12 March 2015
EMA/170998/2015
Committee for Medicinal Products for Human Use (CHMP)

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

Rotarix

rotavirus vaccine, live

Procedure No: EMEA/H/C/000639

P45 046

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

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I. INTRODUCTION

This AR concerns 4 studies (+ 1 study Annex) which were submitted by the MAH to comply with Article 45 of the regulation 1901/2006.

Apart from the 4 study reports and accompanying study Annex, there were investigator approvals and very brief expert statements provided. Neither clinical overview, nor clinical summaries were present in the dossier.

The MAH's experts stated that the submitted paediatric studies do not influence the benefit risk for Rotarix and that subsequently there are neither consequential regulatory actions nor changes to the product information necessary.

II. STUDY SUMMARIES

Study 103478

➢ **General**

A phase IIIb, double-blind, randomized, placebo-controlled, multicentre study to assess the immunogenicity, safety and reactogenicity of 2 doses of GlaxoSmithKline (GSK) Biologicals. oral live attenuated human rotavirus (HRV) vaccine in healthy infants (6-12 weeks of age at first dose) previously uninfected with human rotavirus.

- **Objective(s)**

Primary:

- To show a difference of at least 20% in seroconversion rate at Visit 3 (two months post-dose 2) between HRV and placebo groups.

  Criteria: the primary objective was reached if the lower limit of the two-sided asymptotic standardized 95% CI for treatment difference (HRV minus placebo) was ≥ 20%.

Secondary:

- To assess the reactogenicity and safety of each dose of the HRV vaccine versus placebo.
- To assess the immunogenicity of the HRV vaccine in terms of serum anti-RV IgA antibody concentrations at Visit 3 (at two months post-dose 2).
- To assess the presence of rotavirus (RV) in gastroenteritis (GE) stools collected until Visit 3.

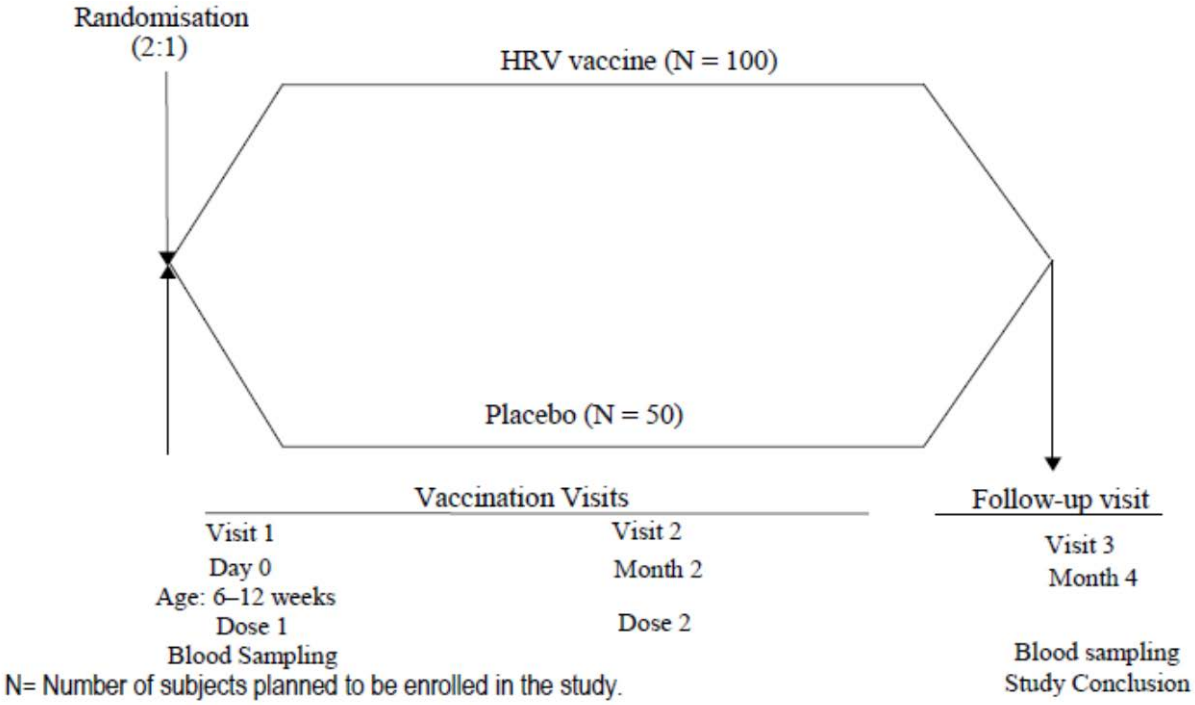
- **Study design**

The study was designed as a randomized (2:1), double-blind, placebo-controlled, self-contained study with two parallel groups that received the following vaccines:

