



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

12 March 2015
EMA/169446/2015 rev. 1
Committee for Medicinal Products for Human Use (CHMP)

Rotarix

rotavirus vaccine, live

Procedure No: EMEA/H/C/000639

P46 076.1

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

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



I. RECOMMENDATION

This assessment report presents the final analysis of the efficacy and safety data collected during the entire study period of study Rota-075 that was conducted in Nanning City, Guangxi Province, China.

According to the Company, the efficacy against severe rotavirus gastroenteritis in study Rota-075 was lower than the one observed in the EU and developed Asian countries, but was in the range of what has been observed in clinical trials conducted in Latin America and Africa, which are already presented in the current Product Information. The data submitted do not influence the benefit-risk balance and no regulatory action to be taken.

On the 19 Dec 2013 the CHMP adopted the following conclusions:

According to the Company, the efficacy against severe rotavirus gastroenteritis in study Rota-075 was lower than the one observed in the EU and developed Asian countries, but was in the range of what has been observed in clinical trials conducted in Latin America and Africa, which are already presented in the current Product Information. Consequently, no change to the SmPC is needed.

The CHMP endorses the Company's conclusion regarding the study outcome and agrees that there is no need for updating the product information as these data are not directly relevant to EU prescribers. The CHMP however noted that the current efficacy information from the Asian continent is very sparse and the new data contribute to a better knowledge of the clinical protection that can be expected.

II. BACKGROUND

According to Article 46 of Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006, the Company submitted to the EMA the clinical study report for paediatric study Rota-075 (EudraCT number 2012-005200-18).

The Company states that, in accordance with Article 16(2) of Regulation (EC) No 726/2004, the data submitted do not influence the benefit-risk balance for the above mentioned product and therefore do not require taking further regulatory action on the marketing authorisation for Rotarix. There is no need for updating the SmPC.

This study was conducted to support the licensure of GSK Biologicals' oral live attenuated liquid HRV vaccine in China and is the first formal efficacy study ever conducted with the liquid formulation. The study has not been conducted in accordance with an agreed paediatric investigation plan.

The Company submits now the responses to the RSI.

III. ANALYSIS OF THE COMPANY'S RESPONSES TO THE REQUEST OF SUPPLEMENTARY INFORMATION

Clinical

Question No. 01 - Clinical

The much less favourable clinical protection rate against severe RV GE (with no overlapping 95% CI) due to circulating wild-type RV in China, especially in comparison with developed Asian countries where the lyophilised formulation was used (72%; 95% CI: 54.1; 83.6) versus 96.1% (95% CI: 85.1; 99.5) (see table Sustained efficacy up to 3 years of age in Asia in section 5.1 of the current SmPC) is striking. Since ethnicity, study design or social status can unlikely explain the differences in efficacy, the liquid formulation itself may be the cause of the less favourable response in China. The clinical protection between the two vaccine formulations was never evaluated in a head to head comparison. Furthermore, the comparable immune responses between the two formulations (demonstrated previously in other studies) do not predict clinical protection since there is no immunological correlate of protection. The MAH should discuss this major issue.

Company's Response (summary)

The Company acknowledges the less favourable clinical protection rate against severe Rotavirus Gastroenteritis (RVGE) due to circulating wild-type RV in China compared to developed Asian countries and is of the opinion that this difference is caused by the difference in socio-economic level between the two study settings. The Chinese efficacy data are aligned with previous efficacy data obtained with Rotarix in countries of the same socio-economic level. This statement is supported by:

- the fact that the vaccine efficacy (VE) and the anti-RV antibody seroconversion rate in study Rota-075 are in line with the data obtained in settings of similar socioeconomic level,
- analyses of various Rotarix efficacy studies suggesting that anti-RV antibody seropositivity can serve as a relative correlate of efficacy against any and severe RGVE in vaccinated children.

1. VACCINE EFFICACY AND IMMUNE RESPONSE

1.1. Socio-economic level of the study settings

Study Rota-075 was conducted in Nanning City, in the Guangxi province in China and this rural province is known to be of low socio-economic status. The prevalence of stunting and underweight in children under 5 years of age was > 40% and > 30%, respectively, in 1992 [FAO, 1999]. The socio-economic level of the region has increased since then, but did not yet reach the level of developed Asian countries. Recent information on Gross Domestic Product (GDP, 2009-2012) and infant mortality rate (estimates for 2013) are provided in Table 1. As far as the Company knows, provincial data on infant mortality rate are not available and therefore national data are provided for this parameter. Study Rota-028, -029, -030 was conducted in an urban setting in high-income countries in Asia (Singapore, Taiwan and Hong Kong) [Phua, 2009].

Table 1 shows that the GDP per capita for Singapore, Hong Kong and Taiwan is more than 15-fold higher than for the Guangxi province in China and more than 4-fold higher than the country data for China. The infant mortality rate is at least 3-fold higher in China (country data) than in Singapore, Hong Kong and Taiwan. These data indicate a clear difference in socio-economic level between the setting of study Rota-075 and the setting of study Rota-028, -029, -030 in recent years.

Table 1 Socio-economic level of study settings

	Gross Domestic Product (GDP)	Infant mortality rate*	Study
Guangxi province in China	2,361	NA£	Rota-075
China	9,300	15.2	
Taiwan	39,400	4.55	Rota-028,-029,-030
Hong Kong	52,300	2.89	
Singapore	61,400	2.59	

* Infant mortality rate = deaths in infants < 1 year of age per 1,000 live births.

£ To the Company's knowledge, provincial data for infant mortality rate are not available for China.

References:

GDP Guangxi province: [USDA](#), 2010, data for 2009.

GDP China, Taiwan Hong Kong, Singapore: [Central Intelligence Agency](#), 2013, data for 2012

Infant mortality rate (all settings): [Central Intelligence Agency](#), 2013, estimates for 2013.

RV vaccines are known to have an excellent efficacy against disease in developed countries and to have a reduced efficacy in countries of lower socio-economic status [Madhi, 2010; Zaman, 2010] and this fact contributed to the difference in VE in study Rota-075 compared to study Rota-028, -029, -030.

1.2. Immunogenicity data

The immunogenicity data of study Rota-075 became available recently (cf. Module 5). A comparison of the immunogenicity data of study Rota-028, -029, -030 and study Rota-075 is provided in Table 2.

Study Rota-075 consisted of two immunogenicity sub-cohorts. Sub-cohort 1 assessed immunogenicity of the liquid Rotarix vaccine (612 subjects in Total Vaccinated Cohort [TVC]), while sub-cohort 2 assessed the immunogenicity of the liquid Rotarix vaccine and co-administered vaccines (306 subjects in TVC). All subjects received routine childhood vaccinations according to the Expanded Program of Immunisation (EPI) recommendations in China and subjects in the immunogenicity sub-cohort 2 received Diphtheria, Tetanus and acellular Pertussis (DTPa) vaccine and Oral Polio Virus (OPV) vaccine concomitantly with the liquid human rotavirus vaccine (HRV) vaccine/placebo dose. Because concomitant administration of OPV may slightly reduce the immune response to RV vaccines and IPV rather than OPV was administered in study Rota-028, -029, -030, the comparison of the immunogenicity data of both studies is based on the immunogenicity sub-cohort 1 of study Rota-075.

Table 2 presents the anti-RV IgA seroconversion rate (defined as the appearance of anti- RV IgA antibodies, i.e. concentration greater than or equal to the cut-off value, in the serum of subjects who were seronegative before vaccination), anti-RV IgA Geometric Mean Concentration (GMC) in seropositive subjects and VE against severe RVGE for studies Rota-075 (China) and Rota-028, -029, -030 (Singapore, Taiwan, Hong Kong).

The anti-RV IgA seroconversion rate after 2 doses was 74.7% in China, while a higher value of 93.9% was reached after 2 doses in Singapore, Taiwan and Hong Kong. This difference in immunogenicity between the 2 settings is in line with the difference in efficacy against severe RVGE and suggests that the lower VE in China (72.0%) as compared to Singapore, Taiwan and Hong Kong (96.1%) may be caused by the lower immune response.

