SCIENTIFIC DISCUSSION

Introduction

Rotarix is an oral vaccine, presented as a powder and solvent, which are mixed to make up an oral suspension. The active ingredient of Rotarix is a live attenuated strain of human rotavirus (RIX4414 strain), which belongs to the G1 serotype and the P[8] genotype. Rotarix is currently indicated for the active immunisation of infants from the age of 6 weeks for the prevention of gastro-enteritis caused by Rotavirus of types G1P[8], G3P[8] and G9P[8]. Two doses of Rotarix should be administered. The first dose may be administered from the age of six weeks and no later than the age of 14 weeks. There should be intervals of at least 4 weeks between doses. It is preferable that both doses should be administered before the age of 16 weeks. Both doses must be given by the age of 24 weeks.

On 12 April 2006 the MAH submitted a variation to change the following sections in the Product Information (PI) for Rotarix:

- Section 4.1: Inclusion of information that efficacy demonstrated against gastro-enteritis due to rotavirus of type G4P[8], based on efficacy data in study Rota-036 conducted in Europe. Inclusion of efficacy against Rotavirus Gastroenteritis (RV GE) due to G2P[4], based on pooled analysis of efficacy obtained in five efficacy trials.
- Section 4.3: More specific information on gastrointestinal congenital malformation has been added.
- Section 4.4: Information on the new serotypes and a statement on the extent of protection has been added.
- Section 4.5: With regard to co-administration, information on co-administration of pneumococcal and meningococcal serogroup C vaccines has been included.
- Section 4.6: A confirmation that breast-feeding would not reduce the protection against rotavirus gastro-enteritis afforded by Rotarix has been included.
- Section 4.8: Amendments concerning information on the now available studies have been included.
- Section 5.1: Update of the efficacy data in function of the results now available from first efficacy follow-up period in European trial Rota-036 and from second efficacy follow-up period in Latin American trial Rota-023. Update of the tabular presentation of immunological data in function of the results now available from European clinical trial Rota-036.

In the new indication (in section 4.1 of the SPC), the serotypes G2P[4] and G4P[8] are added to the listed serotypes.

At the July 2006 Vaccine Working Party, the statistical approach for the meta-analysis/pooling to support the G2 P[4] strain in the indications section of the SPC was discussed and the MAH's approach was endorsed on this meeting .

Clinical aspects

To support the extension of the indication for this variation, the MAH used a meta-analysis/pooling of the data from five studies, Rota-004, -006, -007, - 023 and –036 to support the proposed protection against G2-P[4] strains. Data from studies Rota –036 (full study report) and Rota –023 (2nd year follow-up data) have been submitted with the variation application. Details of the study designs concerning the studies Rota-023 and –036 are presented in table 1.
The study particulars of all studies included in the meta-analysis are summarised below.

Rota-023
Information on efficacy provided in the current SPC was partly based on data generated in the pivotal study Rota-023 conducted in Latin America. Evaluation of vaccine efficacy up to 2 years of age in this trial was ongoing at the time of CHMP review of the information package submitted for marketing authorisation. The primary efficacy endpoint used a case definition of severe GE based on WHO criteria. An episode of severe GE was defined as an episode of diarrhoea with or without vomiting that required hospitalisation and/or re-hydration therapy (equivalent to WHO plan B or C) in a medical facility. The results obtained through the second year efficacy follow-up period are now available and are supporting this variation ("Efficacy and follow-up Safety in the 2nd year Efficacy Subset").

Rota-036
This study evaluated the efficacy, immunogenicity and safety of Rotarix in six European countries and has recently been completed. The primary Objective of this trial was to determine the efficacy of two doses of Rotarix given concomitantly with specific childhood vaccinations against any RVGE caused by the circulating wild-type RV strains during the first efficacy follow-up period."
Results from this study provide an update on the vaccine's efficacy in Europe as well as on the immunogenicity and reactogenicity of specific childhood vaccines, including hexavalent vaccine, meningococcal serogroup C vaccine and pneumococcal vaccine, when co-administered with Rotarix according to local immunisation schedules.

Rota –004
Data from study Rota –004 (Finland) was included in the initial application for Rotarix. The primary objective of this double-blind, randomised, placebo-controlled study was to determine if two doses of Rotarix could prevent any RV GE over one season following vaccination.

Rota -006
This study, carried out in Brazil, Mexico and Venezuela, was also included in the initial application for Rotarix. The primary objective of this double-blind, randomised, placebo-controlled study was to determine if two doses Rotarix could prevent RV GE during the first efficacy follow-up period. furthermore, the effect of unrestricted feeding on the immune response to Rotarix was evaluated.

Study Rota-007:
The primary objective of this double-blind, randomised, controlled study, carried out in Singapore, and included in the initial application for Rotarix, was to determine if two doses of Rotarix could prevent RV GE during the first efficacy follow-up. The safety, reactogenicity and immunogenicity of the Rotarix at 3 viral concentrations were assessed. The immune response to concomitantly administered routine vaccinations and the effect of unrestricted feeding on the immune response to Rotarix were evaluated. The study was not conclusive for efficacy due to the smaller number of documented rotavirus GE cases than expected. Although no case of severe RV GE and RV GE caused by G2P[4] were reported in this study, Rota-007 was taken into account for the pooled analysis in order to ensure a consistent total number of subjects for all integrated estimates of vaccine efficacy.

Study Designs of studies included in the submission (Rota-036, Rota-023)

Study number	*Design* Objectives: **Primary** Secondary	Population **Age** (at time of first dose) Vaccine schedule	(Randomisation) Vaccines (viral concentration) *Concomitant routine vaccine (feeding regimens)*	(Subjects, total number) **Rotarix groups** Placebo groups Enrolled (N)	ATP Efficacy FU periods n 1st	n 2nd	ATP Immuno genicity n
Rota-023 (Latin America)	*Double blind, randomised, placebo controlled* **Efficacy up to 1 year of age §** Efficacy 2nd year; Efficacy combined FU period Safety Immunogenicity (subset) Immune response to routine vaccines (subset)	Healthy infants **6-12 weeks** *(6-13 weeks in Chile)* *0, 2 month*	(1:1) HRV ($10^{6.5}$CCID50) Placebo *Routine vaccinations (DTPw, HBV, Hib) concomitantly admin. OPV separated from study vaccine by 14 days.* *(unrestricted feeding)*	(15183) **7669** 7514	(14286) **7205** 7081	(14237) **7175** 7062	(14286) **7205** 7081
Rota-036 (Europe)	*Double blind, randomised, placebo controlled* **Efficacy up to 1 year of age** Safety, reactogenicity (subset) Immunogenicity (subset) Immune response to routine vaccines (subset)	Healthy infants **6-14 weeks** *0, 1 month* *0, 2 month*	(2:1) HRV ($10^{6.5}$CCID50) Placebo *Childhood vaccinations (DTPa, HBV, IPV, Hib), 7Pn (subset) and Neisseria meningitidis C (subset) concomitantly administered (unrestricted feeding)*	(3994) **2646** 1348	(3874) **2572** 1302	*ongoing*	(1216) **794** 422
Total number of subjects				**19177**	**18160**		**15502**
Subjects receiving the Rotarix				**10315**	**9777**		**7999**
Subjects receiving the placebo				**8862**	**8383**		**7503**

N - Total number of subjects enrolled n - number of subjects who received Rotarix in ATP efficacy and immunogenicity cohorts.
FU period = efficacy follow-up period; DTPa/DTPw = diphtheria and tetanus toxoids and acellular/wholoecell pertussis vaccine; HBV = hepatitis B vaccine; Hib=- Haemophilus influenzae type b; IPV = inactivated polio; OPV= oral polio vaccine
7Pn.= Streptococcus pneumoniae vaccine (Prevenar).
§ Year 1 efficacy, immunogenicity and safety results were previously submitted as part of the CHMP review package. New data with respect to 2nd year efficacy, safety and immunogenicity are subject of the present variation procedure.

Table 1: Summary of studies Rota-023 and Rota-036 and numbers of subjects enrolled in the efficacy and immunogenicity ATP cohort

Study (Region) Schedule	Study Start (Date of first visit)	Start of efficacy follow-up	Duration of first efficacy period (end of period)	Duration of second efficacy period (end of period)
Rota-023 (Latin America) 2, 3 to4 months	August 05, 2003	2 weeks post dose 2	Approx. 10 months (October 14, 2004)	Approx. 11.8 months
Rota-036 (Europe) *	September 08, 2004	2 weeks post dose 2	Approx. 5.7 months (mid-June to end-July 2005)	ongoing

* France and Germany: 2, 3 months; Spain: 2, 4 months; Czech Republic: 3, 4 months; Finland and Italy: 3, 5 months

Table 2: First and second year efficacy follow-up periods as planned in the study protocols of studies Rota-023 and Rota-036

Study Rota-036

The secondary reactogenicity and safety objectives were as follows:

- to assess the vaccine's reactogenicity concomitantly with specific childhood vaccinations compared with placebo in terms of solicited symptoms in the immunogenicity and reactogenicity subset (planned N=1800).
- In all subjects, to assess the safety of two doses of Rotarix given concomitantly with specific childhood vaccinations compared with placebo in terms of unsolicited AEs (within 31 days after each dose) and SAEs during the entire course of the study.

Study cohorts

The "According-To-Protocol" (ATP) cohort for efficacy for the first follow-up period included all subjects for whom unbiased differential treatment effect on efficacy was likely and who had received two doses of Human Rotavirus Vaccine (HRV, Rotarix) 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; had entered into the surveillance period (day of dose one until the last study visit for each of the subjects) and had been followed-up beyond 2 weeks after dose 2. The ATP efficacy cohort for the second efficacy follow-up period includes all subjects from the ATP efficacy cohort of the first efficacy follow-up period who have entered into the surveillance period and have follow-up beyond the end of the first efficacy follow-period. The ATP efficacy cohort for combined efficacy follow-up periods includes all subjects from the ATP efficacy cohort of the first efficacy follow-up period.
A secondary analysis was also conducted on the total vaccinated cohort for the first efficacy period in study Rota-036. The efficacy follow-up periods are given in Table 2.

