22 September 2011
EMA/204552/2013
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Rotarix

Common name: rotavirus vaccine, live

Procedure No.: EMEA/H/C/000639/II/0032

Note

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

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CHMP variation assessment report

Type II variation EMEA/H/C/639/II/32

Invented name/name:	Rotarix
International non-proprietary name/common name:	rotavirus vaccine, live

Indication summary (as last approved):	Prevention of gastro-enteritis due to rotavirus infection
Marketing authorisation holder:	GlaxoSmithKline Biologicals S.A.

1. Scope of the variation and changes to the dossier

Scope of the variation:	To update sections 4.4 and 5.1 of the SmPC to include efficacy data from trial Study Rota-028/029/030 in Asia that was extended up to the age of 3 years. The MAH also took the opportunity to include minor editorial amendments in sections 4.2, 4.3 and 4.4 of the SmPC and to update the list of local representatives in the Package Leaflet.
Rapporteur:	Pieter Neels
Product presentations affected:	See Annex A to the Opinion
Dossier modules/sections affected:	1,2 and 5
Product Information affected:	SmPC and Package Leaflet (Attachment 1 - changes highlighted)

Steps taken for the assessment

Step	Step date
Submission date:	6 May 2011
Start of procedure:	22 May 2011
Rapporteur's preliminary assessment report circulated on:	24 June 2011
Request for supplementary information and extension of timetable adopted by the CHMP on:	21 July 2011
MAH's responses submitted to the CHMP on:	22 August 2011
Rapporteur's preliminary assessment report on the MAH's responses circulated on:	1 September 2011
CHMP opinion:	22 September 2011

2. Scientific discussion

2.1. Introduction

Rotarix is a live attenuated human rotavirus (HRV) vaccine for oral administration that is manufactured by GlaxoSmithKline Biologicals. Rotarix is indicated for prevention of gastroenteritis (GE) due to rotavirus infection in infants from the age of 6 weeks.

Two pharmaceutical forms of Rotarix are currently marketed: the lyophilised vaccine to be reconstituted with a liquid diluent and the liquid formulation ready to use. In terms of components, the formulations only differ from each other in their excipient composition, which is linked to manufacturing and vaccine stability constraints. The active ingredient is identical. The same manufacturing procedures are used up to formulation.

The first license for Rotarix lyophilised was obtained from the Mexican Authorities (12 July 2004). In the European Union, the Company submitted the application for marketing authorisation of Rotarix to the European Medicines Agency (EMA) via the Centralised Procedure on 21 December 2004 and the EU Commission Decision was granted on 21 February 2006. The liquid formulation was granted marketing authorisation as a line extension in the European Union on 1 September 2008. The lyophilised formulation has been registered in a t least 115 countries and the liquid formulation is approved in 77 countries.

This variation aims to include information on efficacy from trial Rota-028/029/030 that was extended up to the age of 3 years in the SmPC. The primary objective of this study conducted in Singapore, Hong Kong and Taiwan was to document the efficacy of Rotarix versus placebo against severe RVGE until two years of age. A study extension up to three years of age was approved by amendment.

The variation can be classified as follows:

Variation(s) requested		**Type**
C.I.4	Variations related to significant modifications of the Summary of Product Characteristics due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	II

To update sections 4.4 and 5.1 of the SmPC to include efficacy data from trial Study Rota-028/029/030 in Asia that was extended up to the age of 3 years. The MAH also took the opportunity to include minor

editorial amendments in sections 4.2, 4.3 and 4.4 of the SmPC and to update the list of local representatives in the Package Leaflet.

2.2. Clinical aspects

Study Design

Study Rota-028/029/030 is a Phase III, double-blind, randomised, placebo-controlled, multi-country and multi-centre study to assess the efficacy, safety and immunogenicity of two doses of Rotarix vaccine in healthy infants in South East Asia. The study was conducted in Singapore, Hong Kong and Taiwan. Routine vaccination schedules varied: 2-4-6 months in Taiwan, 2-4-5 months in Hong Kong and 3-4-5 months in Singapore. The total duration of the study per subject (Visit 1 to Visit 6) was approximately 33-34 months.