Table 2 Efficacy and immunogenicity results of study Rota-075 (China) and Rota-028-029-030 (Singapore, Taiwan, Hong Kong) - (ATP analyses)

	Rota-075 China				Rota-028, -029, -030 Singapore, Taiwan, Hong Kong			
	N	%/value	95% CI		N	%/value	95% CI	
Anti-rotavirus IgA seroconversion rate after Dose 2	257	74.7	68.9	79.9	115	93.9	87.9	97.5
GMC* (U/ml) after Dose 2	192	189.9	158.3	227.9	108	293.0	232.8	368.9
Efficacy against severe RVGE	1575 (HRV) 1573 (placebo)	72.0	54.1	83.6	5263 (HRV) 5256 (placebo)	96.1	85.1	99.5

N (for seroconversion rate) = Number of subjects with available results

N (for GMC) = Number of subjects who were seropositive for anti-RV IgA antibodies

N (for efficacy data) = Number of subjects included in HRV group and in placebo group

GMC* = Geometric Mean antibody Concentration calculated on seropositive subjects

HRV: Human Rotavirus vaccine

Source data:

Rota-075 (113808) Report dated 29 October 2012

Rota-075 (113808) Annex Report dated 8 August 2013, analysis on immunogenicity sub cohort 1 (cohort to assess the immunogenicity of the liquid HRV vaccine)

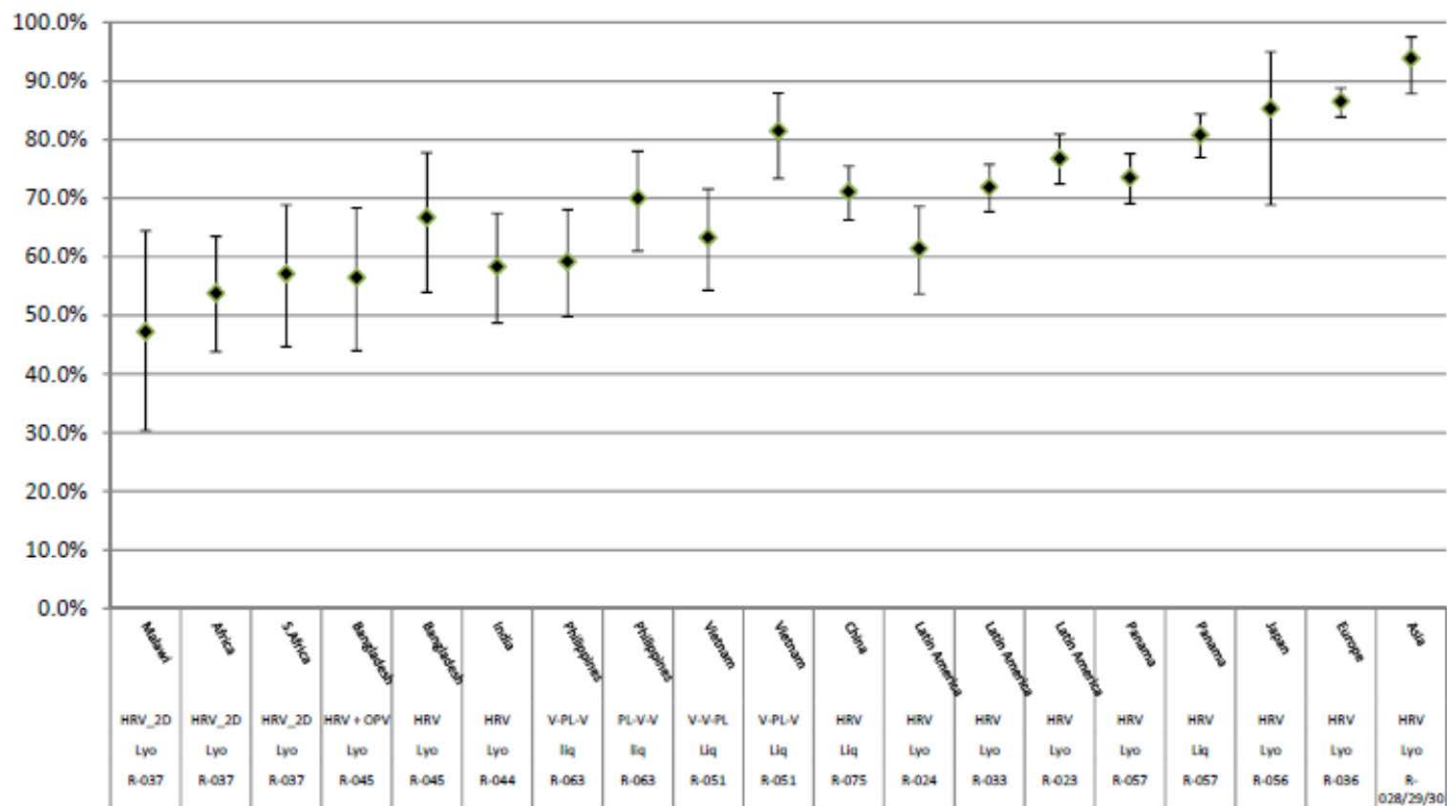
444563 (Rota) 028; 029; 030 Report dated 25 March 2008

The Company performed a further assessment of the seroconversion rate after 2 doses of Rotarix vaccine in Phase II and Phase III studies in countries and regions of different socio-economic level (Figure 1). Because the immunogenicity data of the different studies were considered irrespective of the OPV co-administration status, Figure 1 includes the results of the pooled immunogenicity groups for study Rota-075. Figure 1 shows a trend for an increasing seroconversion rate with increasing socioeconomic level of the country and/or region. From all studies conducted, the lowest seroconversion rate was observed in Malawi, i.e. the country with the lowest socio-economic level.

Assessor's comment

*The Company's analysis of the association between seroconversion rate and socioeconomic level should be regarded with caution since the information in Figure 1 is somewhat misleading. Hence, it is inappropriate to represent the seroconversion rates (>90%) from studies R-028, 29, 30 (Taiwan, Hong Kong, Singapore) as representative for "Asia". Hence, seroconversion rates from studies in Japan, Vietnam, China, the Philippines, India and Bangladesh in Figure 1 are all well below 90%. It is also misleading to consider study results from Malawi and South Africa as representing Africa. Nevertheless, it is reasonable to accept an association between the rate of seroconversion and socioeconomic status. The 75% seroconversion rate in Nanning City, Guangxi province, China, is in line with the rates observed in Bangladesh, India, the Philippines and Vietnam, the liquid formulation being used in the latter two countries during the phase II studies before registration. There is no reason to believe that the liquid formulation is the cause of the lower response. **Issue resolved.***

Figure 1 Seroconversion rate with 95% Confidence Interval after administration of 2 doses of Rotarix in Phase II and Phase III clinical studies in countries/regions of different socio-economic level



For study Rota-033, the pooled data from 3 groups receiving 3 different lots of Rotarix are presented (HRV Pool)

For study Rota-037, only data for the group receiving 2 doses of Rotarix are presented.

For study Rota-051, the seroconversion rate after the second dose of Rotarix is presented.

For study Rota-063, the seroconversion rate after the second dose of Rotarix is presented.

For study Rota-024, seropositivity rate is presented instead of seroconversion rate because no pre-vaccination blood sample was taken in this study.

HRV = Human Rotavirus Vaccine

Lyo = lyophilised formulation; Liq = liquid formulation; 2_D = 2 doses; OPV = Oral Polio Vaccine

V = vaccine, PL = placebo; R = Rota

1.3. Efficacy data

The Company performed a further assessment of the VE against severe RVGE (Vesikari score ≥ 11) of 2 doses of Rotarix vaccine in Phase II and Phase III studies. Table 3 presents the studies of Figure 1 for which data on VE are available. The table contains data on the 2 dose group and the pooled group (2 doses and 3 doses) of study Rota-037 because the study was powered for the analyses on the pooled group. Table 3 shows that the VE against severe RVGE is highest in the countries or regions with the highest socio-economic level.

