratory tract infection in the general population is unknown and the data of the Rota-studies cannot be compared with the incidences reported in the publications. The frequencies observed in Rota-096 are in line with the observations from Rota-081 and Rota-090.

Based on the data provided, we can conclude that, in Rota-096, the incidence of constipation and somnolence related to vaccination, and upper respiratory tract infection requiring medical attention is in line with results from Rota-081 and Rota-090. Moreover, although the available data are very limited, the observed incidences do not seem to be higher than the expected incidences in similar age group irrespective of Rotarix administration.

Issue resolved

Company comment on the assessment report

GlaxoSmithKline Biologicals is providing some comments on the preliminary assessment report in annex to the cover letter of this submission. The Company expects to receive the final assessment report at the end of the procedure for further review for confidential information before it is published as the EPAR.

Assessor Comments

The changes proposed by the MAH are considered acceptable and have been implemented.