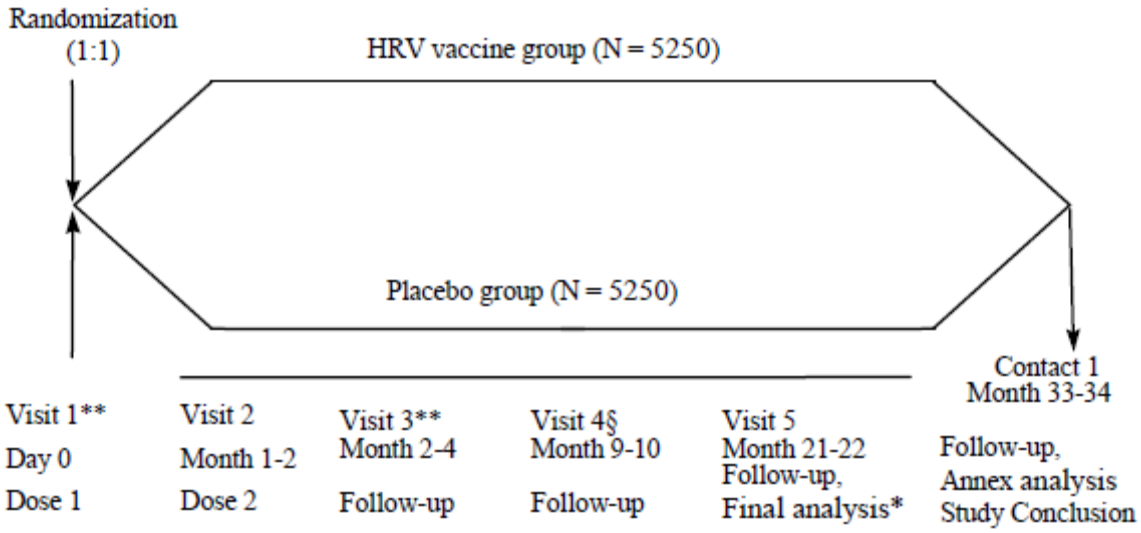
Subjects were randomly assigned (1:1 randomisation ratio) to one of two parallel groups, either the Rotarix vaccine group or the placebo (control) group. The placebo contained the same excipients as Rotarix but did not contain the RIX4414 HRV strain.

According to the individual country recommendations for routine vaccination, infants had to be between 6 and 12 weeks of age in Hong Kong and Taiwan, or between 11 and 17 weeks of age in Singapore, at the time of administration of the first dose of Rotarix. Routine vaccinations were allowed to be administered concomitantly with the study vaccines at 2 or 3 and 4 months of age according to the local regulations in each country. Thereafter, routine vaccinations were allowed to be given at each study visit as appropriate.

The administration of Hepatitis B vaccine (HBV); Bacille Calmette-Guérin vaccine (BCG); Oral Polio Vaccine (OPV) at birth, was allowed according to the National Programs on Immunisation (NPI). Whenever OPV was part of the routine vaccination schedule, a minimum interval of two weeks had to be observed between the administration of study vaccine (either Rotarix or placebo) and the administration of OPV.

The study design of the primary study phase is presented graphically by Figure 1.

Figure 1 Study design of Rota-028/29/30 primary phase



Footnote to Figure 1.

*Final statistical analysis for efficacy and safety performed when all subjects completed Visit 5 at the age of two years

**Blood sampling at Visit 1 and Visit 3 took place only in subjects who were part of the immunogenicity subset (planned N = 100 subjects per country from selected centers). Visit 3 took place only for subjects who were part of the immunogenicity subset.

§: Blood sampling in premature infants (per medical history) in Taiwan enrolled up to 18 May 2005, at Visit 4 or not later than two months after Visit 4 to evaluate immunogenicity

Study Objectives

Co-primary objectives

- Vaccine efficacy against severe RV GE caused by circulating wild-type RV strains during the period starting from 2 weeks after Dose 2 up to two years of age (see Definitions below).
- Vaccine safety with respect to definite intussusception (IS) within 31 days (Day 0-Day 30) after each dose.

Definitions:

Severe GE: A gastroenteritis episode requiring hospitalisation and/or re-hydration therapy (equivalent to the WHO plan B or C in a medical facility with a score ≥11 points on the 20-point Vesikari scale.

Severe RV GE: An episode of severe GE occurring at least two weeks after the full vaccination course in which rotavirus other than the vaccine strain was identified in a stool sample collected during the episode of severe GE.

Secondary efficacy objectives

- Severe RV GE caused by the circulating wild-type RV strains during the period starting from 2 weeks after Dose 2 up to three years of age
- Severe RV GE caused by the wild RV strain of type G1 during the period starting from 2 weeks after Dose 2 until two and three years of age
- Severe RV GE due to each non-G1 type during the period starting from 2 weeks after Dose 2 until two and three years of age
- RV GE caused by the circulating wild-type RV strains and requiring hospitalisation and/or re-hydration therapy (equivalent to WHO plan B or C) in a medical facility during the period starting from 2 weeks after Dose 2 until two and three years of age.

In line with earlier clinical studies in the Rotarix clinical development plan, vaccine efficacy against severe RV GE due to the specific strain G1P[8] (vaccine strain), as well as due to other circulating G/P types such as G2P[4]; G3P[8] and G9P[8] was estimated from 2 weeks after Dose 2 up to two and three years of age. Only the efficacy against the G/P combination G1P[8] was pre-specified because this is the vaccine strain. All efficacy analyses against other G/P combinations are post-hoc analyses.