Severity of GE episodes
The severity of the GE episodes was defined according to the Vesikari scale *(Ruuska T and Vesikari T. 1990).* The Vesikari 20 point scale evaluates the full clinical picture of rotavirus gastro-enteritis by taking into account the severity and duration of diarrhoea and vomiting, the severity of fever and dehydration as well as the need for treatment. The intensity of the GE was also assessed using the 24 point scale Clark scoring system *(Clark HF et al. 1988).*

Calculation of efficacy:

The vaccine efficacy was calculated using the formula:

$$1 - RR = 1 - (ARV/ARU)$$

RR = relative risk = ARV/ARU; ARV =disease attack rate in vaccinated group = nv/Nv = number of subjects reporting at least one RV GE episode / total number of subjects in the vaccine group. The 95% CIs for VE were derived using a conditional to cases approach.

In order to assess VE from Dose 1 onwards, VE against all endpoints evaluated in the ATP analysis was calculated for the period from Dose 1 up to Visit 5. Also, VE against any and severe RV GE were calculated for the period from Dose 1 to before Dose 2 and from Dose 1 up to Day 14 after Dose 2. These analyses were performed only on the total vaccinated cohort. The blood sampling timepoints are presented in table 3.

For the period starting from 2 weeks after Dose 2 up to Visit 5, exploratory VE was also calculated against each isolated RV type, severe RVGE with Clark score >16, by serological status for IgA antibody concentration at Visit 3, by feeding criteria, all cause GE, by country, all cause severe GE and hospitalisation due to all cause GE.

To evaluate the robustness with respect to the statistical analysis, VE against any RVGE, any RVGE due to G1 type and any RVGE due to non-G1 types during the first efficacy follow-up period and their 95% CI were also estimated by the Cox proportional-hazard model including the group effect as

regressor. Furthermore, the time from 2 weeks after Dose 2 of Rotarix or placebo to he onset of any RVGE, any RVGE due to G1 type and any RV GE due to non-G1 types was analysed.

Assessment of the immunogenicity
Seroprotection/seroconversion/seropositivity rates and their exact 95% confidence interval (CI) were calculated by group. GMCs (geometric mean concentrations)/GMTs (geometric mean titres) and their 95% CI were calculated by group. GMCs and their 95% CI were also calculated on the subjects who had seroconverted to anti-rotavirus IgA antibody. The two-sided asymptotic standardised 95% CI for difference (Rotarix minus placebo) in anti-rotavirus IgA seroconversion rates after one to two months after Dose 2 of Rotarix or placebo (Visit 3) was calculated. The two-sided asymptotic standardised 95% CI for difference (Placebo minus Rotarix) in post Dose 2/Dose 3 seropositivity/seroprotection rates was calculated for each co-administered antigen by country. The 95% CI for the ratio of post Dose 2/Dose 3 GMCs/GMTs (Placebo over Rotarix) was computed for each co-administered antigen by country .

The criteria used for seroprotection and seropositivity were as follows:

Seroprotection:
• anti-diphtheria antibody concentrations ≥ 0.1 IU/ml
• anti-tetanus antibody concentrations ≥ 0.1 IU/ml
• anti-poliovirus type 1 antibody titres ≥ 8
• anti-poliovirus type 2 antibody titres ≥ 8
• anti-poliovirus type 3 antibody titres ≥ 8
• anti-PRP antibody concentrations ≥ 0.15 and ≥ 1.0 µg/ml
• anti-HBs antibody concentrations ≥ 10.0 mIU/ml

Seropositivity:
• anti-PT antibody concentrations ≥ 5 EL.U/ml
• anti-FHA antibody concentrations ≥ 5 EL.U/ml
• anti-PRN antibody concentrations ≥ 5 EL.U/ml
• anti-MenC antibody titer ≥ 1/8
• anti-PSC antibody concentrations (ELISA) ≥ 0.3 µg/ml
• antibody concentrations to Streptococcus pneumoniae serotypes 4, 6B, 9V, 14, 18C, 19F and 23F ≥ 0.05 µg/ml

Study (Region)	Age at first vaccination	Schedule (months)	Pre-vaccination Blood sample	Time of blood sampling after dose 2 Post dose 2
Rota-036 (Europe)	6-14 weeks	3-4-5 (Cz Rep) 3-5-11 (Finland) 2-3-4 (France) 2-3-4 (Germany) 3-5-11 (Italy) 2-4-6 (Spain)	Yes	1 month (Czech Republic, France, Germany) 2 months (Finland, Italy, Spain)

Table 3 Blood sampling time points for the assessment of response to the Rotarix

Antibodies to all antigens contained in the co-administered vaccines were measured at the blood sampling time points (see table 4).

Study (Country)	Schedule of Routine vaccines (months)	Antigens evaluated	Time of blood sampling after each dose: nomenclature (nomencl)	
			Dose 2 # Time: nomencl	Dose 3 Time: nomencl
Rota-036 (Czech Republic, Finland, France, Germany, Italy, Spain)	3-4-5 (Cz Rep)	D, T, Pa, IPV, Hib, HBs	--	1 month P3 (1mo)
	3-5-11 (Finland)	D, T, Pa, IPV, Hib, HBs	1 month P2 (1mo)	1 month P3 (1mo)*
	2-3-4 (France) 2-3-4 (Germany)	D, T, Pa, IPV, Hib, HBs, *Streptococcus pneumoniae*	- -	1 month P3 (1mo)
	3-5-11 (Italy)	D, T, Pa, IPV, Hib, HBs	1 month P2 (1mo)	1 month P3 (1mo)*
	2-4-6 (Spain)	D, T, Pa, IPV, Hib, HBs, *Neisseria Meningitis* C	2 months P2 (2mo)	1 month P3 (1mo)

In Finland, Italy and Spain, the immunogenicity of the co-administered childhood vaccinations was also assessed after the first 2 doses of the childhood vaccinations which is an intermediate time point after an incomplete vaccination course of childhood vaccinations

*Subjects in Finland and Italy were to receive the 3rd dose of childhood vaccination series as per the recommended national schedule (without Rotarix). Post Dose 3 immunogenicity of childhood vaccinations are available for the total vaccinated cohort of the immunogenicity and reactogenicity subset.

Table 4: Blood sampling time points for the assessment of the immune response to routine concomitantly administered vaccines in study Rota-036

Laboratory methods

Rotavirus GE was defined as an episode of GE in which rotavirus was identified by ELISA (enzyme-linked immunosorbent assay) in a stool sample collected during the episode. All stool samples that were RV positive were tested by RT-PCR followed by Reverse Hybridisation assay at Delft Diagnostic Laboratory, the Netherlands to determine the G serotype and the P genotype. This technique also allows the discrimination between the G1 vaccine virus and the wild-type G1 RV. Two RVGE episodes were considered as two separate episodes if there were 5 or more symptom-free days between the episodes.

Concomitant routine paediatric vaccines[1]

- Infanrix-Hexa was co-administered with each Rotarix or placebo dose in ach country, except in France where Infanrix-Polio Hib was co-administered with the second vaccine dose or placebo.
- Meningitec was co-administered in Spain
- Prevenar was co-administered in France and Germany

Study Rota-023

Initial data without the now available results from the 2nd year follow-up were already included in the Marketing Authorisation application dossier submitted in December 2004 for Rotarix. The design of this study can be found in table 1. A 0, 1 to 2-month schedule was used for administering the vaccine doses. The age at the time of dose 1 was 6-12 weeks (or 6-13 weeks for subjects from Chile only). Concomitant paediatric vaccines (DTPw-HBV and Hib) were co-administered with Rotarix. The administration of OPV (oral polio vaccine) was separated from the administration of Rotarix or

[1] Infanrix Hexa: GSK Biologicals' combined diphtheria and tetanus toxoids, acellular pertussis, hepatitis B, inactivated polio and Haemophilus influenzae type b vaccine
Infanrix Polio Hib: GSK Biologicals' combined diphtheria and tetanus toxoids, acellular pertussis, inactivated polio and Haemophilus influenzae type b vaccine
Prevenar: Wyeth Pharmaceuticals' pneumococcal polysaccharide conjugate vaccine (7-valent)
Meningitec: Wyeth Pharmaceuticals' meningococcal group C conjugate vaccine

placebo and the co-administered routine vaccines by at least two weeks. As a secondary efficacy endpoint a severe GE episode was also defined according to the Vesikari scale in this study.

Clinical efficacy

Vaccine Efficacy results from Study Rota-036

The vaccine efficacy against any RV GE, during the first efficacy period starting from 2 weeks after dose 2 until one year of age was 87.1% (95% CI: 79.6%; 92.1%) (two-sided Fisher's exact P-value < 0.001).

The vaccine efficacy against severe RV GE, hospitalisation due to RV GE, RV GE requiring medical attention was 95.8% (95% CI: 89.6%; 98.7%), 100% (95% CI: 81.8%; 100%) and 91.8% (95% CI: 84.0%; 96.3%), respectively.

The total vaccinated cohort was used to calculate vaccine efficacy against any and severe RV GE, starting from the first dose onwards, included all participants who received at least one dose.

Results of the total vaccinated cohort analysis were fully consistent with the ATP analysis and demonstrated that the vaccine provided significant protection starting from the first dose onwards. Vaccine efficacy from Dose 1 onwards up to the end of the follow-up period was 87.3% (95% CI: 80.3%; 92.0%) against any RV GE and 96.0% (95% CI: 90.2%; 98.8%) against severe RV GE.

Although Rotarix is a 2-dose vaccine, during the period from Dose 1 to before Dose 2, significant vaccine efficacy of 89.8% (95% CI: 8.9%; 99.8%) was observed against any RV GE (two sided Fisher's exact P-value = 0.019). A similar trend was observed against severe RV GE, but not enough cases were reported to reach statistical significance.

Interim immunogenicity results of study Rota-036 were previously submitted and assessed during the evaluation procedure of the initial Marketing Authorisation application. These data demonstrated that clinical efficacy of Rotarix during the first year of life increased with increasing severity of RV GE. Vaccine protection progressively increased up to 100% (95% CI : 74.5;100) for cases with Vesikari score ≥ 19. Efficacy data in study Rota-036 further confirm this observation. Protection against cases with Vesikari score ≥ 17 was 100% (95% CI: 84.7;100; P-value <0.001).