The VE against severe RVGE during the first efficacy period was within the same range in studies Rota-023, 024 (Latin America), Rota-037 (South Africa, Malawi) and Rota-075 (China). VE against severe RVGE during the first efficacy period was higher in Europe (95.8%) and the 95% CI was very wide for Japan (-26.8; 99.7). Data for the second and combined efficacy period were also within the same range in studies Rota-023 (Latin America) and Rota-075 (China). The data were lower in study Rota-037 (South Africa, Malawi), i.e. the setting with the lowest socio-economic level and highest in studies Rota-056 (Japan) and -036 (Europe), i.e. the settings with the highest socio-economic level.

1.4. Conclusion

The VE in study Rota-075 is in line with data obtained with the lyophilised formulation in settings of the same socio-economic level. In addition, the anti-RV antibody seroconversion rate of study Rota-075 is aligned with data obtained with the lyophilised and liquid formulation in settings of the same socio-economic level.

Assessor's comment

*Table 3 below shows that the VE in study Rota-075 (China) is in line with settings having a low socio-economic status. In Japan, the incidence of severe rotavirus gastroenteritis leading to hospitalisation was too low for demonstrating the vaccine efficacy (VE: 87.4%; 95% IC: -26.8; 99.7). The Company's statement that the VE was highest in Japan is not endorsed. **Issue resolved.***

Table 3 Vaccine efficacy against severe rotavirus gastroenteritis (Vesikari score greater than or equal to 11) of 2 doses of Rotarix in Phase II and Phase III clinical studies

		First efficacy period									Second efficacy period									Combined efficacy period								
		n/N			VE			P-value			n/N			VE			P-value			n/N			VE			P-value		
Study (Country) Formulation	Group	N	n	%	LL	UL	%	LL	UL	P-value	N	n	%	LL	UL	%	LL	UL	P-value	N	n	%	LL	UL	%	LL	UL	P-value
Rota-037 (South Africa, Malawi) Lyophilised	HRV - 2 doses	1496	30	2.0	1.4	2.9	58.7	35.7	74.0	<0.001*	754	22	2.9	1.8	4.4	1.1	-89.1	48.1	1.000^	943	47	5.0	3.7	6.6	32.7	0.7	54.7	0.046^
	HRV - Pooled	2974	56	1.9	1.4	2.4	61.2	44.0	73.2	<0.001*	1500	35	2.3	1.6	3.2	20.9	-43.0	55.2	0.474^	1873	81	4.3	3.4	5.3	41.6	17.9	58.3	0.002^
	Placebo	1443	70	4.9	3.8	6.1					712	21	2.9	1.8	4.5					891	66	7.4	5.8	9.3				
Rota-075 (China) Liquid	HRV	1575	8	0.5	0.2	1.0	75.0	44.7	90.1	<0.001^	1500	13	0.9	0.5	1.5	70.2	43.5	85.3	<0.001^	1575	21	1.3	0.8	2.0	72.0	54.1	83.6	<0.001^
	Placebo	1573	32	2.0	1.4	2.9					1479	43	2.9	2.1	2.1					1573	75	4.8	3.8	5.9				
Rota-024 (Latin America) Lyophilised	HRV	4211	6	0.1	0.1	0.3	84.3	59.0	94.9	<0.001*	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Placebo	2099	19	0.9	0.5	1.4					NA	NA	NA	NA	NA					NA	NA	NA	NA	NA				
Rota-023 (Latin America) Lyophilised	HRV	9009	11	0.1	0.1	0.2	84.8	71.1	92.7	<0.001*	7175	19	0.3	0.2	0.4	81.5	69.6	89.3	<0.001*	7205	28	0.4	0.3	0.6	82.1	73.1	88.5	<0.001*
	Placebo	8858	71	0.8	0.6	1.0					7062	101	1.4	1.2	1.7					7081	154	2.2	1.8	2.5				
Rota-056† (Japan) Lyophilised	HRV	498	1	0.2	0.0	1.1	87.4	-26.8	99.7	0.091^	487	1	0.2	0.0	1.1	93.8	53.5	99.9	0.002^	498	2	0.4	0.0	1.4	91.6	62.4	99.1	<0.001^
	Placebo	250	4	1.6	0.4	4.0					243	8	3.3	1.4	6.4					250	12	4.8	2.5	8.2				
Rota-036 (Europe) Lyophilised	HRV	2572	5	0.2	0.1	0.5	95.8	89.6	98.7	<0.001*	2554	19	0.7	0.4	1.2	85.6	75.8	91.9	<0.001*	2572	24	0.9	0.6	1.4	90.4	85.1	94.1	<0.001*
	Placebo	1302	60	4.6	3.5	5.9					1294	67	5.2	4.0	6.5					1302	127	9.8	8.2	11.5				

For Study Rota-037, the data of the pooled group analysis (2 doses and 3 doses of Rotarix) is presented in addition to the data of the 2 dose group because the study was powered for the analysis on the pooled groups. NA = Not available as the study only had a one year follow-up period. N= number of subjects included in each group

n= number of subjects reporting at least one event in each group

LL, UL = 95 % Lower and Upper confidence limits; VE (%) = Vaccine Efficacy (Conditional Method)

^Two sided Exact P-value conditional to number of cases; *Two-sided Fisher's exact test

† severe rotavirus gastroenteritis leading to medical intervention

2. IMMUNOLOGICAL CORRELATE OF EFFICACY

Although the clinical protection between the two vaccine formulations was never evaluated in a head to head comparison, the Company previously showed non-inferiority of the liquid formulation compared to the lyophilised formulation in terms of anti-RV IgA seroconversion rates after the second dose (CSR for study Rota-061 [107876] dated 01 August 2007 submitted to EMA as part of the line extension application dossier for the Rotarix liquid formulation [EMA/H/C/639/X/010]). The Company acknowledges that there currently is no established correlate of protection for RV vaccines, but is of the opinion that immunogenicity is a good correlate of efficacy based on the following two analyses.

Two analyses were performed with the aim to investigate the predictive value of seropositive post vaccination serum RV IgA antibody concentrations (antibody concentration ≥ 20 U/mL) on VE against RV disease:

- applying the Prentice criteria [Prentice, 1989] for surrogate endpoints to anti-RV IgA antibody concentrations ≥ 20 U/mL one month post-vaccination in a large Phase III efficacy trial (Rota-037)
- a meta-analysis involving 8 Rotarix efficacy studies to measure the correlation between clinical VE and VE predicted from immunogenicity (VEI), i.e. 1 minus the relative risk (RR) of seronegativity rate.

2.1. Analysis based on study Rota-037

Rota-037 (102248) is a phase III, double-blind, randomised, placebo-controlled, multicentre study to assess the efficacy, safety and immunogenicity of two or three doses of GlaxoSmithKline (GSK) Biologicals' oral live attenuated HRV vaccine.

Methodology

The Prentice criteria [Prentice RL, Statistics in Medicine 1989; 8: 431-440] were used in study Rota-037 to determine whether anti-RV IgA antibody seropositivity one month post-vaccination can serve as a surrogate (i.e. predictor) of the occurrence of RVGE.

The analysis was done on the According to Protocol (ATP) cohort for efficacy. Only the follow-up period from the post-vaccination blood sample timepoint onwards is considered for the analysis and only subjects with post-vaccination immunogenicity results (N = 4100) are included. Of these subjects, 285 subjects reported RVGE in the time period after the post-vaccination blood sample. This analysis assumes that efficacy is similar across different RV serotypes.

The 4 Prentice criteria to establish a surrogate endpoint are:

1. The vaccine group effect must be significantly associated with the occurrence of RVGE. This objective was achieved in study Rota-037 and is presented below under model (1). Please refer to CSR for study 102248 (Rota-037) dated 26 March 2009.
2. The vaccine group effect must be significantly associated with the surrogate i.e. anti-RV IgA antibody seropositivity one month post-vaccination. This was achieved in study Rota-037.
3. The surrogate effect must be significantly associated with the occurrence of RVGE. This is presented below under model (2).
4. The surrogate effect on the occurrence of RVGE must capture the vaccine group effect. This is presented below under model (3).