Laboratory methodology

Stool samples were to be collected during each GE episode requiring hospitalisation and/or re-hydration therapy (equivalent to WHO plan B or C) in a medical facility. Stool samples were tested by ELISA for RV detection. All stool samples that were RV positive were tested by Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) followed by Reverse Hybridisation assay to determine the G and P types. This technique also allowed differentiation between the G1 vaccine virus and the wild-type G1 RV.

Study cohorts

Total vaccinated cohort

The total vaccinated cohort included all subjects with at least one vaccine administration documented in the primary study; an efficacy analysis based on the total vaccinated cohort included all vaccinated subjects.

Total Vaccinated Cohort for the third year follow up period

The total vaccinated cohort for the third year follow up period included all subjects from the total vaccinated cohort who had follow up beyond visit 5.

ATP Safety Cohort

The ATP cohort for safety included all vaccinated subjects:

- who had received at least one dose of HRV vaccine or placebo
- for whom the randomisation code had not been broken,
- who had not received a vaccine forbidden by or not specified in the protocol.
- who had not received a replacement vial, except if the appropriate vaccine was administered in "double-blind replacement".

ATP cohort for analysis of efficacy

- The ATP cohort for efficacy included all subjects from ATP cohort for safety who received 2 doses of HRV vaccine or placebo,
- who had entered into the efficacy surveillance period,
  - had follow-up beyond Visit 5 for the analysis of efficacy after Visit 5 up to Visit 6
  - had follow-up beyond 2 weeks after Dose 2 for the analysis of efficacy from 2 weeks after Dose 2 up to Visit 6
- who had no RV other than vaccine strain in GE stool samples collected between the day of Dose 1 administration and 2 weeks after Dose 2 of HRV vaccine or placebo administration

The ATP efficacy cohort was used for the primary analysis of efficacy. A secondary analysis of efficacy based on the total vaccinated cohort was also performed.

Efficacy results

Efficacy against severe RVGE

The main efficacy results until up to 2 and up to 3 years of age can be found in tables 1 and 2 below.

Significantly fewer subjects in the Rotarix group reported severe RV GE caused by circulating wild-type RV strains compared with placebo (0.0% versus 1.2%, p-value <0.001) up to three years of age. Vaccine efficacy up to three years of age was 96.9% (95% CI: 88.3%; 99.6%).

Table 1 Percentage of subjects reporting severe RV GE and vaccine efficacy up to 2 years of age (from 2 weeks after Dose 2 up to Visit 5; ATP cohort for efficacy)

			n/N			Vaccine Efficacy			
			%	95% CI		%	95% CI		
Group	N	n		LL	UL		LL	UL	p-value
HRV	5263	2	0.0	0.0	0.1	96.1	85.1	99.5	<0.001
Placebo	5256	51	1.0	0.7	1.3	-	-	-	-

Severe = episodes requiring hospitalisation and/or re-hydration therapy (equivalent to WHO plan B or C) in a medical facility with score ≥11 points on Vesikari scale
N = number of subjects included in each group
n = number of subjects reporting at least one severe RV GE episode in the considered efficacy period
% = percentage of subjects reporting at least one severe RV GE episode in the considered efficacy period
95% CI = 95% confidence interval; LL = lower limit; UL = upper limit
p-value = two-sided Fisher's exact test (significant level of α=0.05)

Table 2 Percentage of subjects reporting severe RV GE and vaccine efficacy up to 3 years of age (from 2 weeks after Dose 2 up to Visit 6; ATP cohort for efficacy)

			n/N			VE			
Group	N	n	%	LL	UL	%	LL	UL	P-value
HRV	5263	2	0.0	0.0	0.1	96.9	88.3	99.6	<0.001
Placebo	5256	64	1.2	0.9	1.6	-	-	-	-

N = number of subjects included in each group
n = number of subjects reporting at least one severe RV GE episode in the considered efficacy period
%= percentage of subjects reporting at least one severe RV GE episode in the considered efficacy period
LL, UL = 95 % Lower and Upper confidence limits
p-value = two-sided Fisher's exact test (significant level of α=0.05)

Vaccine efficacy from Visit 5 to Visit 6

Table 19 from the CSR of study Rota-028/029/030 Ext Y3 shows a 100% protection against severe RV GE between Visit 5 and Visit 6.