The rotavirus serotype was identified in all RVGE episodes. In the Rotarix group, the most common RV serotype identified was G9P[8] (13 episodes; 54.2%) followed by G1P[8] (4 episodes), G2P[4] (3 episodes), G4P[8] (3 episodes) and G3P[8] (1 episode).
In the placebo group, the most common RV serotype identified was G1P[8] (45 episodes; 47.9%) followed by G9P[8] (27 episodes; 28.7%), G4P[8] wild-type (12 episodes) and G3P[8] wild-type (5 episodes) and G2P[4] (3 episodes). G1P[8] and G4P[8] wild-type RV was identified from one episode. The P genotype could not be identified for one episode in which the G2 type was isolated.

As the CHMP needed clarification on the number of subjects with severe RVGE due to G2P[4] in the vaccine and placebo group as well as on further figures the MAH was requested to clarify these issues in a Request for Supplementary Information adopted in the July 2006 CHMP plenary session. The MAH answered satisfactorily by correcting these figures and the CHMP regarded this issue as resolved.

Immunogenicity of Rotarix in study Rota-036

The impact of incorporating Rotarix into different existing routine immunisation schedules on the immunogenicity of the concomitant vaccines was evaluated during the clinical development of Rotarix. In study Rota-036, the assessment of a potential impact on the response to routine paediatric

vaccines has been further investigated by concomitant administration of Rotarix with other specific childhood vaccines, according to local country schedules in different European countries.

The majority of subjects (98.4% to 100%) in each group of the ATP cohort for immunogenicity received the childhood vaccinations concomitantly with dose 1 and dose 2 of Rotarix or placebo. The 3rd dose of childhood vaccination series was given in accordance with the recommended national Plan of Immunisation schedule of each country .

Rotarix was sufficiently immunogenic as shown by the antirotavirus IgA antibody seroconversion rate of 86.5% (95% CI: 83.9%; 88.8%) and the GMC (calculated on subjects who seroconverted) of 313.7 U/ml observed in the Rotarix group at one to two months after Dose 2 for pooled countries (Table 5 and 6). Seroconversion rates ranged from 82.1% to 94.6%, depending on the country. These minor point estimate differences in seroconversion noted between different countries could reflect the different schedules used in different countries. At one to two months post dose 2, the seroconversion rates in the placebo group ranged from 2.2% to 14.0%, depending on the country.

			SC rate (≥20 U/ml)				GMC (U/ml)		
					95% CI			95% CI	
Group	Timing	N	n	%	LL	UL	value	LL	UL
Rotarix	PII(M3-M4)	787	681	86.5	83.9	88.8	197.2	175.2	222.0
	PII(M5)	184	152	82.6	76.3	87.8	113.3	90.8	141.5
Placebo	PII(M3-M4)	420	28	6.7	4.5	9.5	< 20	--	--
	PII(M5)	90	14	15.6	8.8	24.7	< 20		

N = number of subjects with available results
n/% = number/percentage of subjects with concentration above the cut-off
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PII(M3-M4) = blood sample taken one to two months after Dose 2 of Rotarix or placebo (Visit 3)
PII(M5) = blood sample taken three months after Dose 2 of Rotarix or placebo (visit 4)

Table 5: Seroconversion rates and GMCs for anti-Rotavirus IgA antibodies - ATP cohort for immunogenicity (Rota-036) in all countries

Group	Timing	N	GMC (U/ml) value	GMC (U/ml) 95% CI - LL	GMC (U/ml) 95% CI - UL
Rotarix	PII(M3-M4)	681	313.7	284.2	346.1
	PII(M5)	152	189.0	157.3	226.9
Placebo	PII(M3-M4)	28	290.9	159.3	531.2
	PII(M5)	14	172.9	82.7	361.5

N = number of subjects who seroconverted for anti-rotavirus IgA antibodies
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PII(M3-M4) = blood sample taken one to two months after Dose 2 of Rotarix or placebo (Visit 3)
PII(M5) = blood sample taken three months after Dose 2 of Rotarix or placebo (visit 4)

Table 6 Anti-rotavirus IgA antibody GMC calculated on subjects who seroconverted for anti-rotavirus IgA antibodies at visit 3 (4) – ATP cohort for immunogenicity (Rota-036), all countries

Information form other studies on the immunogenicity to concomitantly administered routine vaccines

The immunogenicity of concomitantly administered routine paediatric vaccines was the secondary objective in studies Rota-005 (USA, Canada) 006 (Brazil, Mexico, Venezuela) 007 (Singapore) and 013 (South Africa), which were previously submitted in the application for the initial marketing authorisation. OPV was concomitantly administered in studies Rota-013 and Rota-014 (South Africa). At that time, there were no data in connection with the immunogenicity of concomitantly administered vaccines among subjects in Europe. For the ATP cohort for immunogenicity, the majority of subjects (98.4% to 100%) in each group received the childhood vaccinations concomitantly with dose 1 and dose 2 of Rotarix or placebo.

Post Dose 2 immunogenicity of concomitantly administered vaccines (ATP cohort for immunogenicity)

In Finland, Italy and Spain, the immunogenicity of the co-administered vaccines was also assessed after the first 2 doses of the childhood vaccinations which is an intermediate time point after an incomplete vaccination course of childhood vaccinations.

- A statistically significant difference was not detected between vaccine and placebo for post Dose 2 seropositivity rate /seroprotection rate to diphtheria, tetanus, PT, FHA, PRN, HBs, poliovirus types 1, 2 and 3, and PRP, and SBA-MenC and PSC (Spain) since the two-sided asymptotic standardised 95% CIs for the treatment differences (placebo minus Rotarix) contain the value zero, except for anti-PRP antibody in Finland (higher response for the Rotarix group).

- A statistically significant difference was not detected between vaccine and placebo for post Dose 2 GMC/GMT for antibodies to diphtheria, tetanus, PT, FHA, PRN, HBs, poliovirus types 1, 2 and 3, and PRP, and SBA-MenC and PSC (Spain) since the 95% CI for the ratios of GMC/GMT (placebo over Rotarix) for each antibody contain the value one, except for anti-poliovirus type 3 antibody in Finland and in Spain (higher response for the Rotarix group).

Anti-PRP antibodies post dose 3 of routine childhood vaccination (Rota-036)
Seroprotection rates and GMC for anti-PRP antibodies were comparable in the vaccine and placebo groups within each country.

Hepatitis B response
The immune response to HBsAg was comparable between the vaccine and placebo group within each country. However, the proportion of subjects showing antibody titres of ≥10 mIU/ml was very low in Germany (when compared with Spain, Czech republic and France). GMCs among seropositive subjects were also significantly lower.

Poliovrus antigen response
Within each country, post-dose 3 antibody GMT and seroprotection rates against poliovirus 1, 2 and 3 were strictly comparable.

Meningococcal C antibodies
All subjects in the vaccine and placebo group developed SBA antibodies in titres of ≥ 1:8, which is considered to be a protective titre.

Anti- Streptococcus pneumoniae types antibodies post dose 3 of Prevenar
There was no difference in seropositivity rates between vaccine and placebo recipients within each country.

Anti-diphtheria and anti-tetanus antibodies post Dose 3 of childhood vaccinations – Evaluation of differences between groups
Although post dose 3 immunogenicity of childhood vaccinations, including anti-diphtheria and anti-tetanus antibodies, tended to be lower in Germany, the CHMP considered that overall, no significant differences could be observed for these antigens. The observed trend towards lower immune response to Infanrix Hexa in both the HRV vaccine and placebo group in Germany compared to the other countries by the fact that the interval between the last dose and the blood sample was less than 21 days for 25% of the subjects and that this was linked to a specific centre. When this centre was excluded from the calculations the immune responses observed in the remaining centres were in the expected range, which could be confirmed by a post-hoc descriptive analysis.

Post dose 3 immunogenicity in Finland and Italy (Total vaccinated cohort)
A high level of seroprotection rate for anti-diphtheria, anti-tetanus, anti-HBs, antipoliovirus-1, anti-poliovirus 2 and anti-poliovirus 3 antibodies was observed in vaccine and placebo groups post dose 3 of childhood vaccinations in Finland. The very small number of subjects in Italy precludes any valid conclusion.

Discussion on differing immune responses to antigens contained in the concomitantly administrated vaccines obtained in different countries

The CHMP considered that data on immune responses to antigens contained in the concomitantly administrated vaccines did not indicate any interference of Rotarix. The proposed up-date of Section 4.5 was considered acceptable to reflect this information.
The CHMP further concluded, that the seropositivity/seroprotection rates or GMCs/GMTs for antibodies to each antigen contained in childhood vaccines were similar between the Rotarix and placebo groups in any of the countries. This confirmed the absence of interference of Rotarix on the immune response to antigens contained in co-administered childhood vaccines like DTPa combinations vaccines as also demonstrated in previous clinical trials of Rotarix (Rota-005, Rota-007) using similar vaccines.

With respect to the immune response induced by Infanrix hexa in France, the CHMP considered that a correlate of protection has been established for PRP, polio antigens-1, -2, -3 and diphtheria. A summary of the immune response observed after a primary course of Infanrix hexa administered according to the 2, 3, 4 month schedule in the 2 Infanrix hexa clinical trials performed by the MAH with this schedule (DTPa-HBV-IPV-025 and DTPA-HBV-IPV-099) showed that seroprotection rates in Rota-036 are in line with previous clinical trials results, except for polio antigen-2. Seroprotection rate against polio antigen-2 tended to be lower in France (93% vs. 96-97% in DTPa-HBV-IPV trials); however, due to the limited number of subjects enrolled in France, this difference was not statistically significant. Furthermore, the MAH pointed out, that geometric mean concentrations/titres (GMC/Ts) are more influenced by the schedule than seroprotection rates. In Rota-036, the GMC/Ts in France should therefore be compared to the GMC/Ts obtained in Germany (excluding centre 7715), as only these 2 countries used the 2, 3, 4 month schedule. Although there is a trend to slightly lower GMC/Ts in France as compared to Germany, the GMC/Ts observed in France are in the same range as those observed in the DTPa-HBV-IPV trials. As explained above, the number of subjects enrolled in France was too small to draw any conclusion with respect of the GMC/Ts as emphasised by the large 95%CI of the values. The CHMP agreed that this explanation was sufficient to address the above-mentioned concerns.