Results from criteria (1), (3) and (4) are presented in this analysis, using a logistic model for p, the probability of reporting RVGE after the one month post-vaccination blood sample:

Model (1) $\text{Logit}(p) = \alpha + \beta * G;$

Model (2) $\text{Logit}(p) = \alpha + \gamma * C$;
Model (3) $\text{Logit}(p) = \alpha + \beta * G + \gamma * C$

where $G=1$ for subjects receiving the vaccine and 0 for subjects receiving placebo, with $C=1$ for seropositive subjects and 0 for seronegative subjects.

Note that criterion (4) requires that the vaccine group effect significance disappears in model (3) when the surrogate is accounted. However, this criterion is acknowledged as being too stringent and is unlikely to be satisfied completely. In practice, it is expected that a surrogate endpoint may explain part but not all the treatment effect. As a result the proportion of explained vaccine group effect by the surrogate as proposed by Lin, (LIN DY et al. Statistics in Medicine 1997; 16: 1515-1527) is also computed as $1 - ([\beta \text{ obtained from model (3)}] / [\beta \text{ obtained from model (1)}])$.

These models were based on all subjects with anti-RV IgA results available one month post-vaccination and who belonged to the ATP cohort of efficacy, defined as all RV naive subjects.

Results

In study Rota-037, subjects were allocated to a 3 dose HRV vaccine group, a 2 dose HRV vaccine with 1 dose placebo group and a 3 dose placebo group according to a 1:1:1 randomization ratio. The study enrolled 4941 subjects, of which 4939 were vaccinated and 4417 comprised the ATP cohort for efficacy. Immunogenicity data one month post dose 3 was missing for 317 subjects, thus 4100 subjects were included in the Prentice criteria analysis.

Since a correlate is expected to be independent of the number of doses and since the primary study objective was to show efficacy of the HRV vaccine pooled group as compared to placebo, the Prentice criteria analysis was applied regardless of the number of HRV vaccine doses i.e. using a pooled HRV vaccine group and the placebo group.

The distribution of anti-RV-IgA antibody concentration one month post-vaccination for the 4100 subjects is summarized by group in Table 4. The table presents also the total number and percentage of subjects reporting RVGE (any and severe) after the blood sample. The results suggest that:

In the HRV vaccine group, anti-RV-IgA antibody concentrations ≥ 20 U/mL appear to be associated with a reduced risk of both any and severe RVGE.

In the Placebo group, anti-RV IgA antibody concentrations ≥ 50 U/mL appear to be associated with a reduced risk of both any and severe RVGE. However the number of subjects with an anti-RV IgA antibody concentration between [20-50[U/mL was limited to 52 (4%) subjects.

A similar level of protection was observed in the HRV group and the Placebo group for anti-RV-IgA antibody concentrations ≥ 50 U/mL. This was observed for both any and severe RVGE.

These observations are formalized using the Prentice criteria described in the method section and applied to the study as shown in Table 5.

Model (1) shows the statistical significance of the vaccine group effect; model (2) shows the statistical significance of seropositivity effect. Although the vaccine group effect in model (1) and seropositivity effect in model (2) are both associated with a $p\text{-value} < 0.0001$, the seropositivity rate is more significant as shown by the larger log-likelihood ratio test.

Model (3) shows the vaccine group effect for subjects when adjusting for the seropositivity status, and the seropositivity effect when adjusting for the vaccine group effect.

The seropositivity effect appears to be stronger than the vaccine group effect, but this does not capture the full vaccine group effect. The proportion of vaccine group effect explained by seropositivity accounts for 43.6% and 32.7% of the vaccine group effect on any RVGE and severe RVGE, respectively. This low proportion of explained vaccine group effect is mainly due to the lower

proportion of subjects reporting RVGE in the vaccine group as compared to the placebo group among seronegative subjects (see Table 4). Accordingly, in this analysis, seropositivity does not fully capture the vaccine group effect.

Table 4 Rota-037: Number and percentage of subjects with any RVGE/severe RVGE by rotavirus IgA antibody concentration

Concentration one mont post vaccination (U/mL)	HRV group	Placebo group
	n/N (%)	n/N (%)
Any RV GE		
<20	83/1025 (8.10)	127/1026 (12.38)
[20-50[	12/319 (3.76)	6/52 (11.54)
[50-100[	13/319 (4.08)	2/48 (4.17)
[100-250[	14/345 (4.06)	1/59 (1.69)
[250-500[	11/255 (4.31)	2/49 (4.08)
[500-1000[	7/231 (3.03)	1/31 (3.23)
≥1000	4/276 (1.45)	2/65 (3.08)
Total	144/2770 (5.20)	141/1330 (10.60)
Severe RV GE		
<20	29/1025 (2.83)	47/1026 (4.58)
[20-50[	5/319 (1.57)	4/52 (7.69)
[50-100[	7/319 (2.19)	0/48 (0.00)
[100-250[	5/345 (1.45)	1/59 (1.69)
[250-500[	2/255 (0.78)	1/49 (2.04)
[500-1000[	2/231 (0.87)	1/31 (3.23)
≥1000	1/276 (0.36)	1/65 (1.54)
Total	51/2770 (1.84)	55/1330 (4.14)

N: Number of subjects with anti-RV IgA antibody concentration in the concentration interval.

n: Number of subjects with anti-RV IgA antibody concentration in the concentration interval who reported RVGE

% = (n/N) X100

Table 5 Prentice criteria applied to study Rota-037

Model	Parameter	Parameter description	Estimated odds ratio (95% CI)	Log-likelihood ratio test	2 sided p-value
Any RVGE					
Model (1)	β	Vaccine group	0.46 (0.36; 0.59)	38.19	<0.0001
Model (2)	γ	Seropositivity rate	0.33 (0.25; 0.44)	71.22	<0.0001
Model (3)	β	Vaccine group	0.65 (0.50; 0.84)	10.83	0.001*
	γ	Seropositivity rate	0.39 (0.29; 0.52)	43.86	<0.0001
Severe RVGE					
Model (1)	β	Vaccine group	0.43 (0.29; 0.64)	17.53	<0.0001
Model (2)	γ	Seropositivity rate	0.39 (0.25; 0.59)	21.12	<0.0001
Model (3)	β	Vaccine group	0.57 (0.38; 0.87)	7.04	0.008*
	γ	Seropositivity rate	0.48 (0.30; 0.75)	10.64	0.001

All models look at effect on RVGE: Model 1 assesses the vaccine group effect, Model (2) assesses the seropositivity effect; Model (3) assesses the part of vaccine group effect not captured by the seropositivity effect.

* The estimated proportion of treatment effect explained by seropositivity is 43.6% for any RVGE and 32.7% for severe RVGE.

2.2. Integrated analysis on correlate of efficacy based on 8 efficacy studies

Methodology

A meta-analysis involving 8 Rotarix VE studies was performed to measure the correlation between clinical VE and VE predicted from immunogenicity (VEI) (i.e. 1 minus the RR of seronegativity rate).

All GSK sponsored HRV efficacy studies reported before 01 December 2011, for which immunogenicity data at one or two months post-vaccination were available, were a priori eligible for this meta-analysis. Rota-007 was excluded due to a low number of RVGEs. Therefore, 8 studies contributed to the meta-analysis. If the seropositivity at one/two months post-vaccination is indicative of protection, it would be expected that VE inferred from immunogenicity (VEI) would be correlated to clinical VE.

In each study clinical VE and VEI were estimated as:

- $VE = 1 - P1/P0$ where P1 and P0 are the proportion of subjects reporting RVGE in the vaccine group and the placebo group, respectively. This was based on the ATP cohort for efficacy.
- $VEI = 1 - ([1 - S+1]/[1 - S+0])$ where S+1 and S+0 are the proportion of seropositive subjects in the vaccine group and the placebo group, respectively.

This was based on the ATP cohort for immunogenicity defined as all subjects who complied with the vaccination and blood sampling schedule, for whom immunogenicity data were available, and who had no RV other than vaccine strain in stool samples. The 95% CI for VE and VEI were based on exact Poisson rate ratio between groups.

The predicted value of VEI_i for the clinical VEI in study i was assessed using the following regression: $\log(1 - VEI_i) = \mu + \omega * \log(1 - VEI_i) + \epsilon_i$, with ϵ_i being a random error normally distributed. The log transformation was used to normalize the distribution.