Table 19 **Percentage of subjects reporting severe RV GE episode (with a score greater than or equal to 11 using the 20 point Vesikari scale) and efficacy of vaccine from Visit 5 to Visit 6 (ATP cohort for efficacy)**

			n/N			VE			
Group	N	n	%	LL	UL	%	LL	UL	p-value
HRV	4222	0	0.0	0.0	0.1	100.0	67.5	100.0	<0.001
Placebo	4185	13	0.3	0.2	0.5	-	-	-	-

N = number of subjects included in each group
n = number of subjects reporting at least one severe RV GE episode in the considered efficacy period
%= percentage of subjects reporting at least one severe RV GE episode in the considered efficacy period
LL, UL = 95 % Lower and Upper confidence limits
p-value = two-sided Fisher's exact test (significant level of α=0.05)

Results for other efficacy endpoints for follow-up from Visit 5 up to Visit 6:

- No subjects in the HRV vaccine group reported severe RV GE episodes caused by the G1 type when compared to 5 severe RV GE episodes reported in the placebo group (0.0% versus 0.1%, p-value 0.031). The VE against severe RV GE caused by G1 type was 100.0% [95% CI: - 8.2%; 100.0%].
- No subjects in the HRV vaccine group reported severe RV GE episodes caused by non-G1 types (G2, G3 and G9) when compared to 8 severe RV GE episodes reported in the placebo group (0.0% versus 0.2%, p-value 0.004). The VE against severe RV GE caused by non-G1 types was 100.0% [95% CI: 78.0%; 99.3%].
- Due to few severe RV GE episodes reported due to each non-G1 RV type vaccine efficacy against each of the non-G1 types was not statistically significant: G2P[4] type (0 case in HRV vaccine group versus 2 case in the placebo group), G3P[8] type (0 case in HRV vaccine group versus 4 cases in the placebo group), and G9P[8] type (0 case in HRV vaccine group versus 2 cases in the placebo group).
- No subjects in the HRV vaccine group reported RV GE caused by the circulating wild-type RV strains that required hospitalisation and/or re-hydration therapy (equivalent to WHO plan B or C) in a medical facility, when compared to 15 RV GE episodes reported in the placebo group. The difference between the two groups was statistically significant (p-value <0.001).The VE was 100.0% [95% CI: 72.4%; 100.0%].

Efficacy against severe GE due to different RV types

Table 3 presents Rotarix vaccine efficacy against severe RV GE by specific RV type, from 2 weeks after Dose 2 up to Visit 5, i.e, up to two years of age.

Table 3 Percentage of subjects reporting severe RV GE episode and vaccine efficacy up to 2 years of age (from 2 weeks after Dose 2 up to Visit 5, by RV type; ATP cohort for efficacy)

				n/N			Vaccine Efficacy			
					95% CI			95% CI		
RV type	Group	N	n	%	LL	UL	%	LL	UL	p-value
G1 wild-type + P8 wild-type	HRV	5263	0	0.0	0.0	0.1	100.0	80.8	100.0	<0.001
	Placebo	5256	21†	0.4	0.2	0.6	-	-	-	-
Pooled non-G1	HRV	5263	2	0.0	0.0	0.1	93.6	74.7	99.3	<0.001
	Placebo	5256	31	0.6	0.4	0.8	-	-	-	-
G2+P4	HRV	5263	0	0.0	0.0	0.1	100.0	-431.7	100.0	0.250
	Placebo	5256	2	0.0	0.0	0.1	-	-	-	-
G3+P8 wild-type§	HRV	5263	1	0.0	0.0	0.1	94.5	64.9	99.9	<0.001
	Placebo	5256	18†*	0.3	0.2	0.5	-	-	-	-
G9+P8 wild-type§‡	HRV	5263	1	0.0	0.0	0.1	91.7	43.8	99.8	0.002
	Placebo	5256	12*	0.2	0.1	0.4	-	-	-	-

Severe = episodes requiring hospitalisation and/or re-hydration therapy (equivalent to WHO plan B or C) in a medical facility with score ≥11 points on Vesikari scale
N = number of subjects included in each group
n/% = number/percentage of subjects reporting at least one severe RV GE episode
95% CI = 95% confidence interval; LL = lower limit; UL = upper limit
p-value = two-sided Fisher's exact test (significant level of α=0.05)
†One subject from the placebo group counted in G1 and G3 categories since both RV types were isolated
* One subject from the placebo group counted in G3 and G9 categories since both RV types were isolated
§ P type was unknown for both G3 and G9 types isolated from one subject in the placebo group.
‡ P type was non-typable for G9 RV isolated from one subject in the placebo group

Table 4 presents Rotarix vaccine efficacy against severe RV GE by isolated RV type from 2 weeks after Dose 2 up to Visit 6, i.e., up to three years of age.

Table 4 Percentage of subjects reporting severe RV GE episodes and vaccine efficacy up to 3 years of age (from 2 weeks after Dose 2 up to Visit 6 by RV type; ATP cohort for efficacy)

RV type	Group	N	n	n/N			VE			p-value
				%	95% CI		%	95% CI		
					LL	UL		LL	UL	
G1 wild-type + P8 wild-type	HRV	5263	0	0.0	0.0	0.1	100.0	84.8	100.0	<0.001
	Placebo	5256	26*	0.5	0.3	0.7	-	-	-	-
G2+P4	HRV	5263	0	0.0	0.0	0.1	100.0	-51.3	100.0	0.062
	Placebo	5256	4	0.1	0.0	0.2	-	-	-	-
G3+P8 wild-type	HRV	5263	1	0.0	0.0	0.1	95.2	70.4	99.9	<0.001
	Placebo	5256	21*	0.4	0.3	0.6	-	-	-	-
G9+P8 wild-type	HRV	5263	1	0.0	0.0	0.1	91.7	43.8	99.8	0.002
	Placebo	5256	12	0.2	0.1	0.4	-	-	-	-

