EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

12 March 2015
EMA/170781/2015
Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report for paediatric studies submitted in accordance with article 46 of regulation (EC) No1901/2006, as amended

Rotarix

rotavirus vaccine, live

Procedure No: EMEA/H/C/000639

P46 072

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

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I. RECOMMENDATION

Based on the review of the paediatric data on safety and immunogenicity collected in study Rota-074 the Rapporteur considers that the benefit-risk balance for the above mentioned product remains unchanged and therefore does not require further regulatory action on the marketing authorisation for Rotarix. The SmPC and PIL remain unchanged.

II. SCIENTIFIC DISCUSSION

The current study was submitted to comply with the requirements of Article 46 of the regulation 1901/2006. The study has not been conducted in accordance with an agreed paediatric investigation plan.

Adhering to the requirements of Chinese regulatory authorities and in order to support the licensure of GSK Biologicals' liquid HRV vaccine in China, it was necessary to conduct a Phase I safety study in the targeted infant population. This study was conducted to collect reactogenicity and safety data of liquid HRV vaccine from infants aged 6 to 16 weeks at the time of the first dose of vaccination. In addition, the immunogenicity of the liquid HRV vaccine was also explored in order to assess the anti-RV IgA antibody concentrations and vaccine take.

1. STUDY METHODOLOGY

1. Objectives

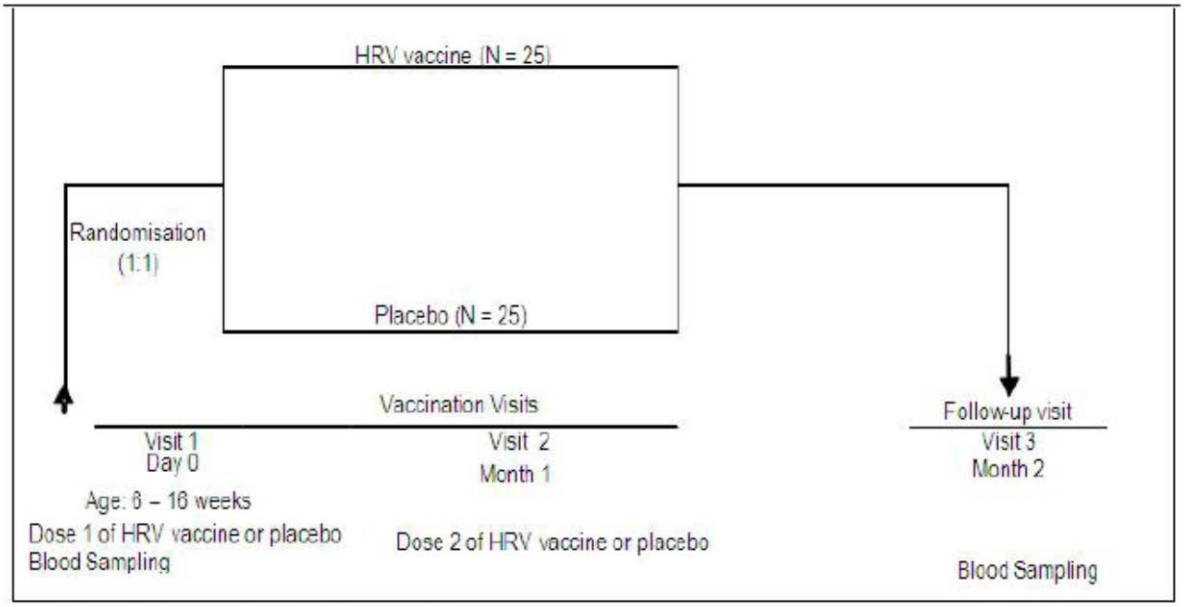
Primary
To assess the reactogenicity of the liquid HRV vaccine when compared to placebo in terms of grade 3 solicited adverse events (AEs).

Secondary
- To assess the reactogenicity of the liquid HRV vaccine when compared to placebo in terms of solicited AEs.
- To assess the safety of the liquid HRV vaccine when compared to placebo in terms of unsolicited AEs and serious adverse events (SAEs).

Exploratory
- To explore the excretion of the rotavirus (RV) antigen in the stool samples collected at predetermined time points after each liquid HRV vaccine/placebo dose.
- To explore the immunogenicity of the liquid HRV vaccine in terms of seroconversion rate and Geometric Mean Concentrations (GMCs) after a two dose primary vaccination course.