To account for the known variability of VE and VEI from each study, the intercept (μ) and the slope (ω) of the regression were estimated with 95% CI using imputation techniques.

Results

Figure 2 presents the scatter plots of the observed RR of reporting RVGE (any and severe) in the vaccine group as compared to the placebo group (i.e. 1-VE) versus the observed RR of the seronegativity rate (i.e. 1-VEI). Each dot represents a study with a horizontal line showing the 95% CI around 1-VEI and a vertical line showing the 95% CI around 1-VE. The estimated regression line is shown in blue with numerical expression annotated.

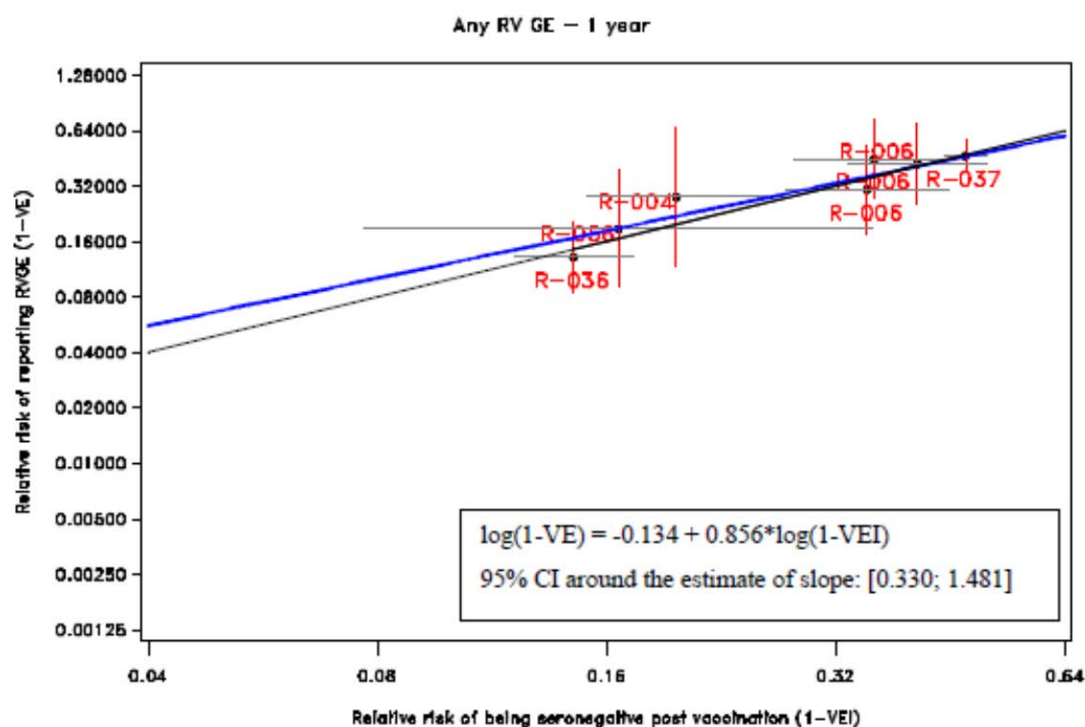
In absence of a predictive value of VEI for VE, a horizontal estimated line would be expected. However, over 1 year follow up of any RVGE, the estimated regression line presents a slope that is statistically significantly different from 0 indicating a relationship between VE predicted from the seropositivity rate and clinical VE (Figure 2A). The regression line is generally above the black line which represents an exact fit between VEI and VE. This suggests that VEI may be an overestimation of the true efficacy. Similar findings were observed when assessing the predictive value of VEI for clinical VE for any RVGE reported within 2 years following vaccination (Figure 2B).

The regression analyses associated with severe RVGE are presented in Figure 2C and Figure 2D over a 1 year and 2 year follow-up, respectively. Again the estimated regression lines present a slope that is statistically significantly different from 0 indicating a relationship between VE predicted from the seropositivity rate and clinical VE. However, in this case the estimated regression line is below the black line which represents an exact fit between VEI and VE. This suggests that VEI may be an underestimation of the true efficacy.

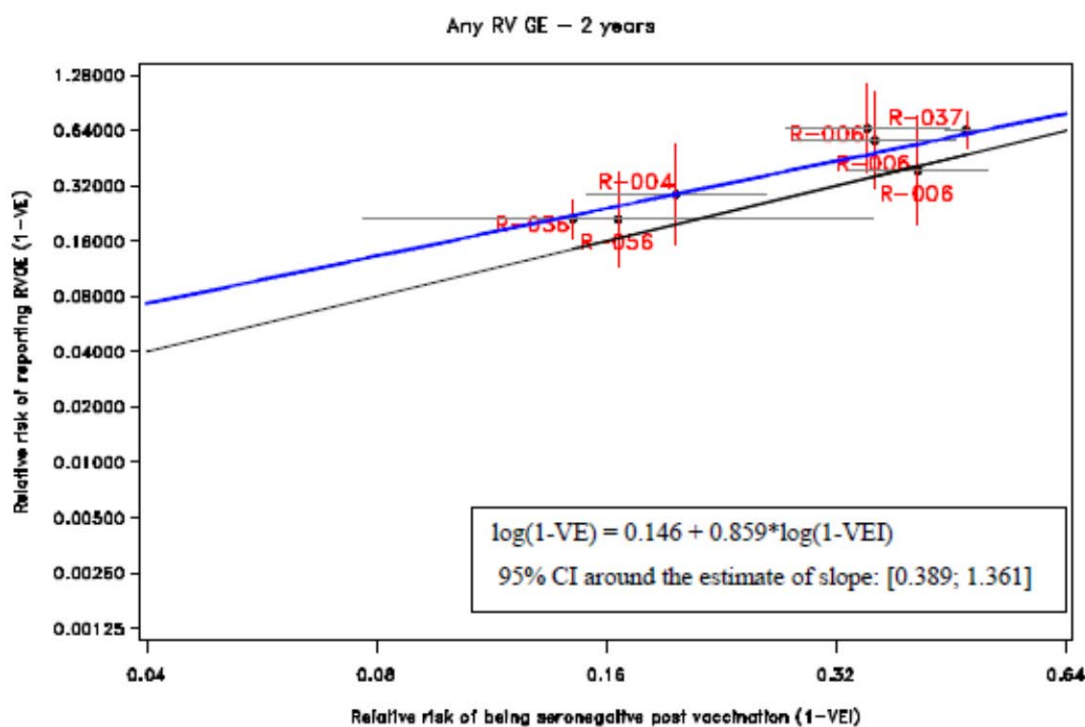
For all considered endpoints, the 95% CI for the slope excludes 0, indicating that there is a relationship between the immunological response and the efficacy of the vaccine.

Figure 2 Meta-analysis: Scatter plots of the relative risk with 95% CI for efficacy and immunogenicity by study

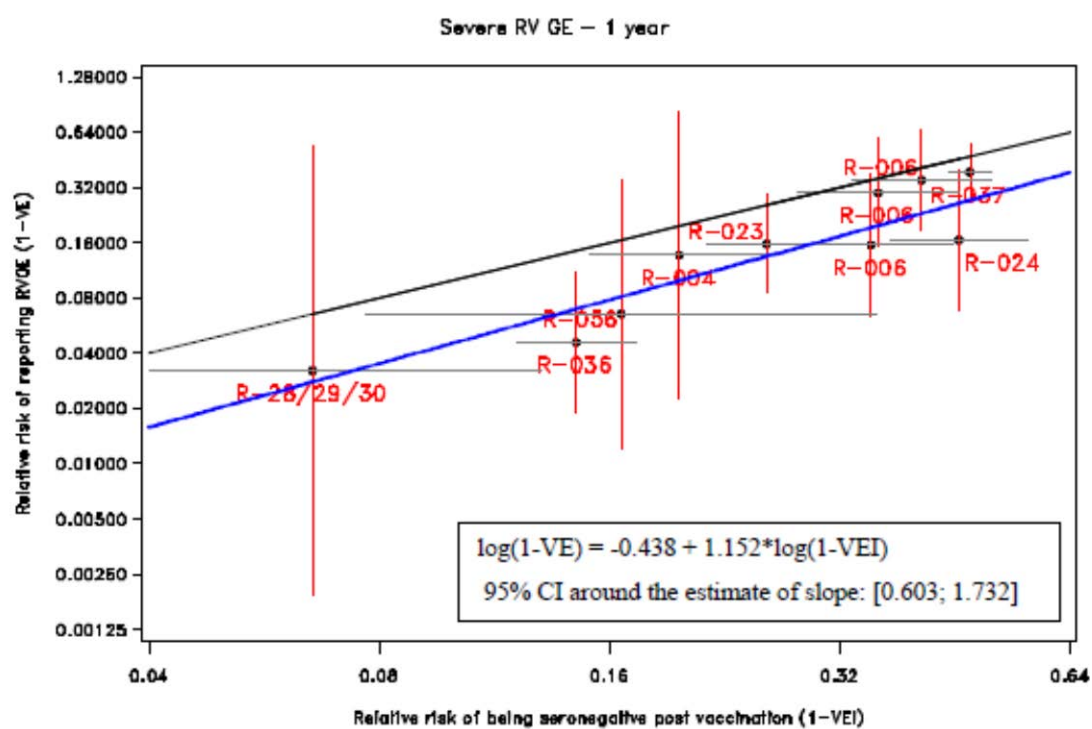
A.