N = number of subjects included in each group
n = number of subjects reporting at least one severe RV GE episode in the considered efficacy period
n/N = percentage of subjects reporting at least one event
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95% Lower and Upper confidence limits
p-value = two-sided Fisher's exact test
*One case of RVGE with G1WT + G3 + P8WT strain was reported in this study

Due to very few reports of severe RV GE episodes caused by the G2 type (Table 3 and Table 4), vaccine efficacy against the G2 type was not statistically significant.

Vaccine efficacy against severe RV GE due to strains with the P[8] genotype

Table 5 presents Rotarix vaccine efficacy against severe RV GE caused by strains with the P[8] genotype from 2 weeks after Dose 2 up to Visit 5, i.e. up to two years of age.

Table 5 Vaccine efficacy against severe RV GE due to P[8] WT containing strains up to 2 years of age (from 2 weeks after Dose 2 up to Visit 5; ATP cohort for efficacy)

Event Type	Group	N	n	n/N			VE			P-value
				%	95% CI		%	95% CI		
					LL	UL		LL	UL	
P8 WT	HRV	5263	2	0.0	0.0	0.1	95.8	83.8	99.5	<0.001
	Placebo	5256	47	0.9	0.7	1.2	-	-	-	-

N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
n/N (%) = percentage of subjects reporting at least one event
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits
P-value = Two-sided Fisher Exact test

Table 6 presents Rotarix vaccine efficacy against severe RV GE caused by strains with the P[8] genotype from 2 weeks after Dose 2 up to Visit 6, i.e. up to three years of age.

Table 6 Vaccine efficacy against severe RV GE due to P[8] wild-type (WT) containing strains up to 3 years of age (from 2 weeks after Dose 2 up to Visit 6; ATP cohort for efficacy)

Event Type	Group	N	n	n/N			VE			P-value
				%	95% CI		%	95% CI		
					LL	UL		LL	UL	
P8 WT	HRV	5263	2	0.0	0.0	0.1	96.6	87.0	99.6	<0.001
	Placebo	5256	58	1.1	0.8	1.4	-	-	-	-

N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
n/N (%) = percentage of subjects reporting at least one event
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits
P-value = Two-sided Fisher Exact test

Vaccine efficacy against RV GE requiring hospitalization and/or re-hydration therapy (equivalent to WHO plan B or C) in a medical facility and vaccine efficacy

Table 7 presents Rotarix vaccine efficacy against RV GE requiring hospitalisation and/or re-hydration therapy (equivalent to WHO plan B or C) in a medical facility from 2 weeks after Dose 2 up to Visit 5, i.e, up to two years of age.

Table 7 Percentage of subjects reporting RV GE requiring hospitalisation and/or re-hydration therapy (equivalent to WHO plan B or C) in a medical facility and vaccine efficacy up to 2 years of age (from 2 weeks after Dose 2 up to Visit 5; ATP cohort for efficacy)

Group	N	n	n/N			Vaccine Efficacy			p-value
				95% CI			95% CI		
			%	LL	UL	%	LL	UL	
HRV	5263	3	0.1	0.0	0.2	94.2	82.2	98.8	<0.001
Placebo	5256	52	1.0	0.7	1.3	-	-	-	-

N = number of subjects included in each group
n = number of subjects reporting at least one RV GE episode in the considered efficacy period
% = percentage of subjects reporting at least one RV GE episode in the considered efficacy period
95% CI = 95% confidence interval; LL = lower limit; UL = upper limit
p-value = two-sided Fisher's exact test (significant level of α=0.05)

Significantly fewer subjects in the Rotarix group reported RV GE caused by the circulating wild-type RV requiring hospitalisation and/or re-hydration therapy in a medical facility compared with the placebo group (0.1% versus 1.0%, p-value <0.001). Vaccine efficacy up to two years of age was 94.2% (95% CI: 82.2%; 98.8%).

Table 8 presents the Rotarix vaccine efficacy against RV GE caused by the circulating wild-type RV strains and requiring hospitalisation and/or re-hydration therapy (equivalent to WHO plan B or C) in a medical facility from 2 weeks after Dose 2 up to Visit 6, i.e. up to three years of age.