- Two oral doses of HRV (HRV vaccine group)
- Two oral doses of Placebo (Placebo group)

All subjects received routine childhood vaccinations according to local immunization recommendation (2, 4, 6 months schedule). All routine vaccinations were to be given at least 14 days prior to administration of HRV vaccine or placebo dose and Hib vaccine was to be administered at the time of HRV or placebo dose. Blood samples were drawn from all subjects prior to the first vaccine dose (Visit 1) and two months after the second vaccine dose (Visit 3).

The study duration was approximately 4 months for each subject.



- **Study population / Sample size**

Inclusion criteria:

Healthy infants aged between 6 and 12 weeks (42-90 days) of age at the time of the first vaccination whom were free of obvious health problems and for whom the vaccination history was available. Written informed consent was obtained from the parent or guardian of the subject.

- **Endpoints**

Primary endpoint

- Percentage of subjects who seroconverted at Visit 3 (percentage of subjects with concentration ≥ 20 U/ ml in subjects who were seronegative before vaccination).

Secondary endpoints

- Occurrence of any grade 2 or grade 3 fever, vomiting or diarrhoea within the 15-day (Day 0 - Day 14) solicited follow-up period after each study vaccine dose.
- For each type of solicited symptoms, occurrence of the symptom within the 15-day (Day 0 - Day 14) solicited follow-up period after each study vaccine dose.
- Occurrence of unsolicited adverse events within 43 days (Day 0- Day 42) after each study vaccine dose according to MedDRA classification.
- Occurrence of serious adverse events throughout the study period.
- Serum anti-RV IgA antibody concentration expressed as Geometric Mean concentration (GMC) at Visit 3.
- Presence of RV in GE stools collected from Dose 1 of HRV vaccine/ placebo up to Visit 3.

- **Statistical Methods**

Analysis of Demography

Demographic characteristics on age at Dose 1 and Dose 2 of HRV vaccine/ placebo, height and weight at Visit 1, gender and race distribution were tabulated by group.

Analysis of Immunogenicity

Immunogenicity analysis was performed on the ATP cohort for immunogenicity (primary analysis) and on the total vaccinated cohort. At each time point that serum anti-rotavirus IgA antibody response was measured, seropositivity/ seroconversion rates and their exact 95% confidence interval (CI) were calculated for each group. Geometric mean concentrations (GMCs) and their 95% CI were calculated for each group. GMCs and their 95% CI were also calculated on the subjects who were seropositive for anti-rotavirus IgA antibody.

The two-sided asymptotic standardized 95% CI for difference in the percentage of subjects who seroconverted for anti-rotavirus IgA at Visit 3 between HRV and placebo groups was computed. The primary objective was reached if the lower limit of the two-sided asymptotic standardized 95% CI for treatment difference (HRV minus placebo) in the percentage of subjects who seroconverted for antirotavirus IgA antibody at Visit 3 was above the pre-defined clinical limit of 20%.

Analysis of Reactogenicity and Safety

The safety analysis was performed on the total vaccinated cohort (primary analysis) and on the ATP cohort. The percentage of doses and of subjects with any symptom (solicited or unsolicited) reported during the 15-day (Day 0 to Day 14) follow-up period and with each solicited symptoms reported during the 15-day solicited follow-up period was tabulated by group with their exact 95% CIs. The percentage of doses and of subjects with unsolicited AEs classified by Medical Dictionary for Regulatory Activities (MedDRA) system reported during the 43-day (Day 0 to Day 42) follow-up period after any HRV vaccine or placebo dose were tabulated by group with their exact 95% CIs.