2. Design

- Phase 1, Double-blind, randomised, placebo-controlled, single centre study, two parallel
- Balanced 1:1 randomisation.
- 6-16 weeks at the time of first vaccination were to receive two oral doses of liquid HRV vaccine or placebo at a 0, 1 month schedule.
- All subjects were to receive routine vaccination according to the local immunisation practice. The study consisted of three visits (Visit 1, Visit 2 and Visit 3).
- Blood samples collected at Visit 1 and Visit 3. Stools samples collected at Day 0 (or a day prior to vaccination), Day 7 and Day 15 after each dose of vaccination and at Visit 3.
- No restrictions on breast feeding



N: Number of subjects planned to be enrolled
HRV: Human rotavirus

Duration of the study:

Start: 13 April 2010
End: 28 June 2010

Outline of study procedures

Table 1 List of study procedures

Age	6-16 weeks		
Visit	Visit 1	Visit 2	Visit 3
Timing	Day 0	Month 1	Month 2
Sampling time point	Pre-vacc	Post-vacc 1	Post-vacc 2
Informed consent	●	-	-
Check of inclusion criteria	●	-	-
Check of exclusion criteria	●	-	-
Check of contraindications	●	●	-
Check of warnings and precautions	●	●	-
Medical history	●	-	-
Physical examination	●	○	○
Pre-vaccination body temperature	●	●	-
Measurement/recording of height and weight	●	-	-
Recording of gestational age	●	-	-
Randomisation	●	-	-
Recording of oral vaccine intake characteristics†	●	●	-
Collection of stool samples from subjects on the day of each dose of HRV vaccine or placebo (Day 0) or a day before, on Day 7 and Day 15 after each dose of liquid HRV vaccine or placebo and at Visit 3	●	●	●
Collection of blood sample from subjects for antibody determination (3mL)	●	-	●
Vaccination (liquid HRV vaccine or placebo)	●	●	-
Daily post-vaccination recording of solicited AEs within 8-day (Day 0–Day 7) by subjects' parents/LARs	●	●	-
Recording of unsolicited AEs within 31-day (Day 0-Day 30) post-vaccination	●	●	●
Return of diary cards	-	○	○
Diary card transcription by investigator	-	●	●
Recording of any concomitant medication/vaccination	●	●	●
Recording of any intercurrent medical conditions	●	●	●
Recording of SAEs	●	●	●
Study Conclusion	-	-	●

● Study procedure that required documentation in the individual eCRF.
○ Study procedure that did not require documentation in the individual eCRF.
† Smooth vaccine intake, vaccine intake interrupted due to coughing or choking, regurgitation after vaccine intake, vomiting after vaccine intake.

Inclusion and exclusion criteria: cf. Clinical Study Report

Composition of HRV vaccine and placebo

Table 3 Composition of HRV vaccine and placebo

Vaccine	Formulation	Presentation	Volume
GSK Biologicals' liquid HRV vaccine	RIX4414 HRV strain at least $10^{6.0}$ median $CCID_{50}$ at the end of shelf life Sucrose 55% w/w Di-sodium Adipate 132.74 mg DMEM 2.26 mg water for injection q.s. as 1.5 mL	Liquid in a pre-filled oral applicator.	1.5 mL
GSK Biologicals' Placebo for liquid HRV vaccine	Sucrose 55% w/w Di-sodium Adipate 132.74 mg DMEM 2.26 mg water for injection q.s. as 1.5 mL	Liquid in a pre-filled oral applicator.	1.5 mL

$CCID_{50}$ = median Cell Culture Infective Dose (quantity of virus causing infection in 50% of exposed cells)
DMEM = Dulbecco's Modified Eagle Medium

Lot number: study vaccine: AROLA158C; placebo vaccine: PROLA007A

3. Laboratory assays and time-points

Stool analysis

Two aliquots were prepared for all stool samples collected at pre-determined time points: One aliquot was shipped frozen to a National Institute for Food and Drug Control (NIFDC in China) [previously known as the National Institute for the Control of Pharmaceutical and Biological products (NICPBP)] and the other aliquot was shipped frozen to GSK Biologicals, Belgium, for back-up.

All stool samples were analysed by ELISA for detection of RV antigen to assess RV antigen excretion. Presence of RV antigen demonstrated by ELISA in any stool collected at pre-determined time points after Dose 1 up to Visit 3 were considered as vaccine virus shedding.

Serum analysis

Two aliquots were prepared for all serum samples collected at Visit 1 and Visit 3: One aliquot was shipped frozen to a qualified laboratory in China and the other aliquot was shipped frozen to GSK Biologicals, Belgium (or Sponsor designated laboratory), for back-up.

Serum obtained from whole blood samples collected from subjects at Visit 1 and Visit 3 were tested by ELISA to measure serum anti-RV IgA antibody concentrations. The assay cut-off was 20 U/mL. Table 5 gives the assay method used for determining the antibody concentration and the assay cut-off.

4. Assessment of safety variables

Adverse events

The following general AEs were solicited as shown in Table 6:

Table 6 Solicited general adverse events

Fever*
Irritability/Fussiness
Diarrhoea
Vomiting
Loss of appetite
Cough/runny nose

*Fever was defined as: axillary temperature ≥ 37.1°C (as defined by the Chinese authorities) or ≥37.5°C (as defined by GSK Biologicals)

Assessment of intensity of Adverse Events

Cf. Clinical Study report p. 43-46

The intensity scales are represented in Tables 7.