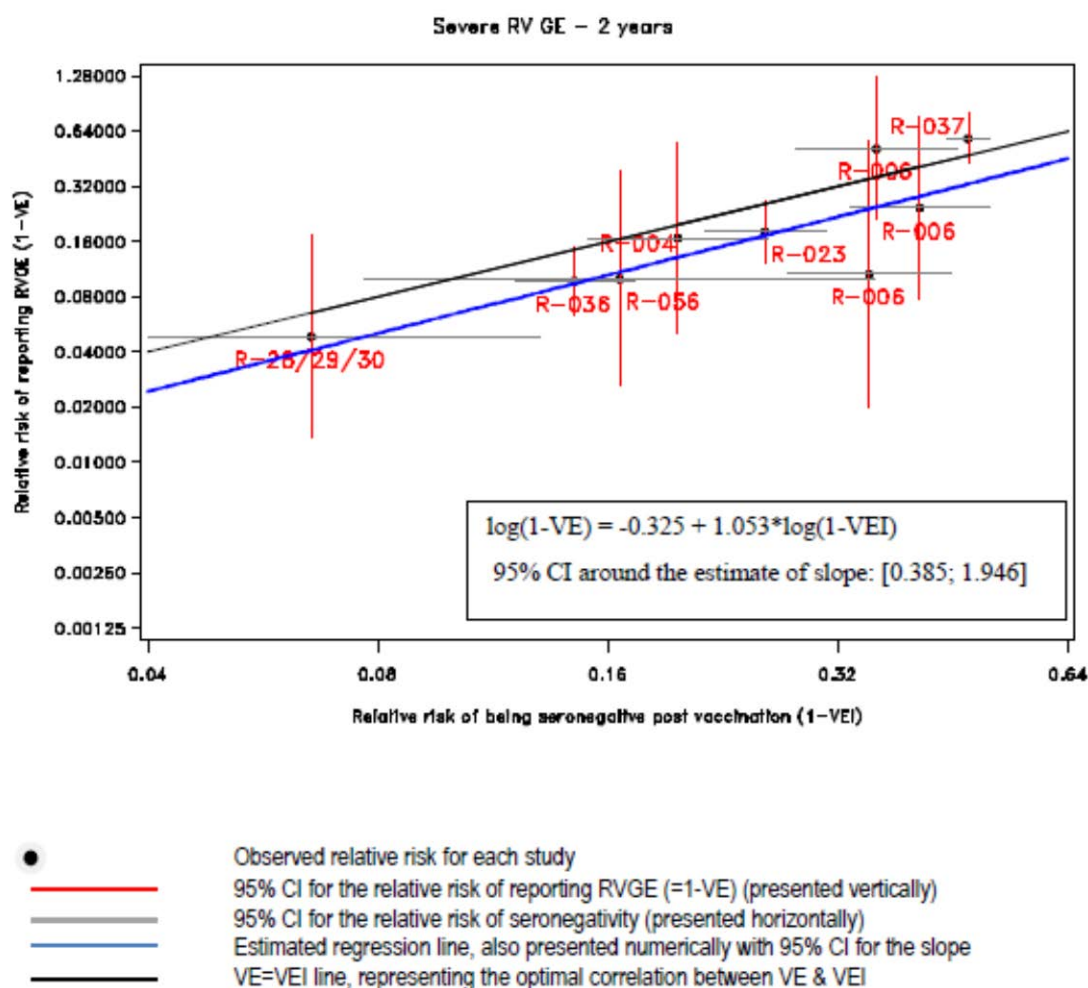
B.



C.



D.



Conclusions based on exploratory analysis of efficacy study Rota-037 and integrated analysis on correlate of efficacy

The analysis of the data of study Rota-037 and a linear regression analysis of a metaanalysis including 8 efficacy studies from Africa, Asia, Europe and South America (Rota- 004, -006, -023, -024, -028 to -030, -036, -037 and -056) indicate that post-vaccination anti-RV IgA antibody seropositivity (i.e. antibody concentration ≥ 20 U/mL) may serve as a useful correlate of efficacy in clinical trials of Rotarix.

Assessor's comment

The Company submitted additional analyses showing that serum IgA anti rotavirus seropositivity (≥ 20 U/ml) correlates with clinical protection against any and severe rotavirus gastroenteritis in children. It is understood that this protection is restricted to the G1P8 rotavirus type.

Question No. 02 - Clinical

The maximum follow-up was 21 months. However, the duration of participation in the study remains unclear. This may be important for appreciating the persistence of protection against G2P[4] during the second year of life. The MAH should provide this information.

Company's Response

The first visit of the first subject took place on 29 August 2010. The duration of the study was driven by the number of cases needed to reach the statistical power for the primary endpoint. Based on a preliminary review of severe gastroenteritis (GE) data during the first year efficacy follow-up, it was anticipated that the required number of cases for the evaluation of VE against severe rotavirus gastroenteritis (RVGE) would not be available at the end of the first year follow-up and therefore, the study was extended to include follow-up during a second rotavirus (RV) season.

The maximum interval allowed for the last study visit was 01 April 2012 to 31 May 2012. The last visit of the last subject occurred on 12 May 2012 and thus the maximum duration of study participation could be up to 21 months.

Table 6 presents the duration of the study for the Total vaccinated cohort. The mean duration was 1.41 years (16.9 months) in the HRV group and 1.40 years (16.8 months) in the placebo group. The maximum duration was 1.68 years (20.1 months) in both groups.

Table 6 **Duration (in years) of efficacy follow-up period - from Dose 1 up to Visit 7 (Total vaccinated cohort)**

		HRV N = 1666	Placebo N = 1667
Characteristics	Parameters	Value	Value
Duration in years	Sum	2351	2334
	Mean	1.41	1.40
	Minimum	0.01	0.05
	Q1	1.39	1.38
	Median	1.50	1.50
	Q3	1.59	1.58
	Maximum	1.68	1.68

HRV = Human Rotavirus Vaccine

N = number of subject included in each group

Total= sum of follow-up period expressed in year

Q1= 25th percentile Q3=75th percentile

The duration of participation in the study for each subject depends on the date of study entry and the date of last study visit. The age at the first vaccine dose, together with the duration of participation in the study, has an impact on the number of children ≥ 12 months of age at the end of the study.

Table 7 presents the number and percentage of subjects younger than 12 months of age and 12 months of age or older at Visit 7 or last contact in the According-To-Protocol (ATP) cohort for efficacy. The age at the last contact was considered if the subject withdrew before Visit 7. The table indicates that the majority of the subjects (97.7% in HRV group and 96.2% in placebo group) included in the evaluation of the primary efficacy objective (on the combined efficacy period) were 12 months of age or older at the end of the study.