The same calculations were done for symptoms rated as grade "3" in intensity and for those assessed as causally related to vaccination. The percentage of doses and of subjects reporting diarrhoea, fever or vomiting graded 2 or 3 in intensity was calculated by group, with exact 95% CIs, over the solicited follow-up period (Day 0 to Day 14). SAEs and withdrawals due to non-serious AEs/ SAEs were described. The percentage of subjects with GE and RV (vaccine strain or wild-type RV) GE from Dose 1 of HRV vaccine or placebo to Visit 3 was tabulated by group with their exact 95% CIs.

- **Results**

Demography

The demographic profile of the two groups at Dose 1 was similar with respect to mean age, height, weight, gender and racial distribution. The mean age of the subjects in the ATP cohort for immunogenicity was 10.3 weeks (range: 7 to12 weeks) at the time of the first vaccination and 19.1 weeks (range: 16 to 21 weeks) at the time of the second vaccination. All subjects were Korean.

Number of subjects:	Total	HRV vaccine group	Placebo group
Planned	150	100	50
Enrolled	161		
Total vaccinated cohort	155	103	52
Completed	151	99	52
According-to-protocol (ATP) cohort for safety	97	67	30
ATP cohort for immunogenicity	72	48	24

Immunogenicity

ATP cohort for immunogenicity:

The anti-rotavirus IgA antibody seroconversion rate was 66.7% [95% CI: 51.6%; 79.6%] in the HRV vaccine group and 4.2% [95% CI: 0.1%; 21.1%] in the placebo group at two months after Dose 2.

The lower limit of the two sided asymptotic standardized 95% CI for the difference in the percentage of subjects who seroconverted for anti-rotavirus IgA antibody at two months after Dose 2 between the HRV vaccine group and (minus) the placebo group was 42.81% which is above the pre-defined clinical limit of 20%. Thus, from the above data, it was concluded that the primary objective was met.

Synopsis Table 1: Anti-rotavirus IgA antibody GMC and seroconversion rates. (ATP cohort for immunogenicity)

			≥ 20 U/ ml				GMC U/ ml		
Group	**Timing**	**N**	**n**	**%**	**95 % CI (LL, UL)**		**value**	**95 % CI (LL, UL)**	
HRV	PRE	48	0	0.0	0.0	7.4	<20	-	-
	PII(M4)	48	32	66.7	51.6	79.6	73.2	44.5	120.3
Placebo	PRE	24	0	0.0	0.0	14.2	<20	-	-
	PII(M4)	24	1	4.2	0.1	21.1	<20	-	-

GMC = geometric mean antibody concentration calculated on all subjects
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
PRE = Pre-vaccination blood sample; PII(M4) = two months after the second dose (visit 3)

Synopsis Table 2: Difference between groups in percentage of subjects who seroconverted at Visit 3 for serum anti-rotavirus IgA antibody (ATP cohort for immunogenicity)

						Difference in seroconversion rate			
Group	**N**	**%**	**Group**	**N**	**%**	**Difference**	**%**	**95 % CI (LL, UL)**	
HRV	48	66.7	Placebo	24	4.2	HRV - Placebo	62.50	42.81	75.52

N = number of subjects with available results; % = percentage of subjects who seroconverted at visit 3; 95%CI = asymptotic standardised 95% confidence interval; LL = lower limit; UL = upper limit

TV cohort:

The anti-rotavirus IgA antibody seroconversion rate was 65.3% [95% CI: 53.1%, 76.1%] in the HRV vaccine group and 5.4% [95% CI: 0.7%, 18.2%] in the placebo group.

The lower limit of the two sided asymptotic standardised 95% CI for the difference between groups in percentage of subjects who seroconverted for anti-rotavirus IgA antibody at Visit 3 was 44.17%. This result was consistent with the result obtained with the ATP cohort for immunogenicity.