Effect of breast- feeding on the vaccine's efficacy
Data presented in the initial submission for marketing authorisation application suggested a limited impact of breast feeding on the Rotarix immunogenicity. However, there was no evidence available to suggest that breast-feeding would reduce the protection against rotavirus gastro-enteritis. In study Rota-036, unrestricted feeding prior to vaccination was permitted and information about the different feeding types was collected. In the ATP efficacy cohort of study Rota-036, 66.0% of subjects were breast-fed at the moment of receiving the two Rotarix/placebo doses, 12.6% were breast-fed at least one of the two doses of Rotarix/placebo and 21.4% of subjects were not breast-fed at all. Table 7 presents the vaccine efficacy against any and severe RV GE by breast feeding status.

In the ATP immunogenicity cohort, 59.1% of subjects were breast-fed at the moment of receiving the two Rotarix/placebo doses, 14.7% were breast-fed at least one of the two doses of Rotarix/placebo and 26.2% of subjects were not breast-fed at all. Seroconversion rates at one to two months after the second Rotarix dose were strictly comparable in the group who received breast-feeding and the group who had not received.

The vaccine's efficacy estimates were similar between children who were breast-fed for at least one dose and children who were not breast-fed, as shown from the largely overlapping confidence intervals. The CHMP agreed that this sub-analysis of efficacy by breast-feeding status in study Rota-036 further confirmed that breast-feeding has no impact on the vaccine's efficacy.

Breast feeding status	Group	N	Subjects		Vaccine Efficacy 95%CI			P-value
			n	n/N %	%	LL	UL	
Any RV GE								
Breast feeding for at least one dose	Rotarix Placebo	2005 1041	20 74	1.0 7.1	86.0	76.8	91.9	<0.001
Breast feeding at none of the doses	Rotarix Placebo	567 261	4 20	0.7 7.7	90.8	72.5	97.7	<0.001
Severe RV GE(Vesikari score ≥11)								
Breast feeding for at least one dose	Rotarix Placebo	2005 1041	4 48	0.2 4.6	95.7	88.2	98.9	<0.001
Breast feeding at none of the doses	Rotarix Placebo	567 261	1 12	0.2 4.6	96.2	74.1	99.9	<0.001

N = number of subjects included in each group
n/% = number/percentage of subjects reporting at least one (severe) RV GE episode caused by the circulating wild type
RV in each group, by feeding criteria
95% CI,LL,UL = Lower and upper limits of the 95% confidence interval
p-value=two-sided Fisher's exact test (significant level of α=0.05)

Table 7: Vaccine efficacy against any and severe RV GE episodes, by feeding criteria - ATP cohort for efficacy (Rota-036)

Vaccine efficacy during the first and second follow-up period in study Rota-023.

Subjects enrolled in the efficacy subset of study 023 were followed during a second follow-up period up to the age of two years for the occurrence of severe RV GE.

Overall, significant protection against severe RV GE *(*severity was classified according to WHO criteria) was observed in the Rotarix group compared to the placebo group. Overall vaccine efficacy was 79.0% during the second follow-up period versus 83.1% during the first follow-up period. Similar efficacy estimates were obtained in a secondary analysis using the Vesikari scale for assessing the severity of GE.

Similar efficacy estimates were obtained in a secondary analysis using the Vesikari scale to assess the intensity of GE episodes. Vaccine efficacy against severe RV GE (i.e. with a score ≥ 11 on the 20-point Vesikari scale) for the combined follow-up period was 82.1% (95% CI: 73.1;88.5).

Efficacy against hospitalisation for RV GE was 85.4% (95% CI, 67.4;94.4) during the first efficacy follow-up period, 81.5% (95% CI, 66.7;90.1) during the second efficacy follow-up period and 83.0% (95% CI, 73.1;89.7) during the combined efficacy follow-up period.

As for the first efficacy follow-up period, multiple RV serotypes were circulating during the second follow-up period. The observed type specific vaccine efficacy against severe RV GE over the **second** and the **combined** follow-up periods was as follows:

G1P[8] type: **72.4**% (95% CI: 34.5;89.9) in the second follow-up period and **82.1%** (95% CI: 64.6;91.9) over the combined periods.

G9P[8] type: **87.7%** (95% CI: 72.9;95.3) in the second follow-up period and **86.6%** (95% CI: 73.0;94.1) over the combined periods.

G3P[8] type **71.9%** (95% CI, -47.7;97.1) in the second follow-up period and **78.9%** (95% CI: 24.5;96.1) over the combined periods.

G4P[8] type, which was **63.1%** (95% CI, 0.7;88.2) over the second follow-up period and **61.8%** (95% CI: 4.1;86.5) over the combined periods. The low number of subjects reporting severe RV GE due to G4P[8] type in the first follow-up period, as compared to the second period, prevented assessment of vaccine efficacy against severe RV GE caused by G4P[8] type in the first follow-up period.

P[8] genotype was 79.5% (95% CI: 67.0;87.9) over the second follow-up period.

Only two subjects had RV GE due to G2P[4] in the second follow-up period (one in each group). Over the combined periods, fewer subjects in the Rotarix group reported severe RV GE episodes caused by G2P[4] type compared with the Placebo group but, as was observed for the first period, the difference between groups did not reach statistical significance (two-sided Fisher's exact P-value = 0.420). Vaccine efficacy against severe RV GE caused by G2P[4] type over the combined periods was **38.6%** (95% CI: -112.9%; 84.2%).

Overall, the CHMP concluded that 2 doses of Rotarix administered at approximately 2 and 4 months of age decreased significantly the number of severe rotavirus GE episodes, as well as, the number of hospitalisations due to rotavirus diarrhoea during the second year of life. The results confirm previous findings, demonstrating that vaccination with Rotarix in the first months of life provided continued protection against severe disease in the second year of follow-up.
The long-term efficacy follow-up results in study 023 were considered to be included the data in Section 5.1 of the SPC.

The CHMP also considered that although the overall vaccine's efficacy in protecting against severe RVGE is maintained over time in study Rota-023 (83% in the first versus 79% in the second year), there is a clear waning of clinical protection against G1P[8] and P8 genotypes over time. The apparent stability of the overall vaccine's efficacy is mainly due to the protective effect against G4P[8], a strain which showed a strong increase in incidence during the second follow-up year. The CHMP further concluded that protection against this strain compensated for the loss of efficacy observed against G1P[8] and the other P8 genotypes

Analysis performed across trials (pooled analyses and meta-analysis)

During the initial application for marketing authorisation, the MAH submitted the results of a meta-analysis on the pooled data from studies Rota-004, 006 and 023 to demonstrate that the vaccine shows a clinical protection against RVG2P[4], which is not an antigen contained in the vaccine. However, due to the limited number of G2P[4] cases, the 95 % CI was wide and no statistical significance could be shown. To allow a more precise estimation of efficacy against severe RV GE due to G2P[4], a pooled analysis of efficacy against severe RV GE (score ≥11 on the Vesikari scale) caused by G2P[4] in studies 004, 006 and 023 was performed during the initial application. The efficacy against severe RVGE (score ≥ 11 on the Vesikari's scale) due to G2P[4] was estimated at 67.2% (95% CI; 14.8%; 87.1%) when calculated at the ATP cohort. The results of the meta-analysis were mentioned in section 5.1 of the SPC, though RVGE due to G2P[4] was not approved as an indication.

The new data from the first follow-up period of study Rota-036 showed the same trend towards protection against severe RV caused by G2P[4], with a point estimate of 74.7% (95% CI: -386,2-99,6%). However, the incidence of RVGE due to G2P[4] was not significantly different in vaccine and placebo recipients.

Data from Rota-036 were also included in a new pooled analysis which included severe (Vesikari score ≥11) G2P[4] cases observed in studies 004, 006, 023 and 036. No cases of severe RV GE were observed in study 007. The new pooled analysis resulted in an efficacy point estimate of 71.4 % with a 95% CI of (20.1%– 91.1%) when calculated on the ATP efficacy cohort (see table 8)

Study	N	Rotarix n	%	N	Placebo n	%	VE	LL	UL
004	245	0	0.0	123	1	0.8	100.0	-1858.0	100.0
006	1392	0	0.0	454	3	0.7	100.0	21.1	100.0
023	9009	5	0.1	8858	9	0.1	45.4	-81.5	85.6
036	2572	1	0.0	1302	2	0.2	74.7	-386.2	99.57
All*	**14792**	**6**	**0.0**	**11296**	**15**	**0.1**	**71.4**	**20.1**	**91.1**

Results from the first efficacy follow-up period on the ATP cohort for efficacy
* VE defined as 1-stratified Poisson rate ratio
LL, UL: lower limit and upper limit of the exact 95% CI
Severe = Vesikari score ≥ 11

Table 8: Pooled analysis of severe RV GE (score ≥11 on Vesikari scale) due to G2P[4] type and efficacy of the vaccine from 2 weeks after Dose 2 up to the end of the first-year follow-up - Studies Rota-004, -006, -007, -023, and -036, ATP cohort for efficacy.

The CHMP pointed out that protective efficacy for G2P[4] were supported by the data, however the number of cases observed among the five studies were considered low (6/14792 in the vaccine groups vs. 15/11926 in the placebo group). Consequently, it was considered crucial that each case included in vaccine and placebo groups were adequately justified and that calculation of efficacy should only be based on G2P[4] strains.
With regard to the meta-analysis that demonstrated clinical protection against severe RVGE due to G2P[4] the CHMP had the following comments:

As all efficacy studies were performed with a similar design and definition of severe RVGE (Vesikari score ≥ 11), but the severity of gastro-enteritis in study Rota-023 was defined according to WHO criteria, which were post hoc converted into Vesikari's scale. The CHMP concluded that the impact of such a conversion on the distribution of cases across the vaccine and placebo groups would be unknown. The proposed wording for section 5.1 of the SPC indicates that all studies were prospectively defined according to Vesikari's scale, therefore the CHMP concluded that it should be specified that the SPC that WHO criteria were used for study Rota-023.