Table 7 Intensity scales for solicited symptoms reported during the solicited follow-up period

Adverse Event	Intensity grade	Parameter
Fever*		Recorded temperature in °C
Irritability/Fussiness	0	Behaviour as usual
	1	Cried more than usual/no effect on normal activity
	2	Cried more than usual/interfered with normal activity
	3	Crying that could not be comforted/prevented normal activity
Diarrhoea¶		Recorded the number of looser than normal stools/day
Vomiting§		Recorded the number of vomiting episodes/day
Loss of appetite	0	Appetite as usual
	1	Ate less than usual/no effect on normal activity
	2	Ate less than usual/interfered with normal activity
	3	Did not at all
Cough/runny nose	0	Normal
	1	Cough/runny nose which was easily tolerated
	2	Cough/runny nose which interfered with daily activity
	3	Cough/runny nose which prevented daily activity

*Fever was defined as: axillary temperature ≥ 37.1 °C (as defined by the Chinese authorities) or ≥37.5°C (as defined by GSK Biologicals).
¶Diarrhoea was defined as passage of three or more looser than normal stools within a day.
§Vomiting was defined as one or more episodes of forceful emptying of partially digested stomach contents ≥ 1 hour after feeding within a day.

The maximum intensity of diarrhoea, vomiting and fever that occurred during the solicited 8-day (Day 0-Day 7) follow-up period was scored as shown in Table 8.

Table 8 Intensity scales for diarrhoea, vomiting and fever reported during the solicited follow-up period

Adverse Experience	Intensity grade	Parameter
Diarrhoea	0	Normal (0 - 2 looser than normal stools/day)
	1	3 looser than normal stools/day
	2	4 - 5 looser than normal stools/day
	3	≥ 6 looser than normal stools/day
Vomiting	0	Normal (no emesis)
	1	1 episode of vomiting/day
	2	2 episodes of vomiting/day
	3	≥ 3 episodes of vomiting/day
Fever*	0	Axillary temperature < 37.1 °C
	1	Axillary temperature 37.1 °C - 37.5 °C
	2	Axillary temperature 37.6 °C - 39.0 °C
	3	Axillary temperature > 39.0 °C
Fever**	0	Axillary temperature < 37.5°C
	1	Axillary temperature ≥ 37.5 – ≤ 38.0°C
	2	Axillary temperature > 38.0 – ≤ 39.0°C
	3	Axillary temperature > 39.0°C

*The maximum intensity of fever using the grading scale as defined by Chinese authorities.
**The maximum intensity of fever using the grading scale as defined by GSK Biologicals.

5. Determination of sample size

Target enrolment was 50 eligible subjects (25 subjects in the HRV Group and 25 subjects in the Placebo Group) in order to obtain 40 evaluable subjects (20 subjects in each group). The estimated drop-out rate was 20%.

The primary objective of the study was to explore the reactogenicity of the vaccine in order to detect a large increase in the HRV Group as compared to the Placebo Group for the percentage of subjects reporting grade 3 solicited AEs during the 8-day (Day 0-Day 7) solicited follow-up period after each dose. With 25 subjects in the HRV Group and 25 subjects in the Placebo Group, Table 10 presents the increase in the percentage of subjects reporting at least one grade 3 solicited AE during the 8-day (Day

0-Day 7) solicited follow-up period after each dose that could have been detected in the HRV Group as compared to the Placebo Group, with 80% power, for a range of incidence rates:

Table 10 Detectable increase in the HRV Group as compared to the placebo control group

Incidence of at least one grade 3 solicited AE in the Placebo Group N = 25 subjects	Incidence in the HRV Group which could be detected with 80% power* N = 25 subjects
1%	28%
3%	33%
5%	36%
7%	40%
10%	44%
15%	51%

* PASS 2005, one–sided test for an inequality test of independent proportions, alpha = 2.5%, power = 80%

6. Study cohorts/data sets analyzed

Total vaccinated cohort (TVC)

The TVC included all subjects with at least one dose of liquid HRV vaccine or placebo administration documented:

- a safety analysis based on the TVC included all vaccinated subjects.
- an immunogenicity analysis based on the TVC included all vaccinated subjects for whom immunogenicity data was available.

ATP cohort for analysis of safety

The ATP cohort for safety included all subjects from the TVC:
- who had received the study vaccine according to the protocol,
- who had not received a vaccine forbidden by or not specified in the protocol,
- for whom the randomisation code had not been broken,
- for whom the study vaccine or placebo was administered according to the protocol,
- who were seronegative for serum anti-RV IgA antibodies on the day of Dose 1.

The TVC was used for the primary analysis of safety. The analysis on the ATP cohort for safety was to be performed only if more than 5% of the vaccinated subjects were excluded from the TVC.

ATP cohort for analysis of immunogenicity

The ATP cohort for immunogenicity included all subjects from the ATP cohort for safety:

- who had not received medication forbidden by the protocol,
- whose underlying medical condition was not forbidden by the protocol,
- for whom immunogenicity data was available, at pre-sampling and post-sampling time points,
- with no protocol violation of demographics (unknown age at study entry or outside reporting),
- who complied with the vaccination schedule,
- who complied with the blood sampling schedule,
- who had no RV other than the vaccine strain in GE stool samples collected up to Visit 3,
- who had no concomitant infection unrelated to the vaccine which might have influenced the immune response.