Synopsis Table 3: Anti-rotavirus IgA antibody GMC and seroconversion rates for subjects seronegative for anti-rotavirus IgA antibody at pre vaccination (Total vaccinated cohort)

			≥ 20 U/ ml				GMC		
					95% CI			95% CI	
Group	**Timing**	**N**	**n**	**%**	**LL**	**UL**	**value**	**LL**	**UL**
HRV	PRE	79	0	0.0	0.0	4.6	<20	-	-
	PII(M4)	72	47	65.3	53.1	76.1	82.4	53.4	127.0
Placebo	PRE	40	0	0.0	0.0	8.8	<20	-	-
	PII(M4)	37	2	5.4	0.7	18.2	<20	-	-

GMC = geometric mean antibody concentration calculated on all subjects
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
PRE = Pre-vaccination blood sample; PII(M4) = two months after the second dose (visit 3)

Synopsis Table 4: Difference between groups in percentage of subjects who seroconverted at Visit 3 for serum anti-rotavirus IgA antibody (Total vaccinated cohort)

						Difference in seroconversion rate			
								95 % CI	
Group	**N**	**%**	**Group**	**N**	**%**	**Difference**	**%**	**LL**	**UL**
HRV	72	65.3	Placebo	37	5.4	HRV - Placebo	59.87	44.17	71.32

N = number of subjects with available results
% = percentage of subjects who seroconverted at visit 3
95%CI = asymptotic standardised 95% confidence interval; LL = lower limit; UL = upper limit

- **Safety results**

- The incidence of any symptom (solicited or unsolicited) reported during the 15-day (Day 0 to Day 14) follow-up period was similar between the two groups. There was no increase in the incidence of symptoms after Dose 2 compared to Dose 1.
- The incidence of symptoms (solicited or unsolicited) rated as grade 3 in intensity reported during the 15-day (Day 0 to Day 14) follow-up period was similar in the two groups.
- The incidence of symptoms (solicited or unsolicited) considered by the investigator as causally related to vaccination reported during the 15-day (Day 0 to Day 14) follow-up period was also similar between the two groups. There was no increase in incidence of causally related symptoms (solicited or unsolicited) with subsequent doses.
- The percentage of subjects reporting diarrhoea, fever or vomiting graded 2 or 3 in intensity during the 15-day follow-up period after vaccination was similar in both the groups.
- The percentage of subjects with report of at least one unsolicited symptom within the 43-day follow-up period after any vaccination was similar in both the groups: 53.4% [95% CI: 43.3%; 63.3%] in the HRV vaccine group and 59.6% [95% CI: 45.1%; 73.0%] in the placebo group.
- RV was isolated from two reported GE episodes with available stool samples for RV testing from Dose 1 up to Visit 3 (one subject in each group). The wild type of the serotype G1P[8] was isolated from both stool samples. Onset of RV GE episode was reported 30 days and 10 days after Dose 2 for the subjects in the HRV vaccine group and placebo group, respectively. The intensity of RV GE episodes were graded by the investigator as grade 1 (mild) for the HRV vaccine recipient and grade 2 (moderate) for placebo recipient. No vaccine strain was detected in any of the stool samples tested.
- SAEs: No fatal SAEs were reported during the study. Non-fatal SAEs were reported in 11 subjects (9 subjects in the HRV vaccine group and 2 subjects in the placebo group). All SAEs except one in the HRV vaccine group (idiopathic thrombocytopenic purpura in n□□227) were considered by the investigator not to be causally related to study vaccination. All subjects recovered from the SAEs.
- No intussusception case was reported during the study.
- There was no report of discontinuation from the study due to an AE/ SAE.

Synopsis Table 5: Percentage of subjects reporting each solicited general symptoms including those graded "3" in intensity and those considered to be related to vaccination, during the 15-day (Day 0 to Day 14) follow up period, for all doses (Total vaccinated cohort)