As viral concentrations lower than the commercial formulation were used in studies Rota-004 and Rota-006, the CHMP considered that the pooled analysis might be negatively biased in disfavour of the vaccine. As in studies Rota-004 and -006 a different method was used for determination of viral concentrations in the vaccines than in study Rota-036 , the MAH was asked to justify the claim that the viral concentration in vaccines used in Rota-004 and -006 were lower than the commercial vaccines used in the other trials.
The CHMP considered that the MAH's claim that the meta-analysis would underestimate the vaccine's efficacy against G2P[4] is exclusively based on the data from study Rota-006 where three vaccines strengths were used. Furthermore, the pooled efficacy is lower than the vaccine efficacy observed with the highest vaccine strength (85.6%). Considering the non-significant trend in the incidence of severe RVGE across the respective vaccine strengths, the clinical relevance of the increasing vaccine efficacies associated with increasing vaccine strengths remains questionable. Consequently, the CHMP did not support the MAH's statement that the meta-analysis underestimates the vaccine's efficacy against G2P[4] by including vaccine strengths lower than the commercial formulation .

The CHMP further pointed out that the meta-analysis considered only protection against severe G2P[4] gastro-enteritis during the first year of follow-up, and that there is no evidence that any cross-protection would exist beyond the first year. The MAH was therefore asked to reflect this issue in the SPC.

Following the MAH's response addressing persistence of clinical protection, the CHMP discussed further if a recalculation of the vaccine efficacy (VE) would be necessary, as the increase observed in

VE in the 2. year against G4P8 and G9P8 could possibly not be taken as an evidence of increased VE over time.
Although there is great uncertainty in VE (wide CI with negative lower limits (LLs)) for G2P4, G3P8 and G4P8, the 95% CIs of G1P8 and P8 for the 1. and 2. year overlap. Consequently, a waning VE cannot be confirmed. Furthermore, the CHMP discussed that the analyses should have been performed on the same subjects at different time points in order to estimate growth decrease or persistence of VE.
The CHMP agreed, that the distribution of cases is similar between those followed-up and those lost to follow-up the 2nd year. Therefore, the CHMP discussed if the MAH should recalculate the VE for the first follow-up year after removing the subjects lost to follow-up the 2nd year to indicate persistence. As the proposed compromise to mention the data in SPC section 5.1 in a table was considered acceptable, the CHMP considered that no recalculation of the VE would be necessary.

The CHMP further considered that results of the meta-analysis for the pooled data of the second follow-up periods of the five studies are awaited and the MAH committed to submit the requested data in the 2nd quarter of 2007.

As tabulated data from study Rota-023 included in the pooled analysis showed minor inconsistencies with other tables in the submission, the MAH was also requested to clarify this point and the CHMP considered the MAH's answer appropriate.

Concerning mixed infections, the pooled analysis excluding the mixed cases and the cases with unknown P type has been performed and still lead to statistically significant VE against severe RV GE cause by G2P[4] type. The CHMP accepted this approach and agreed that the issue has been sufficiently clarified

As the MAH had only severe cases occurring in the first follow-up period from the ATP-cohort included in the pooled analysis and in order to strengthen the support for protective efficacy against G2P[4], the CHMP requested that a calculation of efficacy against any RV GE should also be performed. Furthermore, the MAH was asked to commit to perform the pooled analysis of the protective efficacy based on the second and the combined follow-up period when data from the second follow-up period of study Rota-036 is available.

The MAH presented a pooled analyses including G2P[4] cases of any severity observed in studies 004, 006, 007, 023 and 036 (see Table 13). The MAH explained that only GE leading to hospitalisation or specific healthcare facilities were collected in Rota-023 while other RV GE cases were collected in the other studies. For this reason, the MAH carried out two pooled analyses to assess possible bias by including/excluding study Rota-023. In the pooled analysis including the Rota-023 study, vaccine efficacy against any RV GE caused by G2P[4] is 65.2 % with a 95% CI of (19.8%– 85.3%). The results with the G2 type are therefore in line with the results obtained with other serotypes where efficacy against RV GE of any severity is always slightly lower than against severe RV GE. Of note, the lower limit of the 95% CI is positive and close to 20 %.
In the pooled analysis excluding the Rota-023 study, vaccine efficacy against any RV GE caused by G2P[4] is higher, 81.0 %, with a 95% CI of (31.6%– 95.8%).

The CHMP agreed with the MAH's conclusions and considered this issue as resolved.

Study	Group	N	n	%	VE	95% CI	
004	Placebo	123	1	0.81	100.00	-1858	100.00
	Rotarix	245	0	0.00			
006	Placebo	454	3	0.66	89.13	-35.40	99.79
	Rotarix	1392	1	0.07			
007	Placebo	559	1	0.18	100.00	-1285	100.00
	Rotarix	1574	0	0.00			
023	Placebo	8858	10	0.11	41.01	-79.15	82.38
	Rotarix	9009	6	0.07			
036	Placebo	1302	4	0.31	62.03	-124.4	94.44
	Rotarix	2572	3	0.12			
All with Rota-023	Placebo	11296	19	0.17	65.22	19.76	85.83
	Rotarix	14792	10	0.07			
All without Rota-023	Placebo	2438	9	0.37	81.04	31.58	95.76
	Rotarix	5783	4	0.07			

Table 9: Pooled analysis of any RV GE due to G2P[4] type and efficacy of the vaccine from 2 weeks after Dose 2 up to the end of the first-year follow-up - Studies Rota-004, -006, -007, -023, and -036, ATP cohort for efficacy

The CHMP also mentioned that the variation dossier contained information on the P-types of G2-strains causing RV GE in studies Rota-004 and -006. However, according to the data submitted with the initial MAA one subject in study Rota-004 was re-infected with a G1-strain approx. one year after the first G2-infection (Vesikari scores 15 and 12, respectively). The CHMP considered that information on the P-type of this strain could throw some light on the possible role of cross-protective immunity caused by VP4. The MAH was therefore requested to provide the P-type for that G1 strain. Furthermore, the MAH was requested, to submit data on the G-and P-type of all isolates from individuals who experienced re-infections in order to substantiate arguments with regards to cross-protection between P[8]- and P[4]-strains.

The MAH clarified that no subjects with more than one episode of rotavirus gastro-enteritis were observed in studies Rota-007 (from dose 1 up to the end of the 2nd efficacy follow-up), Rota-023 (from dose 1 up to the end of the 2nd efficacy follow-up) and Rota-036 (from dose 1 up to the end of the 1st efficacy follow-up). The MAH presented the data from five subjects from studies Rota-004 and Rota-006 which experienced two episodes of GE caused by RV.
The MAH concluded that a vast majority of the subjects that reported a RV GE experienced only one episode of RV GE up to 2 years of age. Among the 5 subjects that reported 2 RV GE, the second episode was of severe intensity for only one of them and in each case, the Vesikari score was lower for the second episode than for the first one. The CHMP agreed with the MAH that data from the clinical trials were in line with literature data showing that natural immunity induced by RV infection protects infants from subsequent episodes of severe disease

Discussion on efficacy and molecular mechanisms responsible for cross-protection

Efficacy

The CHMP considered that it would not be not justified to restrict the indication to severe gastroenteritis (GE) caused by G2P[4], as a pooled analysis of rotavirus (RV) GE of any severity caused by G2P[4] type gives a vaccine efficacy of 65.2% with the 95% CI of (19.8%; 85.8%), which is also mentioned in Section 5.1 of the SPC. From a medical point of view, it is also very unlikely that vaccine efficacy against G2P[4] would drop to zero for RV GE with Vesikari scores < 11 while it is around 70% for Vesikari scores ≥ 11. Furthermore, the MAH stated that the distinction between GE of any severity and severe GE in the therapeutic indications section would induce confusion for the prescriber.

The CHMP further pointed out that there are insufficient data at this time to determine whether Rotarix can protect against infection with other G types. Clinical studies from which efficacy data were derived were conducted in Europe and Central and South America. Furthermore, the vaccine's efficacy against gastro-enteritis due to G2P[4] was exclusively demonstrated on pooled data, not in separate clinical trials.

The CHMP considered that study Rota-036 has shown that the efficacy between the first and the second doses of Rotarix is statistically significant (p-value of 0.019 and 95%CI LL of 8.9%). When the period is enlarged up to 2 weeks post-dose 2 (timepoint before which an immune response to the 2nd dose is still unlikely), only 2 RV GE in 2646 Rotarix recipients have been observed compared with 8 RV GE in 1348 placebo recipients, confirming the significant protection induced by the first dose of Rotarix (p-value of 0.004 and 95%CI LL of 36.2%).

The CHMP further commented that in study Rota-023, severity of gastro-enteritis was prospectively defined according to WHO criteria, which were a posteriori transformed into Vesikari's scale for the purpose of data pooling. Since the SPC suggests that all studies were prospectively defined according to Vesikari's scale, the CHMP recommended that the SPC should specify that WHO criteria were used for study Rota-023. The MAH revised the SPC proposal accordingly.

The MAH acknowledged that here is no evidence that protection against RV strains with P[8] genotype significantly decreases during the 2nd year of life as compared to the 1st year of life. It can therefore be expected that protection against G2P[4] would persist beyond the 1st year of life. The MAH believed that the addition of the sentence proposed by the CHMP would induce an unjustified negative perception about Rotarix efficacy against G2P[4].

The MAH also committed to provide the pooled analysis of the protective efficacy against GE caused by G2P[4] RV strains based on the second and the combined follow-up period as soon as data from the second follow-up period of study Rota-036 are available .

The CHMP considered that the protection against G2P4 will persist at the same level during the second year.