Table 7 Number and percentage of subjects in the age categories younger than 12 months and 12 months or older at Visit 7 or last contact in the ATP cohort for efficacy

	HRV N = 1575		Placebo N = 1573		Total N = 3148	
Age category	n	%	n	%	n	%
< 12 months	36	2.3	59	3.8	95	3.0
≥12 months	1539	97.7	1514	96.2	3053	97.0

HRV = Human Rotavirus Vaccine

N = number of subjects in the respective treatment group

n = number of subjects in the treatment group belonging to the respective age category

% = (n/N) x100

Table 8 presents the vaccine efficacy (VE) against any and severe RVGE caused by G2P[4], respectively, during the combined efficacy period (i.e. Visit 1 until Visit 7). VE against any RVGE caused by G2P[4] was 58.9% (95% CI 40.5, 72.0) and VE against severe RVGE caused by G2P[4] was 72.5% (95% CI 45.5, 87.3) during the combined efficacy period. These results are aligned with VE against any RVGE and severe RVGE caused by circulating wild-type RV during the combined efficacy period (58.1% [95% CI 44.3; 68.8] and 72.0% [95% CI 54.1; 83.6], respectively.

Table 8 Percentage of subjects reporting any and severe rotavirus gastroenteritis and efficacy of the vaccine during the combined efficacy period for G2P[4] (ATP cohort for efficacy)

				n/N			VE			
Event Type	Group	N	n	%	LL	UL	%	LL	UL	P-value
Any rotavirus gastroenteritis										
G2+P4	HRV	1575	42	2.7	1.9	3.6	58.9	40.5	72.0	<0.001
	Placebo	1573	102	6.5	5.3	7.8	-	-	-	-
Severe rotavirus gastroenteritis										
G2+P4	HRV	1575	11	0.7	0.3	1.2	72.5	45.5	87.3	<0.001
	Placebo	1573	40	2.5	1.8	3.4	-	-	-	-

HRV = Human Rotavirus Vaccine

N = number of subjects included in each group

n = number of subjects reporting at least one event in each group

HRV = Human Rotavirus Vaccine

P-value = Two sided exact P-value conditional to number of cases

VE (%) = Vaccine Efficacy

LL, UL = 95 % Lower and Upper confidence limit

Severe RVGE: Vesikari score ≥ 11

The protocol defined the maximum allowed interval for Visit 6 as 1 year of age ± 30 days. Table 9 presents the number of subjects younger than 12 months of age and 12 months or older at Visit 6 or last contact in the ATP cohort for efficacy. The age at the last contact was considered if the subject withdrew before Visit 6. Of the subjects evaluated for efficacy during the first year follow up, about 55% were younger than 12 months of age and about 45% were 12 months of age or older. To further investigate the age distribution, Table 10 presents the age at Visit 6 or last contact by month and indicates that the majority (98.9%) of the subjects are in the age of 11 months (54.8%) or 12 months (44.2%) at Visit 6.

Table 9 Number and percentage of subjects in the age categories younger than 12 months and 12 months or older at Visit 6 or last contact in the ATP cohort for efficacy

Age category	HRV N = 1575		Placebo N = 1573		Total N = 3148	
	n	%	n	%	n	%
< 12 months	862	54.7	886	56.3	1748	55.5
≥12 months	713	45.3	687	43.7	1400	44.5

HRV = Human Rotavirus Vaccine

N = number of subjects in the respective treatment group

n = number of subjects in the treatment group belonging to the respective age category

% = (n/N) x100

Table 10 Number and percentage of subjects in the ATP cohort for efficacy age in months at visit 6 or last contact

Age Category	HRV N = 1575		Placebo N = 1573		Total N = 3148	
	n	%	n	%	n	%
3	0	0.0	1	0.1	1	0.0
4	1	0.1	2	0.1	3	0.1
5	3	0.2	0	0.0	3	0.1
6	0	0.0	1	0.1	1	0.0
7	0	0.0	3	0.2	3	0.1
8	2	0.1	0	0.0	2	0.1
9	1	0.1	1	0.1	2	0.1
10	6	0.4	2	0.1	8	0.3
11	849	53.9	876	55.7	1725	54.8
12	709	45.0	681	43.3	1390	44.2
13	1	0.1	4	0.3	5	0.2
14	2	0.1	2	0.1	4	0.1
15	1	0.1	0	0.0	1	0.0

HRV = Human Rotavirus Vaccine

N = number of subjects in the respective treatment group

n = number of subjects in the treatment group belonging to the respective age category

HRV = Human Rotavirus Vaccine

% = (n/N) x100

Table 11 presents the VE against any and severe RV GE caused by G2P[4], respectively, during the first efficacy period (i.e. from 2 weeks after Dose 2 until Visit 6). Because the majority of the subjects are 11 or 12 months of age at Visit 6, this represents VE in subjects 11 to 12 months of age. VE against any RVGE caused by G2P[4] was 67.2% (95% CI 46.2, 80.7) and VE against severe RVGE caused by G2P[4] was 72.0% (95% CI 33.5, 89.8).

Table 11 Percentage of subjects reporting any and severe RVGE episode and efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 6 for G2P[4] (ATP cohort for efficacy)

				n/N			VE			
Event Type	Group	N	n	%	LL	UL	%	LL	UL	P-value
Any gastroenteritis										
G2+P4	HRV	1575	22	1.4	0.9	2.1	67.2	46.2	80.7	<0.001
	Placebo	1573	67	4.3	3.3	5.4	-	-	-	-
Severe gastroenteritis										
G2+P4	HRV	1575	7	0.4	0.2	0.9	72.0	33.5	89.8	0.002
	Placebo	1573	25	1.6	1.0	2.3	-	-	-	-

HRV = Human Rotavirus Vaccine

N = number of subjects included in each group

n = number of subjects reporting at least one event in each group

HRV = Human Rotavirus Vaccine

P-value = Two sided exact P-value conditional to number of cases

VE (%) = Vaccine Efficacy

LL, UL = 95 % Lower and Upper confidence limit

Severe RVGE: Vesikari score ≥ 11

Visit 6 = 1 year of age $\pm$ 30 days

To further evaluate the VE in subjects aged 12 months or older, the VE against any and severe RVGE caused by G2P[4] during the second efficacy period (i.e. Visit 6 until Visit 7) was calculated (Table 13). The ATP cohort for efficacy for the second year follow-up period only included subjects of the ATP cohort of efficacy who had follow-up beyond Visit 6 (year 1). Table 12 shows that all subjects included in the ATP cohort for efficacy for the second year follow-up period were 12 months of age or older.

Table 12 Number and percentage of subjects in the age categories younger than 12 months and 12 months or older at Visit 7 or last contact in the ATP cohort for efficacy - second year follow up

	HRV N = 1500		Placebo N = 1479		Total N = 2979	
Age category	n	%	n	%	n	%
≥ 12 months	1500	100	1479	100	2979	100

HRV = Human Rotavirus Vaccine

N = number of subjects in the respective treatment group

n = number of subjects in the treatment group belonging to the respective age category

% = (n/N) x100

VE against any RVGE caused by G2P[4] was 43.7% (95% CI -0.3, 69.2) and VE against severe RVGE caused by G2P[4] was 73.7% (95% CI 17.5, 93.6) during the second year follow-up.

Table 13 Percentage of subjects reporting any and severe rotavirus gastroenteritis and efficacy of the vaccine during the second efficacy period for G2P[4] (ATP cohort for efficacy for second year follow-up)

				n/N			VE			
Event Type	Group	N	n	%	LL	UL	%	LL	UL	P-value
Any rotavirus gastroenteritis										
G2+P4	HRV	1500	20	1.3	0.8	2.1	43.7	-0.3	69.2	0.051
	Placebo	1479	35	2.4	1.7	3.3				
Severe rotavirus gastroenteritis										
G2+P4	HRV	1500	4	0.3	0.1	0.7	73.7	17.5	93.6	0.018
	Placebo	1479	15	1.0	0.6	1.7				

HRV = Human Rotavirus Vaccine

N = number of subjects included in each group

n = number of subjects reporting at least one event in each group

P-value = Two sided exact P-value conditional to number of cases

VE (%) = Vaccine Efficacy

LL, UL = 95 % Lower and Upper confidence limit

Severe RVGE: Vesikari score $\geq$ 11

Taken together, the data indicate that the primary analysis of the study (combined efficacy period) is a good representation of the VE in subjects of 12 months or older. In addition, Table 13 clearly shows that the vaccine provided protection against severe RVGE caused by G2P[4] during the second year of life.