The primary analysis was based on the ATP cohort for analysis of immunogenicity. If, in any vaccine group, the percentage of vaccinated subjects with serological results excluded from the ATP cohort for analysis of immunogenicity was 5% or more, a second analysis based on the TVC was to be performed to complement the ATP analysis.

2. STUDY RESULTS

Subject disposition

Table 12 Number of subjects enrolled into the study as well as the number of subjects excluded from ATP analyses with reasons for exclusion

	Total			HRV Group		Placebo Group	
Title	n	s	%	n	s	n	s
Total cohort	50			25		25	
Total vaccinated cohort	**50**		**100**	**25**		**25**	
Study vaccine dose not administered according to the protocol (code 1070)	4	4		2	2	2	2
Others: Initially sero-positive or unknown status for anti-RV IgA on the day of Dose 1 (code 1500)	5	5		3	3	2	2
ATP cohort for safety	**41**		**82**	**20**		**21**	
Essential serological data missing (code 2100)	9	9		5	5	4	4
ATP cohort for immunogenicity	**32**		**64**	**15**		**17**	

HRV Group= Human Rotavirus vaccine
Placebo Group= Placebo
Note: Subjects may have more than one elimination code assigned
n = number of subjects with the elimination code assigned excluding subjects who have been assigned a lower elimination code number
s = number of subjects with the elimination code assigned
% = percentage of subjects in the considered ATP cohort relative to the TVC
ATP cohort for safety includes all vaccinated subjects with no elimination codes beginning with one thousand.
ATP cohort for immunogenicity includes all vaccinated subjects with no elimination codes beginning with one or two thousand

Table 13 Summary of demographic characteristics (Total vaccinated cohort)

Characteristics	Parameters or Categories	HRV Group N = 25		Placebo Group N = 25		Total N = 50	
		Value or n	%	Value or n	%	Value or n	%
Age (weeks) at vaccination Dose: 1	Mean	10.3	-	11.8	-	11	-
	SD	2.7	-	2.43	-	2.66	-
	Median	10	-	13	-	11	-
	Minimum	6	-	7	-	6	-
	Maximum	16	-	15	-	16	-
Age (weeks) at vaccination Dose: 2	Mean	15.2	-	16.4	-	15.8	-
	SD	2.71	-	2.38	-	2.6	-
	Median	15	-	17	-	16	-
	Minimum	11	-	11	-	11	-
	Maximum	20	-	20	-	20	-
	Unknown	2	-	3	-	5	-
Gender	Female	13	52	10	40	23	46
	Male	12	48	15	60	27	54
Geographic Ancestry	Asian - East Asian heritage	25	100	25	100	50	100

HRV Group = Human Rotavirus vaccine
Placebo Group = Placebo
N = total number of subjects
n (%) = number (percentage) of subjects in a given category
Value = value of the considered parameter
SD = standard deviation
Age (weeks) =age expressed in weeks
Unknown = Subjects who didn't receive Dose 2

A. Immunogenicity results

The exploratory analyses for immunogenicity was performed on the ATP cohort for immunogenicity and on TVC since more than 5% of the vaccinated subjects were eliminated from the ATP cohort for immunogenicity.

ATP cohort for immunogenicity analysis

Table 21 presents the anti-RV IgA antibody GMC and seroconversion rates for the ATP cohort for immunogenicity. Table 22 presents the anti-RV IgA antibody GMC calculated on subjects seropositive for anti-RV IgA antibodies at Visit 3 for the ATP cohort for immunogenicity.

Table 21 Anti-RV IgA antibody GMC and seroconversion rates (ATP cohort for immunogenicity)

Antibody	Group	Timing	N	≥ 20 U/ml				GMC		
				n	%	95% CI		value	95% CI	
						LL	UL		LL	UL
Anti-RV IgA	HRV	PRE	15	0	0	0	21.8	<20	-	-
		POST	15	13	86.7	59.5	98.3	272.8	99.8	746
	Placebo	PRE	17	0	0	0	19.5	<20	-	-
		POST	17	0	0	0	19.5	<20	-	-

HRV Group = Human Rotavirus vaccine
Placebo Group = Placebo
GMC = geometric mean antibody concentration calculated on all subjects
N = number of subjects with available results
n (%) = number (percentage) of subjects with concentration ≥ 20 U/mL
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PRE=Blood sample taken prior to Dose 1
POST=Blood sample taken after Dose 2 at Visit 3

Table 22 Anti-RV IgA antibody GMC calculated on subjects seropositive for anti-RV IgA antibodies at Visit 3 (ATP cohort for immunogenicity)

Antibody	Group	Timing	N	GMC		
				value	95% CI	
					LL	UL
Anti-RV IgA	HRV	POST	13	453.7	204.1	1008.4

HRV Group = Human Rotavirus vaccine
Placebo Group = Placebo
GMC = geometric mean antibody concentration calculated on subjects with concentration ≥ 20 U/mL
N = Number of subjects with concentration above ≥20 U/mL
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
POST=Blood sample taken after Dose 2 at Visit 3

Stool sample results

Table 23 presents the percentage of subjects with RV in stool samples (shedding) collected at pre-determined time points for the ATP cohort for immunogenicity.