Considering the natural decay of antibodies, maternal IgG antibodies are still abundant in the serum of vaccinated children 1 to 2 months after the second vaccine dose, when blood samples are taken in Rota studies to assess immune response to Rotarix. In order to overcome the issue of maternal neutralising antibodies that interfere in the measure of neutralising IgG antibodies induced by vaccination, the geometric mean concentration (GMC) of neutralising antibodies in the IgA seroconverters (subjects who take the vaccine) was compared to the GMC observed in placebo recipients and non IgA seroconverters (subjects considered without vaccine take). The level of serologic neutralising antibodies induced by vaccination was studied as characterisation tool of the overall immune response in a subset of subjects enrolled in study Rota-006. Some neutralising antibody responses were observed against the vaccine strain RIX4414, and the three prototype strains Wa (G1P[8]), P (G3P[8]) and WI61 (G9P[8]) (see Table 10)

IgA Sero-status at 2-month post dose II	**N**	**Neutralising antibodies . GMC (U/ml)**					
		Wa (G1P[8])	**P (G3P[8])**	**VA70 (G4P[8])**	**WI61 (G9P[8])**	**DS1 (G2P[4])**	**RIX 4414 (G1P[8])**
IgA Seroconverters	57	57	22	12	18	8	119
Pooled IgA non-seroconverters and placebo	29	15	11	10	7	8	14

Table 10: Post-vaccination geometric mean concentration (GMC) of neutralising antibody against the vaccine strain RIX4414 and 5 RV prototype strains

No increase in neutralisation antibody titre against VA70 (G4P[8]) and DS1 (G2P[4]) strains has been observed. Nevertheless, vaccine efficacy against RV GE caused by G4P[8] has been demonstrated in Rota-036 (88.3 % against any RV GE and 100 % against severe RV GE). Similarly, an efficacy against severe RV GE caused by G4P[8] of 61.8 % has been shown during the combined efficacy period of Rota-023. These data indicate an absence of correlation between the presence of neutralising antibodies, as detected by the MAH's assay, and protection. Similar picture is observed against G2P[4] for which no neutralising antibodies are observed although statistical pooled analysis showed a significant vaccine efficacy.

The CHMP agreed with the MAH that the SPC should mention the data for subjects who were available at both the first and second timepoint for the following reasons:

1. Efficacy during the 1st year was the primary efficacy objective of study 023. Efficacy during the 2nd year was a secondary objective to be assessed on a subcohort only. Consequently the SPC should present data derived from the primary efficacy analysis rather than the subcohort that was followed over 2 years.
2. Using the same cohort is much less relevant for the evaluation of efficacy persistence than for the evaluation of immunogenicity persistence. Indeed, different external variables such as the variability of circulating strains during successive years plays an important role in the evaluation of efficacy. Furthermore, subjects infected during the 1st year will likely not be infected during the second year but are more likely to drop from the 2nd year follow up period. Using the cohort of subjects enrolled in a second year efficacy to present year 1 efficacy may therefore lead to a biased underestimation of year 1 vaccine efficacy (VE). Although the study has no power to test year 1 VE between subjects included and excluded from the year 2 cohort, a post-hoc analysis shows an efficacy of 100% in subjects excluded from the year 2 cohort, suggesting a potential bias.
3. Using the cohort of subjects enrolled in a second year efficacy to present year 1 efficacy is leading to loss in accuracy (i.e. larger 95% CI due to discarding data from approximately 4000 subjects). This is well illustrated by the 95%CI LL of 7.8% for the year 1 VE against G9P[8] when taking into account the year 2 efficacy subset compared with 61.7 % when taking into account the full year 1 cohort (for a point estimate quite similar).

The CHMP agreed on the related changes as shown in section V below.

Regarding immunogenicity, the CHMP pointed out that the new data from study Rota-036 support the previously submitted data and agreed that the differences in seroconversion rates between the countries could be due to differences in the schedules used. However, the elevated GMC observed in Finland compared to the other countries could potentially be due to additional factors, especially as Italy uses the same schedule. The MAH was therefore asked to comment. Additionally, the CHMP proposed that the time-points for determination of the seroconversion rates are indicated: The MAH presented the percentage of subjects with serum anti-rotavirus IgA antibody titres 20U/ml (by ELISA) after the second dose of vaccine or placebo as observed in different studies one to two months after Dose 2 of the Rotarix or placebo. The CHMP agreed on the wording proposed by the MAH as discussed in section V and as presented in Attachment 7 below.

Molecular mechanisms responsible for cross-protection

The MAH provided an overview of the molecular mechanisms that may be responsible for inducing cross-protection against G1P[8] and G2P[4], indicating that one genotype can provide protection against a heterotypic serotype. However, in the view of the CHMP empirical evidence remains the main criterion for demonstrating such a protection.

The following observations support protection against a heterotypic serotype (cross-protection):

- The Rotavirus outer capsid contains two proteins: VP7 forms the capsid surface and is responsible of the G type, whereas VP4 spikes at the capsid surface define the P-type. Heterotypic protection may be explained by the biological basis of significant overlap in epitopes between the various serotypes.

- Antibodies are known to be directed against viral proteins, including VP4, VP7 and VP6 (which is common to all group A rotaviruses) that carry serotype-cross-reactive epitopes. Antibodies have also been reported to be directed against other structural and non structural proteins: VP1, VP2, NSP4 (viral enterotoxin) and other NSP proteins *(Ray P et al.).* Cell mediated immunity has been demonstrated against VP7, VP4, VP6 and against other VPs or NSPs.(*Franco MA et al. 1997, McNeal MM, et al. 1997, Offit P. et. al., 1993; Riepenhoff-Talty M et al. 1983, Totterdell BM. et al. 1988, and Franco MA 1995)*. Amino acids analysis between RIX4414 G1P[8] and G2P[4] (DS-1) shows more than 83% identity for at least 3 proteins likely important for immune protection (90% for VP4, 92% for VP6 and 83% for NSP4).
- In addition to these potential targets for cross-immune responses, Rotarix clinical data demonstrated that the vaccine provides a good protection against all strains of P[8] genotypes encountered in clinical trials, suggesting that, at least, part of the protection could be associated to VP4 protein.
- This was further substantiated by literature data showing that immune response to VP4 could be as high as against VP6 and higher than against VP7 and that responses to VP4 (natural infection or vaccination) are both homotypic and heterotypic (*Gorrell RJ et al.1999 and Yuan L et al. 2004)*

Therefore, the antigenic relationship between VP4 of P[4] and P[8] genotypes with a 90% identity might explain the protection against G2P[4] strains observed in clinical trials. This antigenic relationship is not surprising as P[4] and P[8] VP4 were previously sharing the same serotype P1. These 2 serotypes were only discriminated in sub-types P1A and P1B based on more discriminative monoclonal antibodies. A close antigenic relationship and a high level of cross-reactivity (associated to peptides A and C of VP8 subunit) have also been described *(Larralde G et al. 1992).*

The CHMP concluded that the molecular characteristics of the rotavirus provide evidence that antigens are shared between the G1P[8] vaccine strain and G2P[4]. The high level of identity between the VP4 of the Rotarix strain RIX4414 and the VP4 protein of G2 strains likely explains the clinical protection observed with Rotarix against G2P[4] strains.

The CHMP supported the arguments that the vaccine induces cross-protection against P[8]-strains with different G-types and thus indicates that VP4 are of importance in cross-protection against strains of the same P-type but different G-type. However, even though the VP4 of P[8] and P[4] show antigenic similarity, it cannot be concluded that this explains the trend towards protection against G2P[4] strains observed in clinical trials. It is of note, that during the assessment of the initial Marketing Authorisation application it was demonstrated that the vaccine did not induce a neutralising antibody response to the DS1 (G2P[4]) RV strain, whereas neutralising antibodies were induced to a varying degree to the other examined strains containing P[8]. The applicant stated at this time that their NT assay had been developed as a characterisation tool and that assay performance has to be optimised and that comparison with clinical data suggests a lack of ass sensitivity.

The MAH was further asked by the CHMP to address this issue in relation to the claims for G2P[4] and was requested to provide any available data on the optimisation of the NT assay.

In conclusion, although induction of neutralising antibody against G2P[4] and G4P[8] has not been shown by the limited testing performed by GSK, the CHMP agreed with the MAH that the vaccine efficacy observed in clinical trials supports a claim of protection against both G2P[4] and G4P[8].

As a further point for discussion, the MAH argued that 83 % identity in the amino acid sequences between RIX4414 and G2P[4] (DS-1) would represent a strong argument for protection of the vaccine against G2P[4]. The CHMP considered that it is known that even a 2-3% difference in amino acid sequence homology can separate the viruses into different serotypes, indicating that 83 % identity may not be a strong argument to support cross-protection. The MAH was also requested by the CHMP to address this issue.

The CHMP agreed with the MAH that the mechanism of heterotypic protection against RV strains is not yet elucidated and different hypotheses, involving different RV proteins implicated in humoral or cell mediated immunity, have been made. But the stronger argument to explain crossprotection given by Rotarix is based on the VP4 protein, in addition to the immunodominant VP6 protein which is common amongst Rotaviruses strains of group A. A piglet model confirmed the importance of VP4 protein for protection. Immunising and challenges by RV strains only needs to share VP4 antigen to reach protection. With regards to homology of amino-acid sequences, VP4 of P[8] genotypes share 91 to 100% identity with the RIX4414 strain, just followed by the P[4] genotype with between 85% and 90% of identity. Beyond one hypervariable region, which allows to discriminate between the two types, most of the epitopes or potential epitopes are well conserved. Indeed, the P[8] and P[4] genotypes were previously classified based on antibodies recognition under the same serotype P1 (subtype P1A and P1B), showing the strong antigenic relationship between VP4 of P[8] and P[4] genotypes. A high level of cross-reactivity associated to peptides A and C of VP8 subunit has been described *(Larralde G et al. 1992).* Rotarix clinical data strongly support the importance of VP4 protein in heterotypic protection as demonstrated by results of study Rota-036 where protection against severe RV GE caused by G1P[8], G3P[8], G4P[8], or G9P[8] ranged from 94.7% to 100%.

The CHMP concluded that the high level of identity between the VP4 protein of the Rotarix strain RIX4414 and the VP4 protein of G2 strains may explain at least part of the clinical protection observed with Rotarix against G2P[4] strains.

The CHMP agreed that there were valid arguments (homology of amino acid sequence among P8 genotype, the RIX4414 vaccine strain and the P4 genotype ; antibody recognition under the same serotype P1) that indicate an antigenic relationship between the P4 and P8 genotypes. As this may explain, at least in part, the clinical protection observed in meta-analysis, the CHMP considered this issue as resolved.

In his response, the MAH has provided data from all subjects experienced a second RV infection from all studies in order to substantiate arguments with regard to cross-protection between P8 and P4 strains, whereas only one placebo subject (study 004) experienced a first infection by G2P4 followed by a G1wtP8.