Table 8 **Percentage of subjects reporting RV GE requiring hospitalisation and/or re-hydration therapy (equivalent to WHO plan B or C) in a medical facility and vaccine efficacy up to 3 years of age (from 2 weeks after Dose 2 up to Visit 6; ATP cohort for efficacy)**

			n/N			VE			
Group	N	n	%	LL	UL	%	LL	UL	P-value
HRV	5263	3	0.1	0.0	0.2	95.5	86.4	99.1	<0.001
Placebo	5256	67	1.3	1.0	1.6	-	-	-	-

N = number of subjects included in each group
n = number of subjects reporting at least one RV GE episode in the considered efficacy period
%= percentage of subjects reporting at least one RV GE episode in the considered efficacy period
LL, UL = 95 % Lower and Upper confidence limits
p-value = two-sided Fisher's exact test (significant level of α=0.05)

Significantly fewer subjects in the Rotarix group reported RV GE caused by the circulating wild-type RV requiring hospitalisation and/or re-hydration therapy in a medical facility compared with the placebo group (0.1% versus 1.3%, p-value <0.001). Vaccine efficacy up to three years of age was 95.5% [95% CI: 86.4%; 99.1%] (Table 8).

Discussion on efficacy

Protocol amendments

The study protocol of study Rota-028/029/030 originally anticipated an attack rate of 1.5% for severe RVGE during the first year. During January 2005, a status update on severe RVGE estimated the attack rate on 0.1% (CSR for study Rota 028/029/030 p. 59). Such a low prevalence did not allow demonstrating clinical protection during the first year using the sample size based on the 1.5% attack rate. The study was extended until two years of age by Amendment 3 dated 7 February 2005 (the study started on 8 December 2003) and another extension up to three years was approved by Amendment 6 dated 21 December 2005. The attack rate of severe RVGE was only 0.3% up to visit 4 (approx 12 month of age; CSR for Study Rota 028/029/030 Table 23 p.90) and 0.7% between Visit 4 and Visit 5 (approx 24 months of age; CSR for Study Rota 028/029/030 Table 24 p.91). It is obvious that there was a need for extending the study duration up to the age of 24 month in order to demonstrate the vaccine's efficacy against severe RVGE due to the individual and most frequent genotypes.

Number of subjects available and vaccine's efficacy at Visit 5 and Visit 6

According to Table 1 10519 subjects were available at Visit 4 (=up to one year of age). A total of 104 subjects did not enter the second efficacy follow-up period. As a consequence, the number of subjects available at Visit 5 was 10415 (n=5221 in the HRV group, n=5194 in the placebo group).

In view of Table 2, it should be noted that of the 10415 subjects available at Visit 5, 2008 did not enter the third efficacy follow-up, which is a loss of about 19%. The total number of subjects at Visit 6 was 8407 (n=4222 in the HRV group and n=4185 in the placebo group).

According to the CSR, all subjects included in the ATP cohort for efficacy from 2 weeks after Dose 2 up to Visit 4 were included in the ATP cohort for efficacy from 2 weeks after Dose 2 up to Visit 6. Thus, the ATP cohort for efficacy from 2 weeks after Dose 2 up to Visit 6 also included 10519 subjects (5263 subjects in the HRV vaccine group and 5256 subjects in the placebo group.

In view of the number of subjects in the ATP cohort for efficacy, the MAH clarified that because 104 subjects dropped out after Visit 4, there were 10,415 subjects (HRV group: 5,221 subjects; placebo group: 5,194 subjects) remaining for efficacy evaluation between Visit 4 and Visit 5 (two years of age).

The total number of subjects who entered into the efficacy follow-up period between Visit 5 (two years of age) and Visit 6 (three years of age) was indeed 8,407 (HRV vaccine group: 4,222 subjects; placebo group: 4.185 subjects).

As foreseen in the study protocol, the efficacy up to a certain point in time was calculated on the ATP cohort for efficacy, which included all subjects who had entered that specific efficacy period, i.e. all subjects who had a follow-up beyond 2 weeks after the second vaccination. For this 'time to event' analysis all the subjects at risk are included, and thus not only the ones who completed the concerned efficacy follow-up period.

Therefore, the ATP cohort for efficacy from 2 weeks after Dose 2 up to Visit 5, as well as the ATP cohort for efficacy from 2 weeks after Dose 2 up to Visit 6 (three years of age) included 10,519 subjects, as per the protocol definition of ATP cohort for efficacy.

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

- who received two doses of HRV vaccine or placebo,
- who had entered into the efficacy surveillance period,
  - had follow-up beyond 2 weeks after Dose 2 for the analysis of efficacy from 2 weeks after Dose 2 up to Visit 4 (for efficacy up to one year of age)
  - had follow-up beyond 2 weeks after Dose 2 for the analysis of efficacy from 2 weeks after Dose 2 up to Visit 5 (for efficacy up to two years of age)
  - had follow-up beyond 2 weeks after Dose 2 for the analysis of efficacy from 2 weeks after Dose 2 up to Visit 6 (for efficacy up to three years of age)
- who had no RV other than vaccine strain in GE stool samples collected between the day of Dose 1 administration and 2 weeks after Dose 2 of HRV vaccine or placebo administration.