Table 23 Percentage of subjects with RV in stool samples (shedding) collected at pre-determined time points (ATP cohort for immunogenicity)

Dose 1 of HRV vaccine or placebo									
Group	Day 0 of Dose 1			Day 7 of Dose 1			Day 15 of Dose 1		
	N	n	%	N	n	%	N	n	%
HRV vaccine	15	0	0	14	2	14.3	15	0	0
Placebo	17	0	0	17	0	0	17	0	0
Dose 2 of HRV vaccine or placebo									
Group	Day 0 of Dose 2			Day 7 of Dose 2			Day 15 of Dose 2		
	N	n	%	N	n	%	N	n	%
HRV vaccine	15	0	0	15	0	0	13	0	0
Placebo	17	0	0	15	0	0	17	0	0

Visit 3			
Group	Day 0 of Visit 3		
	N	n	%
HRV vaccine	14	0	0
Placebo	17	1	5.9

HRV Group = Human Rotavirus vaccine
Placebo Group = Placebo
N = number of subject with available stool results at the specified time point
n (%) = number (percentage) of subjects with RV in stool collected at the specified time point

Vaccine take

Assessor's note

"Vaccine take" is a combined immunogenicity endpoint based on seroconversion and/or shedding of the vaccine strain in stools. It is considered as being positive when serum IgA to RV in post-vaccination sera is at a concentration of ≥20 U/ml and/or when vaccine virus is shedding in any stool sample collected from Dose 1 of HRV vaccine or placebo up to Visit 3 (=one month after the last vaccine dose) in subjects who were negative for RV before Dose 1 of HRV vaccine or placebo.

Table 24 presents percentage of subjects with vaccine take at Visit 3 for the ATP cohort for immunogenicity. The percentage of subjects with vaccine take at Visit 3 was 86.7% [95% CI: 59.5; 98.3] in the HRV Group.

Table 24 Percentage of subjects with vaccine take at Visit 3 (ATP cohort for immunogenicity)

Group	Vaccine take on combined doses				
	N	n	%	95%CI : LL	95%CI : UL
HRV	15	13	86.7	59.5	98.3
Placebo	17	1	5.9	0.1	28.7

HRV Group = Human Rotavirus vaccine
Placebo Group = Placebo
N = number of subjects with available anti-RV IgA results at Visit 3 or with vaccine virus* in stools collected after Dose 1 of HRV vaccine or placebo up to Visit 3
n (%) = number (percentage) of subject who seropositive at Visit 3 or with vaccine virus* in stools collected after Dose 1 of HRV vaccine or placebo up to Visit 3
95% CI = exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit
*RV in stools collected at pre-determined time points up to Visit 3
*Presence of RV antigen demonstrated in the HRV group by ELISA in any stool collected at pre-determined time points after Dose 1 up to Visit 3 will be considered as vaccine virus shedding.

Total vaccinated cohort analysis

The immunogenicity results of the TVC are shown in Supplements 46, 47, 48 and 49.

Supplement 46 **Anti-RV IgA antibody GMC and Seropositivity rates (Total vaccinated cohort)**

Antibody	Group	Timing	N	≥ 20 U/ml				GMC		
				n	%	95% CI		value	95% CI	
						LL	UL		LL	UL
Anti-RV IgA	HRV	PRE	25	3	12	2.5	31.2	<20	-	-
		POST	20	18	90	68.3	98.8	323.7	147	713.1
	Placebo	PRE	25	2	8	1	26	<20	-	-
		POST	21	2	9.5	1.2	30.4	<20	-	-

HRV Group = Human Rotavirus vaccine
Placebo Group = Placebo
GMC = geometric mean antibody concentration calculated on all subjects
N = number of subjects with available results
n (%) = number (percentage) of subjects with concentration ≥ 20 U/mL
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PRE=Blood sample taken prior to Dose 1
POST=Blood sample taken after Dose 2 at Visit 3

Supplement 47 **Anti-RV IgA antibody GMC calculated on subjects seropositive for anti-RV IgA antibodies at Visit 3 (Total vaccinated cohort)**

Antibody	Group	Timing	N	GMC		
				value	95% CI	
					LL	UL
Anti RV.IgA	HRV	PRE	3	621.8	<20	322171.3
		POST	18	476.4	253.9	894
	Placebo	PRE	2	1555.8	<20	8.635E13
		POST	2	96.3	<20	3246.1

Footnote: cf Supplement 46

Supplement 48 **Percentage of subjects with vaccine take at Visit 3 (Total vaccinated cohort)**

Group	Vaccine take on combined doses				
	N	n	%	95%CI : LL	95%CI : UL
HRV	20	18	90	68.3	98.8
Placebo	21	3	14.3	3	36.3

HRV Group = Human Rotavirus vaccine
Placebo Group = Placebo
N = number of subject with available anti-RV IgA results at Visit 3 or with vaccine virus* in stools collected after Dose 1 of HRV vaccine or placebo up to Visit 3
n (%) = number (percentage) of subject who seroconverted at Visit 3 or with vaccine virus* in stools collected after Dose 1 of HRV vaccine or placebo up to Visit 3
95% CI = exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit
*RV in stools collected at pre-determined time points up to Visit 3
*Presence of RV antigen demonstrated in the HRV group by ELISA in any stool collected at pre-determined time points after Dose 1 up to Visit 3 will be considered as vaccine virus shedding.