The CHMP shared the view that the presented data are sufficient and that additional data on homology would not solve the question. The only data that could help in this respect are data from additional trials and post-marketing surveillance on the occurrence of the strains in the vaccinated population.
In this respect the CHMP has been informed by WHO that a blinded trial in Africa is currently ongoing, with already more than 120 children with a G2P[4] diarrhoea. It was considered that these data will show to what degree there is cross protection in the clinical setting.

Concerning neutralising antibody response to the DS-1 (G2P[4]) RV strain the MAH argued that there is no correlation between VE and the level of neutralising antibodies, and that VE must be shown from clinical protection studies. However, the CHMP considered that not all clinical cases indicate cross-protection between G2P4 and G1P8.

The MAH's response concerning identity in the amino acid sequences, where VP4 of various P8 strains is said to share 91-100% homology with the RIX4414 strain, followed by the P4 genotype with 85- 90% homology, raised the question whether the homology of the reference virus strains used in the neutralisation assay has been compared with the sequences of VP4 of the vaccine strain. The MAH has in his response documented that the homology between peptides A, B and C of RIX4414 and DS-1 (g2P4) is 86,1% and the homology between the complete VP4 protein is 91%. The CHMP considered, that it would not be necessary to further discuss the difference in homology concerning the low cross-reactive IgA GMC to the DS-1 strain in the neutralisation assay due to the reasons outlined above.

Clinical safety

The safety data submitted describe the final reactogenicity or safety analyses coming from the two clinical trials Rota –023 and Rota-036:

Demographic characteristics
The analysis of demographic characteristics of the safety cohorts for study Rota-023 (Year 2 subset) and Rota-036 showed that the majority of the vaccinated subjects where white in study Rota-036 and hispanic in study Rota-023. Within each study, the demographic characteristics of the study groups were comparable. Reactogenicity was assessed in a subset of 914 subjects in study Rota-036.

Study	Region	Age at 1st dose (weeks)	Schedule (months)	Number of subjects receiving Rotarix	Number of Rotarix doses ($10^{6.5}$CCID50/dose)
Rota-023	Latin America	6-12*	2-4	15129	29749
Rota-036	Europe	6-14	2, 3 (France, Germany) 2, 4 (Spain) 3, 4 (Czech Republic) 3, 5 (Finland and Italy)	2646 (914) ‡	5267 (1819) ‡

*6-13 weeks in Chile
‡. 5267 Rotarix doses evaluated for safety and unsolicited adverse events in 2646 subjects of the total vaccinated cohort. 1819 Rotarix doses evaluated for reactogenicity (solicited symptoms) in a subset of 914 subjects

Table 11: Overall number of Rotarix doses administered in studies Rota-023 and Rota-036 evaluated for reactogenicity/safety

Adverse Events in study Rota-036

Common Adverse Events
Specific childhood vaccines were given concomitantly with Rotarix or placebo. The general solicited symptoms reported by subjects included in the reactogenicity subset of the total vaccinated cohort in study Rota-036 were presented by the MAH. Unsolicited symptoms classified as general disorders and administration site conditions, Infections and Infestations and Gastrointestinal disorders were the most frequently reported symptoms.
Overall, irritability was the most frequently reported solicited general symptom in both groups after each dose, which was also known from previous observations. The incidence of grade 3 solicited symptoms was similarly low in both groups.

There was no increase in incidence of solicited symptoms with subsequent doses. A higher incidence of fever was observed on the day and the day after each dose in both groups, and the incidence of fever was similar between Rotarix and placebo recipients (23.1% versus 23.4%, respectively). Since the fever incidences were similar between the Rotarix and placebo group, it can be assumed that co-administered childhood vaccinations have likely contributed to post-vaccination fever. The majority of fever reports were rated as grade 1 or 2 and reports of grade 3 fever were rare (2 subjects in the Rotarix group and 4 subjects in the placebo group after dose 2). No statistically significant differences between groups in the percentage of subjects reporting each solicited symptom during the solicited 8 days post vaccination follow-up period were found.

The CHMP considered that the data from study Rota-036 did not reveal any statistical significant difference between the Rotarix group and the placebo group with regards to reporting solicited symptoms during the 8-day follow-up period and are in agreement with data from previous studies. Irritability, which was most frequently reported in both groups, is mentioned in section 4.8 of the current SPC. The CHMP noted that the incidence of grade 3 solicited symptoms were low in both groups.

Symptoms reported more frequently in subjects receiving Rotarix as compared to placebo were flatulence (3.8% versus 2.4%, p value =0.027), irritability (21.0% versus 17.0%, p value = 0.003) and irritability considered related to vaccination (14.1% versus 10.9%, p value = 0.005).

Symptoms reported less frequently in subjects receiving Rotarix as compared to placebo were diarrhoea (0.0% versus 0.1%, p value =0.047), stridor (0.0% versus 0.1%, p value = 0.047), grade 3 bronchiolitis (0.2% versus 0.6%, p value = 0.16), grade 3 otitis externa (0.0% versus 0.1%, p value = 0.047) and grade 3 rhinorrhoea (0.0% versus 0.4%, p value= 0.001
The CHMP considered that a previously observed very weak signal of SAEs due to bronchiolitis and pneumonia post vaccination with the Rotarix is therefore not supported by the observations in study Rota-036.

Serious adverse events (SAEs) and deaths in study Rota-036
No fatal events were reported. The incidence of SAEs in study Rota-036, by vaccine group, was presented by the MAH. Among the 3994 subjects followed for the first efficacy follow-up period, a total of 240 subjects (145 subjects or 5.5% in the Rotarix group versus 95 subjects or 7.0% in the placebo group) reported at least one SAE (p value = 0.049).

SAEs reported by two subjects were assessed as related to vaccination, including one case of intussusception (Case ID B0349505A) for which the treatment code was broken at the investigator's request. SAEs in an additional four subjects were ongoing at the end of the first efficacy follow-up period: pyelonephritis, hypotonia, and bronchial spasm. None of these SAEs were assessed as related to vaccination.

	Rotarix					Placebo					Risk Difference (Rotarix minus Placebo)			P
				95% CI					95% CI			95% CI		
	N	n	%	LL	UL	N	n	%	LL	UL	%	LL	UL	
At least one SAE	2646	145	5.5	4.6	6.4	1348	95	7.0	5.7	8.5	-1.57	-3.26	-0.01	0.049
At least one IS	2646	1	0.0	0.0	0.2	1348	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.457

N=number of subjects having received at least one dose of Rotarix/placebo
n/%= number/percentage of subjects reporting at least one SAE/IS between the day of administration of dose 1 of Rotarix/Placebo up to Visit 5 or last contact if Visit 5 not performed
95% CI = exact 95% confidence interval, LL = lower limit, UL = upper limit
95% CI* = asymptotic standardised 95% confidence interval; L.L. = lower limit, U.L. = upper limit
P-value = results of comparison of percentage of subjects reporting the specified unsolicited adverse event within 31 days after any doses between groups by two-sided asymptotic score test for the null hypothesis of identical incidence in both groups (P-value less than 0.05 will be used as an aid to highlight potential difference worth further attention. However care must be taken when interpreting putative statistically significant findings since there is no multiplicity adjustment and clinical significance must be taken into account).

Table 12: Study Rota-036. Percentage of subjects with SAEs/Intussusceptions occurring from dose 1 of Rotarix/Placebo up to visit 5 (Total vaccinated cohort)

Other significant adverse events

A total of 50 subjects (1.25%) dropped out from the study during the first efficacy follow-up, 50% of them for reasons other than adverse events (e.g. protocol violations etc..).

The analysis of adverse events by organ system or syndrome did not show a difference between the vaccine and placebo group. A potential imbalance between vaccine and placebo was noted for following adverse events:

- flatulence, irritability (more frequently in vaccine group)
- diarrhoea, stridor, grade 3 bronchiolitis, grade 3 otitis externa and grade 3 rhinorrhoea (more frequent in placebo recipients)

The CHMP considered that the weak signal of SAE due to bronchitis, bronchiolitis, pneumonia and bronchopneumonia associated with the vaccine in study Rota-023 in the initial dossier was not generated in study Rota-036.

Serious Adverse events in study Rota-023

During the second year follow-up period of (from visit 4 up to visit 6), 678.4 per 10,000 subjects in the Rotarix group and 787.4 per 10,000 subjects in the placebo group reported at least one SAE (P- = 0.010) All SAEs occurring after visit 4 up to visit 6 were assessed as not related to vaccination by the respective investigators. A potential imbalance in favour of the Rotarix was noted for infections and infestations, gastro-enteritis, dengue fever and lymphadenopathy, which were mostly considered as chance findings, while gastro-enteritis reflects the efficacy of the Rotarix in preventing GE related symptoms that was shown by the efficacy analysis. There was no imbalance in favour of the placebo group. SAEs in six subjects were ongoing at visit 6 or last contact, all assessed as unrelated to vaccination (Study report for further details).
A total of 568 subjects (3.74%) dropped out during the second follow-up period, mainly because of migration from the study area.

There were 11 fatal cases during the second follow-up, none were related to vaccination (5 deaths in the Rotarix group and 6 deaths in the Placebo group, reported after Visit 4 up to Visit 6).

The CHMP noted that of the 250 (145 in the Rotarix group and 95 in the placebo group, 5.5% and 7.0 %, respectively) reported SAEs during the first follow-up period of study Rota-036, only two, including a case of intussusception in the Rotarix group, were assessed as being possibly related to the investigational product. Thus the CHMP concluded that safety data from European countries support a mild safety profile for the Rotarix when co-administered with common childhood vaccines. None of the SAEs reported from Visit 4 to Visit 6 or the six SAEs ongoing at Visit 6 or at last contact, as well as the 11 deaths, reported during the 2nd follow-up period of study Rota-023, were assessed as related to vaccination. The data from the 2nd follow-up period of Rota 023 regarding SAEs do not indicate a statistical significant imbalance between the Rotarix and the placebo group in disfavour of the vaccine group.