		HRV					Placebo				
Symptom	**Type**	**N**	**n**	**%**	**95 % CI (LL, UL)**		**N**	**n**	**%**	**95 % CI (LL, UL)**	
Cough/ runny nose	All	100	48	48.0	37.9	58.2	52	30	57.7	43.2	71.3
	Grade 3	100	4	4.0	1.1	9.9	52	0	0.0	0.0	6.8
	Related	100	0	0.0	0.0	3.6	52	0	0.0	0.0	6.8
Diarrhoea	All	100	9	9.0	4.2	16.4	52	9	17.3	8.2	30.3
	Grade 3	100	4	4.0	1.1	9.9	52	3	5.8	1.2	15.9
	Related	100	5	5.0	1.6	11.3	52	0	0.0	0.0	6.8
Fever (Axillary) (°C)	All	100	17	17.0	10.2	25.8	52	8	15.4	6.9	28.1
	Grade 3	100	0	0.0	0.0	3.6	52	1	1.9	0.0	10.3
	Related	100	0	0.0	0.0	3.6	52	0	0.0	0.0	6.8
Irritability	All	100	54	54.0	43.7	64.0	52	33	63.5	49.0	76.4
	Grade 3	100	4	4.0	1.1	9.9	52	4	7.7	2.1	18.5
	Related	100	5	5.0	1.6	11.3	52	0	0.0	0.0	6.8
Loss of appetite	All	100	38	38.0	28.5	48.3	52	22	42.3	28.7	56.8
	Grade 3	100	0	0.0	0.0	3.6	52	0	0.0	0.0	6.8
	Related	100	3	3.0	0.6	8.5	52	0	0.0	0.0	6.8
Vomiting	All	100	27	27.0	18.6	36.8	52	17	32.7	20.3	47.1
	Grade 3	100	7	7.0	2.9	13.9	52	3	5.8	1.2	15.9
	Related	100	1	1.0	0.0	5.4	52	1	1.9	0.0	10.3

N = number of subjects with at least one documented dose
n (%) = number (percentage) of subjects reporting at least once the specified symptom
All = any occurrence of the specified symptom, irrespective of intensity grade and relationship to vaccination
Grade 3 = any occurrence of the specified symptom rated as grade 3
Related = any occurrence of the specified symptom assessed as causally related to the vaccination
95% CI = Exact 95% confidence interval; LL = lower limit, UL = upper limit

➢ **Conclusions:**

- GSK Biologicals. HRV vaccine was immunogenic in Korean infants who were a part of the ATP cohort for immunogenicity as shown by the anti-rotavirus IgA antibody seroconversion rate of 66.7% [95% CI: 51.6%, 79.6%] observed in the HRV vaccine group at two months after Dose 2.
- The anti-rotavirus IgA antibody seroconversion rate observed in the HRV vaccine group at two months after Dose 2 in the total vaccinated cohort was 65.3% [95% CI: 53.1%; 76.1%].
- The lower limit of the two-sided asymptotic standardized 95% CI for treatment difference (HRV minus placebo) in the percentage of subjects who seroconverted for anti-rotavirus IgA antibody at two months after Dose 2 was above the pre-defined clinical limit of 20% in the ATP cohort for immunogenicity thus, meeting the primary objective of the study. The results obtained in the total vaccinated cohort were consistent with those of the ATP cohort for immunogenicity.
- The reactogenicity profiles of the HRV vaccine group and placebo group were similar.
- There was no evidence of a clinically meaningful difference between the HRV vaccine group and the placebo group for SAEs reported from Dose 1 up to Visit 3 or unsolicited AEs reported within 43 days (Day 0 to Day 42) after vaccination.

Assessor's comment: *Study 103478 sought to investigate the immunogenicity and safety of the Rotarix vaccine in children aged 6 to 12 weeks whom have never suffered a rota-virus infection prior to vaccination. Review of the study did not raise any issues regarding neither the safety nor the immunogenicity in this study group and the MAH's conclusions are corroborated.*

Study 103792

- **General**

A phase IIIb, randomised, multicentre double-blind, placebo-controlled study of the immunogenicity and safety of two doses of GlaxoSmithKline (GSK) Biologicals. oral live attenuated human rotavirus (HRV) vaccine (RIX4414) as primary dosing in healthy infants in India of approximately 8 weeks of age at the first dose.

- **Objective(s)**

Primary:

- To assess the immunogenicity of GSK Biologicals. HRV vaccine in terms of seroconversion rates to rotavirus (RV) after two doses of HRV vaccine versus two doses of placebo.