Supplement 49 Percentage of subjects with RV in stool samples (shedding) collected at pre-determined time points (Total vaccinated cohort)

Dose 1 of HRV vaccine or placebo									
Group	Day 0 of Dose 1			Day 7 of Dose 1			Day 15 of Dose 1		
	N	n	%	N	n	%	N	n	%
HRV	25	0	0	23	2	8.7	23	0	0
Placebo	25	0	0	24	0	0	22	0	0
Dose 2 of HRV vaccine or placebo									
Group	Day 0 of Dose 2			Day 7 of Dose 2			Day 15 of Dose 2		
	N	n	%	N	n	%	N	n	%
HRV	23	0	0	21	0	0	19	0	0
Placebo	22	0	0	19	0	0	22	0	0
Visit 3									
Group	Day 0 of Visit 3								
	N	n	%						
HRV	19	0	0						
Placebo	21	1	4.8						

HRV Group = Human Rotavirus vaccine
Placebo Group = Placebo
N = number of subject with available stool results at the specified time point
n (%) = number (percentage) of subjects with RV in stool collected at the specified time point

B. Safety results

Total vaccinated cohort

Overall incidence of adverse events

All subjects in the TVC had received at least one dose of liquid HRV vaccine or placebo. The majority subjects received two doses vaccine (23 of 25 subjects) or placebo (22 of 25 subjects). Table 15 presents the percentage of doses and of subjects reporting any AEs (solicited and unsolicited) reported during the 8-day (Day 0-Day 7) post vaccination period.

Table 15 Percentage of doses and of subjects reporting any AEs (solicited and unsolicited) during the 8-day (Day 0-Day 7) post vaccination period (Total vaccinated cohort)

	Group	General symptoms				
		N	n	%	95% CI	
					LL	UL
Dose 1	HRV	25	7	28	12.1	49.4
	Placebo	25	7	28	12.1	49.4
Dose 2	HRV	23	5	21.7	7.5	43.7
	Placebo	22	10	45.5	24.4	67.8
Overall/dose	HRV	48	12	25	13.6	39.6
	Placebo	47	17	36.2	22.7	51.5
Overall/subject	HRV	25	9	36	18	57.5
	Placebo	25	13	52	31.3	72.2

HRV Group = Human Rotavirus vaccine
Placebo Group = Placebo
For each dose and overall/subject:
N = number of subjects with at least one administered dose
n (%) = number (percentage) of subjects presenting at least one type of symptom
For overall/dose:
N = number of administered doses
n (%) = number (percentage) of doses followed by at least one type of symptom

95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit

Grade 3 solicited AEs

Table 16 shows the percentage of doses and subjects reporting grade 3 solicited AEs.

Table 16 Percentage of doses and of subjects reporting grade 3 solicited AEs during the 8-day (Day 0-Day 7) post vaccination period (Total vaccinated cohort)

	Group	General symptoms				
		N	n	%	95% CI	
					LL	UL
Dose 1	HRV	25	2	8	1	26
	Placebo	25	1	4	0.1	20.4
Dose 2	HRV	23	2	8.7	1.1	28
	Placebo	22	1	4.5	0.1	22.8
Overall/dose	HRV	48	4	8.3	2.3	20
	Placebo	47	2	4.3	0.5	14.5
Overall/subject	HRV	25	3	12	2.5	31.2
	Placebo	25	1	4	0.1	20.4

HRV Group = Human Rotavirus vaccine
Placebo Group = Placebo
For each dose and overall/subject:
N = number of subjects with at least one administered dose
n (%) = number (percentage) of subjects presenting at least one type of symptom
For overall/dose:
N = number of administered doses
n (%) = number (percentage) of doses followed by at least one type of symptom
95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit

Table 17 presents the percentage of doses and of subjects reporting grade 2 or grade 3 fever, vomiting or diarrhoea during the 8-day (Day 0-Day 7) solicited follow-up period. Table 18 presents percentage of subjects reporting each solicited general symptom including those graded 3 in intensity and those assessed as related to vaccination during the 8-day (Day 0-Day 7) solicited follow-up period.