Discussion and conclusion on clinical safety

Overall, the incidences of all solicited general symptoms and the incidences of all unsolicited adverse events were similar between the Rotarix groups and the placebo. The new data derived from study 036 and 023 further confirm the mild reactogenicity profile of Rotarix.
The CHMP also considered that no amendment to the Risk Management Plan was considered neccessary as the proposed change is an extension to the currently approved indications and not a significant new indication.
There was also no evidence for a difference between groups in disfavour of the Rotarix with respect to SAEs reported. Only few fatal cases were reported and all were considered not vaccine related. Reports of non-fatal SAEs considered vaccine related were rare and balanced between groups. Only on rare occasions subjects dropped out of the study due to an adverse event considered by the investigator as related to vaccination. Based on the above it can be concluded that the new reactogenicity and safety data generated in studies Rota-036 and Rota-023 are in agreement with previous findings and further confirm the safe profile of Rotarix. The symptoms reported more frequently in the Rotarix group (irritability and flatulence) are already mentioned in Section 4.8 of the current SPC. Since no trends or signals were observed with respect to new reactogenicity or safety data, the CHMP considered that there is no need for an update in the SPC relating to reactogenicity or safety information.

Overall discussion and benefit/risk assessment

The pooled analysis of the data from the five studies Rota-004, -006, -007, - 023 and -036 indicate protection against G2-P[4] strains. However, the CHMP noted some deviations between the numbers of G2-cases included in the present pooled efficacy calculation and the number of cases caused by G2-

strains observed in the individual studies, which were clarified by the MAH. Furthermore the MAH presented a reassuring re-calculation of the efficacy against G2P[4] based on adequately justified cases support protective efficacy. The CHMP considered that the data was sufficient to support the extension of indication.

The new data from study Rota-036 indicate that Rotarix induces protection against G4P[8] strains. Consequently, the indication can be extended to comprise G4P[8] strains and Sections 4.1, 4.4 and 5.1 were updated accordingly.

The immunogenicity, efficacy and safety data from study Rota-036 were in line with previous observations. The co-administration of Rotarix and common childhood vaccines according to the various schedules used in Europe did not indicate any interactions with regard to efficacy, immunogenicity or safety. Immunogenicity data resulting from European study 036 demonstrate that specific childhood vaccines (including hexavalent vaccine, meningococcal serogroup C vaccine and pneumococcal vaccine) can be co-administered with Rotarix according to the local immunisation schedule without interference between products. The SPC wording on co-administration with hexavalent vaccine and with pneumococcal vaccine therefore remains valid. The MAH proposed a revision of Section 4.5 of the SPC, in order to introduce co-administration with meningococcal serogroup C vaccine, which was agreed by the CHMP.

The analysis of immunogenicity and efficacy data from breast-fed and non-breast-fed subjects was also reflected in Section 4.6 of the SPC.

Efficacy data from the 2nd follow-up period of study Rota-023 indicate that the protection is maintained in the second year of life against G1P[8], G3P[8], and G9P[8] strains. However, the negative lower confidence limit of the efficacy against G3P[8] strains during the 2nd follow-up period may indicate a weak signal towards fading protective efficacy against this strain. On the other hand, the efficacy over the combined follow-up periods had a positive lower confidence limit. Furthermore, the safety data indicate that there were no imbalance in favour of the placebo group for SAEs and there were no increased risk of definite IS diagnosed from Visit 1 up to Visit 6.

A trend towards protection against severe RVGE due to G2P[4] type was previously observed during the first year in study Rota-023. The same trend towards protection against severe RV GE due to G2P[4] type was confirmed during the first year follow-up in study Rota-036 (point estimate of 74.7%). A new pooled analysis to further substantiate efficacy against RVGE due to G2P[4], including severe (Vesikari score ≥11) G2P[4] cases observed in studies 004, 006, 023 and 036, results in an efficacy point estimate of 71.4 % (95% CI; 20.1%, 91.1%) when calculated on the ATP efficacy cohort.

There was a positive trend of vaccine efficacy against G2P[4] in all 4 efficacy studies conducted by the MAH, and a pooled analysis with a lower limit of the 95% CI well above zero (71.4%; 95%CI: 20.1; 91.1). This can be considered as a valid approach “to evaluate an additional efficacy outcome that requires more power than the individual trials can provide” (CHMP/EWP/2330/99). Furthermore, scientific data supports heterotypic protection. Therefore, the CHMP considered that efficacy against severe RVGE caused by rotavirus serotype G2P[4] is supported by clinical data, which is reflected in Section 4.1 ”Therapeutic indications” as well as in Section 5.1 “Pharmacodynamic properties” of the SPC.

In general efficacy and safety data from the two studies Rota-023 and Rota-036 were consistent with previous observations.

Changes to the product Information

As Variation II-005 has been adopted in parallel to this procedure, these changes were also included in the Annexes to the Opinion of this procedure.

The detailed changes can be found in the present/ proposed Appendix and final approved highlighted SPC/ Labelling/ PL 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:

SPC:

SECTION 4.1 THERAPEUTIC INDICATIONS
The CHMP agreed in general with the revised wording of section 4.1 as all remaining concerns regarding the pooled / meta-analysis were solved, but as the efficacy calculation concerning G2P[4] has been based on severe RV GE the CHMP initially discussed if this should be mentined in this section of the SPC. However, due to the fact that the MAH presented also a meta-analysis on any cases of RV GE in his response, as discussed above, the CHMP considered that it would be sufficient to reflect issues concerning the meta-analysis in section 5.1

SECTION 4.3 CONTRAINDICATIONS
The MAH proposed to specify the contraindication of gastrointestinal congenital malformations by adding, that it would apply for uncorrected malformations and proposed to give an example (Meckel's diverticulum). The CHMP considered that it would not be useful to include this specific example and recommended to keep the wording more general by deleting the example.

Section 4.4 Special warnings and precautions for use
The CHMP considered that the recalculation of the efficacy against G2P[4] strains based on acceptably justified cases and/or G2P[4] strains only, supports protection and the proposed text could be regarded as acceptable. However, the CHMP discussed that the efficacy calculation has only been based on severe RV GE, which should be reflected in the SPC:.

It was agreed that it would not be justified to restrict efficacy against G2P[4] strains to severe GE and that the vaccine's efficacy against GE due to G2P[4] strains was demonstrated on pooled data is clearly mentioned in section 5.1. The CHMP agreed therefore that the section 4.4 is not the place to give details about clinical data.

Concerning protection against other serotypes, the CHMP agreed with the MAH to change the wording by including a statement saying that the extent of protection that Rotarix might provide against other serotypes is unknown.

Section 4.5 Interaction with other medicinal products and other forms of interaction
The CHMP considered that it should be specified that the immune response to conjugated pneumococcal and meningococcal serogroup C vaccines is not affected by concomitant Rotarix vaccination.

Section 4.8 Undesirable effects
The CHMP discussed if the data related to intussusception (IS) in study Rota-036 should be included in this section (1/2646 in the vaccine group versus 0/1348 in the placebo group (Total vaccinated cohort). The CHMP considered that the sample size of the study Rota-036 (with an unbalanced randomisation ratio of 2:1) and the number of IS cases reported (only 1 case) are too small to draw any conclusion on the relative risk of IS. Furthermore, study Rota-023, which was designed and powered to evaluate the risk of IS, allowed to conclude that there was no evidence of increased risk. In conclusion, the CHMP considered that the IS data from study Rota-036 should not be mentioned in the SPC.

Section 5.1 Pharmacodynamic properties

Protective efficacy
The MAH proposed to include a table on type specific vaccine efficacy against severe rotavirus gastro-enteritis observed in study Rota-036.
The CHMP agreed with the MAH that the efficacy results for the first year from year 1 ATP cohort should be presented in the SPC. To avoid any confusion, the sample size has been added to each cohort and the type of cohort (ATP) as well as the statistical significance of the results has been added in a footnote.

The CHMP considered that the wording initially proposed by the MAH concerning possible efficacy as from the first dose observed in study Rota-036 should be deleted, as it suggests that a single dose would be sufficient since it provides a protection of 89%, which is strictly comparable with the protection conferred by two doses.

Considering that the confidence interval of the 89.8% vaccine efficacy after a single dose is very wide (8.9%; 99.8%) the CHMP did not believe that this information would be relevant for the prescriber.
Furthermore, the CHMP highlighted that all vaccines may provide some degree of protection already after the first dose, but this fact should not be reflected in the PI
The CHMP therefore concluded that this paragraph should be deleted.

Furthermore, as agreed between CHMP and MAH it was added that the severity of gastro-enteritis was defined in Study Rota-023 according to WHO criteria.

The CHMP further considered that a sentence related to the persistence of protection in the 2nd year would however not be acceptable, as a waning efficacy against gastro-enteritis due to G1P8 and the P8 genotype was observed during the second year in study Rota-023. The CHMP however agreed to include the results of year 1 and year 2 overall efficacy in the second table of section 5.1.

The CHMP also considered that the table on severe GE should also mention the number of subjects who were available at both the first and second year time point and also include the results of G4P[8] from Study Rota-023, which were not presented in the initially proposed SPC.
However, as the vaccine efficacy against severe GE due to serotype G4P[8] during the first year follow-up of Rota-023 was only based on three subjects (1 case in the Rotarix and 2 cases in the placebo group) and as emphasised by the large 95 %CI (-844; 99.2), the CHMP considered that no conclusion can be drawn from this estimation. In addition, the CHMP agreed that this point estimate would not be in line with efficacy data against the same RV type in the European study. Therefore the CHMP agreed to add this information in the table summarising the efficacy results of study Rota-023 in section 5.1 of the SPC.
As a consequence, the MAH proposed to include a statement saying that the numbers of cases, on which the estimates of efficacy against G4P[8] were based, were very small.

As a further change, the MAH revised a sentence concerning the results of the updated pooled meta-analysis**.** The CHMP considered that the analysis of pooled data was done on five studies, not on four as mistakenly written. In the fifth study Rota-007 (Singapore) no point estimation of the vaccine's efficacy was obtained, as there were no severe cases of RV GE. The CHMP agreed to include therefore a statement reflecting this fact.

Immune response
The sentence indicating the time-points for determination of seroconversion has been slightly reworded to avoid redundancy.

The table has also been modified to present the pooled immunogenicity data by vaccination and includes the 95% confidence intervals.

Section 6.3 Shelf life
The text in this section with regards to the handling of the reconstituted vaccine was slightly revised.

CONCLUSION

On 18 October 2006 the CHMP considered this Type II variation to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics, Labelling and Package Leaflet, subject to the additional commitment undertaken (see Letter of Undertaking, Attachment 8).

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