Assessor's comment

*The main interest of Question 2 was to know whether the vaccine protects during the second year of life against RGVE due to G2P4. We are not interested in combined efficacy estimations in subjects 12 months or older, which is potentially driven by protection during the first year of life, not by protection during the second year of life. It is reassuring to see in Table 13 that protection against severe RVGE due to G2P4 is very well preserved during the second year of life. **Issue resolved.***

Question No. 03 - Clinical

The immunogenicity results are missing in the clinical study report. As a consequence, the immunological data of study Rota-075 should be submitted in due time.

Company's Response

The Annex Clinical Study Report (CSR) describing the immunogenicity data of study Rota-075 is provided in Module 5. The submission of this Annex CSR is part of the ongoing EMEA/H/C/639 Article P46 076 clinical procedure.

Assessor's comment

Issue resolved, cf. response to Question 1.

Labelling

Question No. 1 - Labelling

The efficacy data from China should be added to section 5.1 of the SmPC. A clarification should be given that the study was performed using the liquid formulation. The efficacy tables already available in the current SmPC should clarify that the studies were conducted with the lyophilised formulation.

Company's Response

As explained in the response to Question 1, the vaccine efficacy and immune response of the liquid formulation is similar to the vaccine efficacy and immune response of the lyophilised formulation in countries of the same socio-economic level. Furthermore, the difference in vaccine efficacy and immune response of the liquid formulation in China (study Rota-075) and the lyophilised formulation in Singapore, Hong Kong and Taiwan (study Rota-028-029-030) is believed to be due to the difference in socio-economic level between the 2 settings. Please refer to the response to Question 1 for more details.

In addition, the data obtained with the liquid formulation in China fall within the range of the vaccine efficacy and immune response measured in the regions in which the highest (Europe and developed countries in Asia) and lowest (Africa) values are observed. It should be noted that this range of data is already presented in the current SmPC.

In order to further assess the CHMP request, the Company has reviewed the available labelling EU guidelines:

The guideline related to Section 5.1 of the SmPC in the 'Notice to Applicants: A guideline on summary of product characteristics (SmPC) September 2009' gives guidance on the inclusion of data from clinical trials for all pharmaceutical products. The guideline mentions the inclusion of clinical efficacy data and specifies that the information has to be concise, clear, relevant and balanced, and should summarise evidence from relevant studies supporting the indication.

Further guidance on the content of Section 5.1 can be found in the 'Guideline on clinical evaluation of new vaccines' (adopted in October 2006) and the annex to the guideline describing SmPC requirements. These guidelines highlight that the most pertinent immunological data and estimates of efficacy considered to be valid should be mentioned in Section 5.1.

The current version of the Rotarix liquid SmPC contains a section on the "*Protective efficacy of the lyophilised formulation*" that presents efficacy results in different areas of the world. In addition the following statement is included

"Protective efficacy of the liquid formulation"

Since the immune response observed after 2 doses of Rotarix liquid formulation was comparable to the immune response observed after 2 doses of Rotarix lyophilised formulation, the levels of vaccine efficacy observed with the lyophilised formulation can be extrapolated to the liquid formulation".

Based on the data (including the data of study Rota-075), the information in the response to Question 1 and the additional information provided above, the statement on "Protective efficacy of the liquid formulation" remains correct.

Because the statement in the current SmPC remains correct and taking into account the guidelines in relation to inclusion of concise and clear information and presentation of the most pertinent data, the Company is of the opinion that there is no added value in presenting similar data twice in the SmPC and therefore recommends not to update the SmPC with the data of study Rota-075.

Assessor's comment

*The Company did not provide an acceptable justification for not adding the Rota-075 efficacy data to section 5.1 under the heading "Sustained efficacy up to 3 years of age in Asia". The statement that the Chinese data are a duplication of data already available in the SmPC is not endorsed since the less favourable data are exclusively from Africa. For the sake of completeness and to avoid that the SmPC becomes a purely promotional instrument instead of an objective source of information for the prescriber, the SmPC should be updated with the Chinese data. So, the Company is requested to introduce a type II variation in order to update the SmPC using an appropriate wording. Persistent protection against severe RVG due to G2P4 during the second year of life should be part of the new information. **Issue not resolved.***

V. RAPPORTEUR'S CONCLUSION

According to the Company, the efficacy against severe RV GE in study Rota-075 was lower than the one observed in the EU and developed Asian countries, but was in the range of what has been observed in clinical trials conducted in Latin America and Africa, which are already presented in the current Product Information. Consequently, no change to the SmPC is needed.

The Rapporteur endorses the Company's conclusion regarding the study outcome. However, in contrast to the Company's opinion that there is no need for updating the product information, the Rapporteur believes that the efficacy data should be added to section 5.1 of the SmPC. Hence, the current efficacy information from the Asian continent is very sparse and the new data contribute to a better knowledge of the clinical protection that can be expected. There is no reason for not mentioning this information under the heading "Sustained efficacy up to 3 years of age in Asia".

Comments were received from (Member state)

(Member state) agrees with the Rapporteur's conclusion that the questions have been addressed satisfactorily. The suggestion from the MAH that the reason for low efficacy results in China is related to low immune response, which is in turn related to low socioeconomic status, and not to the liquid formulation, is considered acceptable.

However, (Member state) tends to support the MAH's position that these results are not so essential that they need to be added to section 5.1 of the SmPC, which is already very comprehensive. These data are not directly relevant to EU prescribers and are consistent with the range of efficacy rates already described. Therefore, the request for a type II variation is not supported.

Rapporteur's comment to the (Member state) comment

Although it is correct that the Chinese data are not relevant to the EU prescriber the (Member state)s arguments for not adding this information to the SmPC are not endorsed. The SmPC contains already a lot of information that is irrelevant to the EU prescriber. During the recently CHMP approved variation II-47 (July 2013) related to the updating of section 5.1, the CHMP requested (and the MAH committed) to mention the lack of protection against RV G2 among aboriginal infants in Australia. This information is obviously not relevant to the EU prescriber. Furthermore, the currently ongoing updating of the intussusception information is exclusively based on populations living outside Europe (Mexico, Brazil, USA, Australia) and not necessarily applicable to the EU, especially with respect to the attributable risk that is proposed to be added to the SmPC.

There is obviously no need for redundant efficacy or effectiveness data from all countries in the world. However, is inappropriate to suggest that the Chinese data are redundant because they are in the range of efficacy rates already mentioned. The Chinese efficacy rates fit only in the African ones, not in those from other areas. This similarity cannot be observed when Chinese results are missing. Furthermore, the current information from Asia is incomplete, only information being available from Singapore, Hong Kong and Taiwan. Considering that the socioeconomic level of the population is a major determinant for vaccine efficacy (as shown in the MAH's response) and that many, if not most, areas in China have a living standard below the levels of Singapore, Hong Kong or Taiwan, the 72% vaccine efficacy against severe RVGE in study Rota-075 is more relevant for China than the 100% in

the former three areas. Finally, when not mentioning the Chinese data, some major information about persistent protection against G2P4 during the second year of life will remain hidden to the prescriber. Hence, the latter phenomenon was not observed in Singapore, Hong Kong or Taiwan because of the very low incidence of RV infection.

The benefit-risk balance is not compromised.

On the 19 Dec 2013 the CHMP adopted the following conclusions:

According to the Company, the efficacy against severe rotavirus gastroenteritis in study Rota-075 was lower than the one observed in the EU and developed Asian countries, but was in the range of what has been observed in clinical trials conducted in Latin America and Africa, which are already presented in the current Product Information. Consequently, no change to the SmPC is needed.

The CHMP endorses the Company's conclusion regarding the study outcome and agrees that there is no need for updating the product information as these data are not directly relevant to EU prescribers. The CHMP however noted that the current efficacy information from the Asian continent is very sparse and the new data contribute to a better knowledge of the clinical protection that can be expected.

VI. REQUEST FOR SUPPLEMENTARY INFORMATION

None