Table 17 Percentage of doses and of subjects reporting grade 2 or grade 3 fever, vomiting or diarrhoea during the 8-day (Day 0-Day 7) solicited follow-up (Total vaccinated cohort)

	Group	General symptoms				
		N	n	%	95% CI	
					LL	UL
Dose 1	HRV	25	4	16	4.5	36.1
	Placebo	25	2	8	1	26
Dose 2	HRV	23	4	17.4	5	38.8
	Placebo	22	5	22.7	7.8	45.4
Overall/dose	HRV	48	8	16.7	7.5	30.2
	Placebo	47	7	14.9	6.2	28.3
Overall/subject	HRV	25	6	24	9.4	45.1
	Placebo	25	6	24	9.4	45.1

HRV Group = Human Rotavirus vaccine
Placebo Group = Placebo
For each dose and overall/subject:

N = number of subjects with at least one administered dose
n (%) = number (percentage) of subjects presenting at least one type of symptom
For overall/dose:
N = number of administered doses
n (%) = number (percentage) of doses followed by at least one type of symptom
95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit

Table 18 **Percentage of subjects reporting each solicited general symptom including those graded 3 in intensity and those assessed as related to vaccination during the 8-day (Day 0-Day 7) solicited follow-up period (Total vaccinated cohort)**

Symptom	Type	HRV Group					Placebo Group				
		N	n	%	95 % CI		N	n	%	95 % CI	
					LL	UL				LL	UL
Dose 1											
Cough	All	25	3	12	2.5	31.2	25	5	20	6.8	40.7
	Grade 3	25	0	0	0	13.7	25	0	0	0	13.7
	Related	25	0	0	0	13.7	25	0	0	0	13.7
	Grade 3 * Related	25	0	0	0	13.7	25	0	0	0	13.7
Diarrhoea	All	25	4	16	4.5	36.1	25	2	8	1	26
	Grade 3	25	2	8	1	26	25	1	4	0.1	20.4
	Related	25	0	0	0	13.7	25	1	4	0.1	20.4
	Grade 3 * Related	25	0	0	0	13.7	25	1	4	0.1	20.4
Irritability	All	25	5	20	6.8	40.7	25	6	24	9.4	45.1
	Grade 3	25	0	0	0	13.7	25	0	0	0	13.7
	Related	25	0	0	0	13.7	25	0	0	0	13.7
	Grade 3 * Related	25	0	0	0	13.7	25	0	0	0	13.7
Loss of appetite	All	25	3	12	2.5	31.2	25	5	20	6.8	40.7
	Grade 3	25	0	0	0	13.7	25	0	0	0	13.7
	Related	25	0	0	0	13.7	25	0	0	0	13.7
	Grade 3 * Related	25	0	0	0	13.7	25	0	0	0	13.7
Fever /(Axillary) (°c) according GSK scale	All	25	1	4	0.1	20.4	25	0	0	0	13.7
	Grade 3	25	0	0	0	13.7	25	0	0	0	13.7
	Related	25	0	0	0	13.7	25	0	0	0	13.7
	Grade 3 * Related	25	0	0	0	13.7	25	0	0	0	13.7
Fever /(Axillary) (°c) according Chinese scale	All	25	1	4	0.1	20.4	25	2	8	1	26
	Grade 3	25	0	0	0	13.7	25	0	0	0	13.7
	Related	25	0	0	0	13.7	25	0	0	0	13.7
	Grade 3 * Related	25	0	0	0	13.7	25	0	0	0	13.7
Vomiting	All	25	2	8	1	26	25	1	4	0.1	20.4
	Grade 3	25	1	4	0.1	20.4	25	0	0	0	13.7
	Related	25	1	4	0.1	20.4	25	0	0	0	13.7
	Grade 3 * Related	25	0	0	0	13.7	25	0	0	0	13.7
Dose 2											
Cough	All	23	3	13	2.8	33.6	22	4	18.2	5.2	40.3
	Grade 3	23	0	0	0	14.8	22	0	0	0	15.4
	Related	23	0	0	0	14.8	22	0	0	0	15.4
	Grade 3 * Related	23	0	0	0	14.8	22	0	0	0	15.4
Diarrhoea	All	23	4	17.4	5	38.8	22	4	18.2	5.2	40.3
	Grade 3	23	1	4.3	0.1	21.9	22	1	4.5	0.1	22.8
	Related	23	2	8.7	1.1	28	22	1	4.5	0.1	22.8
	Grade 3 * Related	23	0	0	0	14.8	22	0	0	0	15.4
Irritability	All	23	1	4.3	0.1	21.9	22	5	22.7	7.8	45.4
	Grade 3	23	0	0	0	14.8	22	0	0	0	15.4
	Related	23	0	0	0	14.8	22	2	9.1	1.1	29.2
	Grade 3 * Related	23	0	0	0	14.8	22	0	0	0	15.4
Loss of appetite	All	23	2	8.7	1.1	28	22	5	22.7	7.8	45.4
	Grade 3	23	0	0	0	14.8	22	0	0	0	15.4
	Related	23	0	0	0	14.8	22	1	4.5	0.1	22.8
	Grade 3 * Related	23	0	0	0	14.8	22	0	0	0	15.4