The CHMP therefore agreed that the following number of subjects can be considered for the ATP cohort:

- up to Visit 4 (1 year of age): n= 10519
- up to Visit 5 (2 years of age): n= 10415
- up to Visit 6 (3 years of age): n= 8407

Protection against severe RVGE up to the end of the third year of life

In addition, the CHMP highlighted that persistent protection against severe RVGE up to the end of the third year of life was only demonstrated for the pooled group of genotypes, not for the individual ones. However, the 100% protection rate observed during the period between Visit 5 and Visit 6 (Table 19) may in reality be an overestimation of the reality just because of the very low incidence during that period. It should be noted that the protection against severe RVGE (pooled genotypes) between Visit 4 and Visit 5 was 94.5%, however in general after vaccination a natural trend of declining protection can be anticipated over time, but not an increasing one.

The CHMP further expressed doubts if persistent protection up to the age of three years observed in the Asian population that attended study Rota 028/029/030 can be extrapolated to other ethnic groups especially those who experience RVGE early in life such as children on the African continent. The CHMP

however agreed that such a statement would not needed to be reflected in the SmPC, as statements on extrapolation to other populations have also not been included for other studies in the SmPC.

The CHMP considered that vaccine efficacy from Visit 5 to Visit 6 (3rd efficacy period) on overall efficacy against severe RVGE and protection against RVGE episodes requiring hospitalization or rehydration can be seen as the only evidence for persisting protection against severe RVGE up to the age of 36 months (Visit 6). With such a low attack rate of severe RVGE between Visit 5 and Visit 6 it is obvious that the vaccine's efficacy against the pooled genotypes at Year 3 (Visit 6) will be nearly identical with the one observed at Year 2 (Visit 5).

Efficacy in view of individual genotypes

As shown above, the incidence of severe RVGE associated with the individual genotypes in the placebo group during the period between Visit 5 and Visit 6 was too small for demonstrating a difference between the vaccine and placebo group if a difference existed in reality. It is obvious that protection at Visit 6, calculated on the basis of the cumulative incidence, is expected to be very similar as the one observed at Visit 5. The observed protection at Visit 6 therefore cannot be considered as a proof for persistent protection. As a consequence, the vaccine's efficacy against severe GE due to the individual genotypes up to Visit 6 (as shown in Table 4) can not be established within this study. Considering that persisting protection against the individual genotypes remained unproven during the period between Visit 5 and Visit 6 an efficacy rate for each individual genotype at Visit 6 cannot be given.

Overall, protection against the individual non-G1 types was not statistically significant in the period between Visit 5 and Visit 6 because of the very low attack rate and it was therefore not endorsed to claim protection against the individual non-G1 types in the Product Information.

ATP cohort for efficacy at Visit 6

According to the study report for Rota- 028/029/030 all subjects included in the ATP cohort for efficacy from 2 weeks after Dose 2 up to Visit 4 were included in the ATP cohort for efficacy from 2 weeks after Dose 2 up to Visit 6, even subjects who did not attend Visit 6. The MAH clarified that in study Rota-028/029/030 and in all other Rotarix efficacy studies, the vaccine efficacy was calculated on the ATP cohort for efficacy, as foreseen in the study protocol. Subjects who did not comply with the criteria of the ATP cohort for efficacy were eliminated from the Total Vaccinated Cohort before analysis. In other words, and as per protocol definition, the ATP cohort for efficacy over a certain time period includes all subjects from the ATP cohort for safety who have entered into that specific efficacy follow-up period (FUP). For this 'time to event' analysis, all the subjects at risk are included, and thus not only the ones who completed the efficacy FUP. According to the MAH, Clinical protection was assessed in the ATP cohort for efficacy, which includes all subjects from the ATP cohort for safety who entered into the concerned efficacy follow-up period.

In practice, this means that for analysis of the efficacy during the efficacy follow-up until 2 years of age (Visit 5) and until 3 years of age (Visit 6), all subjects are included who had a follow-up beyond 2 weeks after dose 2. The ATP cohorts for the efficacy FUP up to two and three years of age are therefore identical.

Clinical Safety

There were no safety endpoints pertaining to the third year follow-up period. SAEs were not routinely collected as part of study procedure from Visit 5 to Visit 6. However, the MAH was to be informed if the investigator became aware of any unusual safety data or any safety data that was considered to be significant and which was related to vaccination. The verbatim of SAEs obtained from the investigators

were reviewed by a GSK Biologicals' physician and the signs, symptoms and diagnoses were coded to the most appropriate lowest level term according to the MedDRA, which was then linked to the primary SOC and PT for analysis.

The safety data (including those observed during the extension period) were assessed as part of the 10th PSUR, which covered the period from 12 July 2004 up to 11 July 2010. No update of section 4.8 of the SmPC was considered necessary based on the safety data from this trial. Therefore, the assessment of safety was not discussed in the present variation assessment.