Symptom	Type	HRV Group					Placebo Group				
		N	n	%	95 % CI		N	n	%	95 % CI	
					LL	UL				LL	UL
Fever /(Axillary) (°c) according GSK scale	All	23	0	0	0	14.8	22	3	13.6	2.9	34.9
	Grade 3	23	0	0	0	14.8	22	0	0	0	15.4
	Related	23	0	0	0	14.8	22	1	4.5	0.1	22.8
	Grade 3 * Related	23	0	0	0	14.8	22	0	0	0	15.4
Fever /(Axillary) (°c) according Chinese scale	All	23	3	13	2.8	33.6	22	6	27.3	10.7	50.2
	Grade 3	23	0	0	0	14.8	22	0	0	0	15.4
	Related	23	1	4.3	0.1	21.9	22	3	13.6	2.9	34.9
	Grade 3 * Related	23	0	0	0	14.8	22	0	0	0	15.4
Vomiting	All	23	1	4.3	0.1	21.9	22	1	4.5	0.1	22.8
	Grade 3	23	1	4.3	0.1	21.9	22	0	0	0	15.4
	Related	23	1	4.3	0.1	21.9	22	0	0	0	15.4
	Grade 3 * Related	23	1	4.3	0.1	21.9	22	0	0	0	15.4

HRV Group = Human Rotavirus vaccine
Placebo Group = Placebo
For each dose:
N= number of subjects with at least one administered dose
n (%) = number (percentage) of subjects reporting the symptom at least once
95%CI= Exact 95% confidence interval; LL = lower limit, UL = upper limit
All = all reports of the specified symptom irrespective of intensity grade and relationship to vaccination
Grade 3 Vomiting = ≥ 3 episodes of vomiting/day
Grade 3 Diarrhoea = ≥ 6 looser than normal stools/day
Grade 3 Irritability/ Fussiness = Crying that could not be comforted/ prevented normal activity
Grade 3 Loss of appetite = Did not eat at all
Grade 3 Cough/runny nose = Cough/runny nose which prevented daily activity
Grade 3 symptom = symptom that prevented normal activity
Related = symptoms considered by the investigator to have a causal relationship to vaccination
All - Fever was defined as: axillary temperature ≥ 37.1 °C as defined by the Chinese authorities or ≥37.5°C as defined by GSK Biologicals.
Grade 3 fever was defined as: axillary temperature ≥ 39.0 °C as defined by both Chinese authorities and GSK Biologicals.

Unsolicited adverse events

During the 31-day (Day 0-Day 30) follow-up period at least one unsolicited symptom was reported for six subjects (24%) in the HRV group and three subjects (12%) in the placebo Group. Nasopharyngitis was the most frequently reported unsolicited symptom in both the groups (four subjects (16%) in the HRV group and three subjects (12%) in the placebo group). Grade 3 unsolicited AEs were reported for one subject (4%) in each group. None of the subjects reported any unsolicited AEs with causal relationship to vaccination.

ATP cohort for safety analysis

Safety results of the ATP cohort for safety were in line with those of the TVC.

III. DISCUSSION AND MAH'S OVERALL CONCLUSIONS (SUMMARY)

The occurrence of unsolicited AEs and SAEs observed in this study was similar to that of the studies conducted in the other Asian populations of similar age group. At least one unsolicited symptom was reported for 14.6% (95% CI: 6.1-27.8) of the doses in the HRV Group, which is similar to that observed in a group of subjects who received liquid HRV vaccine according to a 0, 1 month schedule in

studies conducted in Vietnam (15.6% [95% CI: 12.4: 19.3]) and the Philippines (15.7% [95% CI: 12.5: 19.5]) [Anh, 2011]. There were no SAEs with causal relationship to vaccination nor fatal SAEs reported in this study, which is similar to that observed in a study conducted in Korea [GSK Biologicals Clinical Report 112269/068, 2011].

In the stool samples collected at pre-determined time points, RV antigen was detected in stool samples collected from two subjects in the HRV Group at Day 7 after Dose 1 of HRV vaccine which is similar that of a trial conducted in Singapore were shedding of vaccine (RIX4414) virus was detected in a large proportion of vaccinated infants on the seventh day after administration of the first dose of HRV vaccine [Phua, 2005]. RV detected in the stool sample collected at Visit 3 from one of the subject in the Placebo group was probably due to natural infection.

The results of this study support the conduct of further clinical studies with the liquid HRV vaccine in the infant population in China.

IV. RAPPORTEUR'S CONCLUSION

The MAH's conclusion is endorsed.

V. REQUEST FOR SUPPLEMENTARY INFORMATION

None

References

Anh DD, Carlos CC, Thiem DV, et al. Immunogenicity, reactogenicity and safety of the human rotavirus vaccine RIX4414 (Rotarix™) oral suspension (liquid formulation) when co-administered with expanded program on immunization (EPI) vaccines in Vietnam and the Philippines in 2006-2007. Vaccine. 2011 Mar 3; 29(11):2029-36.

Phua KB, Quak HQ, Lee BW, et al. Evaluation of RIX4414, A Live, Attenuated Rotavirus Vaccine, in a Randomized, Double-Blind, Placebo-Controlled Phase 2 Trial Involving 2464 Singaporean Infants. The Journal of Infect Dis. 2005; 192: S6-16.