Changes to the Product Information

The detailed changes can be found in the final approved highlighted SmPC attached to this report. Further to the assessment and the scientific discussions held at the CHMP, the following changes to the Product Information were requested and subsequently implemented by the MAH:

SmPC Section 5.1
Protective efficacy in Europe

The text initially proposed by the MAH referring to the Vesikari 20-point scale was removed to avoid repetition.

Definitions for severity of gastro-enteritis (Vesikari scale and WHO criteria)

To avoid repeating the same information in the footnote of each table, the following information was added under the heading "Protective efficacy":

"Clinical protection was assessed in the ATP cohort for efficacy, which includes all subjects from the ATP cohort for safety who entered into the concerned efficacy follow-up period."

Footnotes to the tables presenting protective efficacy data

The symbol "§" was removed from the efficacy tables as well as the footnote referring to it since it is obvious that all efficacy data are collected from the ATP cohort for efficacy.

Efficacy up to 3 years of age in Asia

With regard to the paragraph proposed by the MAH:

"A clinical study conducted in Asia (Hong Kong, Singapore and Taiwan) in more than 10000 subjects evaluated Rotarix given according to different schedules (2, 4 months of age; 3, 4 months of age).

After two doses of Rotarix, the protective vaccine efficacy (Vesikari definition) observed up to 3 years of age is presented in the following table":

The CHMP commented that it is inappropriate to suggest that more than 10000 subjects were available during the third year. The exact number of subjects in the ATP cohort for efficacy available at Visit 6 should be given. The CHMP also added that the Vesikari's definition for efficacy does not exist.

The following modifications were therefore made:

"A clinical study conducted in Asia (Hong Kong, Singapore and Taiwan) (Rotarix: N = 5,359; placebo: N = 5,349) ~~in more than 10000 subjects~~ evaluated Rotarix given according to different schedules (2, 4 months of age; 3, 4 months of age).

The protective vaccine efficacy after two doses of Rotarix, ~~the protective vaccine efficacy (Vesikari definition)~~ observed against severe rotavirus gastro-enteritis up to ~~3~~2 years of age is presented in the following table. (…)"

Concerning the table presenting vaccine efficacy in Asia the following amendments were made:

The column showing the efficacy up to 3 years initially proposed by the MAH was deleted since the study was not powered to demonstrate the vaccine's efficacy against severe RV GE associated with the individual genotypes between Visit 5 and Visit 6 as outlined above.

In addition, a clarification is now given for the missing efficacy data during the first year below the table:

"Significantly fewer subjects in the HRV vaccine group reported severe RV GE caused by the circulating wild-type RV compared to the placebo group from 2 weeks after Dose 2 up to Visit 4 (0.0% versus 0.3%, p-value <0.001), with vaccine efficacy of 100% (95% CI: 72.2; 100)".

Furthermore, protection against severe RVGE (pooled genotypes) as well as protection against hospitalisation/rehydration during the period between Visit 5 and Visit 6 was included in the table and text.

In view of protection against the individual genotypes between Visit 5 and Visit 6 the CHMP noted that their incidence during that period is extremely low and could therefore not be proven based on the data. In that case, the protection at Visit 6 will automatically be comparable to Visit 5, suggesting that protection persists up to Visit 6 (3 years of age). The only evidence of persisting protection is the vaccine's efficacy against severe RVGE after pooling all genotypes. The CHMP did not agree to mention a rate of protection against the individual genotypes even when it is obvious that a "pooled protection" can only be the consequence of individual protection. Strain-specific efficacy data for the third year of life are therefore not presented in the SmPC. A revised wording highlighting the low incidence of severe RV GE was included in the SmPC.

Conclusions and Benefit / Risk Assessment

Based on the available efficacy data from trial Rota-028/029/030, the CHMP considered that it is appropriate to reflect the main findings from this trial in section 5.1 of the SmPC, however including a claim for sustained protection against severe GE due to strains G1P[8], G3P[8] and G9P[8] in children up to three years of age was not endorsed.

The incidence of severe GE due to the individual strains between Visit 5 and Visit 6, the extension period of study Rota-028/029/030, was too low for demonstrating a difference between the vaccine and placebo group if a difference existed.

In such a situation it is obvious that protection at Visit 6 will necessarily be very similar as the one observed at Visit 5.

Persistent protection against severe RVGE up to the end of the third year of life was only demonstrated for the pooled group of genotypes, not for the individual ones, as well as for the rate of RV gastro-enteritis requiring hospitalisation. It was acceptable to add this information to the SmPC.

Overall, taking into account the new data on efficacy over 3 years from the above study and the appropriate amendments to the Product Information, the CHMP considered that the data confirm previous findings from other populations and considered that the benefit-risk balance of Rotarix remains favourable.

3. Conclusion

On 22 September 2011 the CHMP considered this Type II variation to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics and Package Leaflet.