Secondary:

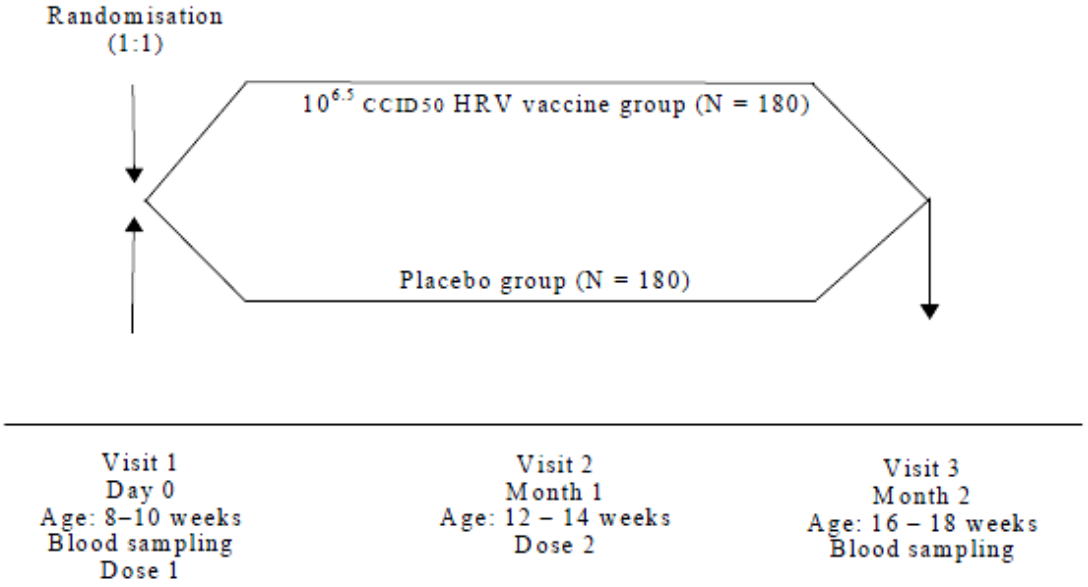
- To assess the safety and reactogenicity of each dose of GSK Biologicals' HRV vaccine versus placebo.
- • To assess the immunogenicity of GSK Biologicals. HRV vaccine in terms of serum anti-RV IgA antibody concentrations at Visit 3 (at one month post-Dose 2).
- • To assess the presence of RV in gastroenteritis (GE) stools collected until Visit 3.

- **Study design**

This was a phase IIIb, double-blind, randomised, placebo-controlled, self-contained study with two groups. The treatment groups were:

- Group HRV received $10^{6.5}$ $CCID_{50}$ HRV vaccine
- Group Placebo received placebo.

The administration of hepatitis B, Bacille Calmette-Guerin (BCG) and oral poliovirus vaccine (OPV) vaccinations at birth were allowed according to local universal immunisation program (UIP) schedule and were to be documented in the case report form (CRF). Following the UIP recommendation in India, routine diphtheria-tetanus-whole cell pertussis-hepatitis B (DTPw-HB), *Haemophilus influenzae* type b (Hib) and OPV vaccines was administered at 6, 10 and 14 weeks of age (given with a two week separation from the first and subsequent dose of the study vaccine/placebo). Blood samples were collected from all subjects for the assessment of immunogenicity of the HRV vaccine at Visit 1 and at Visit 3.



N = Number of subjects planned to be enrolled

- **Study population / Sample size**

Inclusion criteria

A healthy male or female infant between and including, 8 to 10 weeks of age at the time of first vaccination and who was administered the first dose of diphtheria, tetanus, pertussis, hepatitis B, Hib, oral poliovirus vaccine (DTPw/Hib/OPV) as per the local universal immunisation program (UIP) at 6 weeks of age were enrolled. Written informed consent was obtained from the parents/guardians of each subject.

- **Endpoints**

Primary endpoint

- Percentage of subjects who seroconverted for anti-RV IgA one month after Dose 2 (Visit 3)

Secondary endpoints

- Serum anti-RV IgA antibody concentrations expressed as Geometric Mean Concentration (GMC) at Visit 3
- For each type of solicited symptom, occurrence, intensity and relationship to the vaccination of symptom during the 8-day (Day 0 - Day 7) solicited follow-up period after each study vaccine dose.
- Occurrence of unsolicited symptoms during the 31-day follow-up period (Day 0 - Day 30) after each study vaccine dose, according to MedDRA classification.
- Presence of RV in GE stools collected from Dose 1 of HRV vaccine/placebo up to Visit 3.
- Occurrence of SAEs throughout the study period.

- **Statistical Methods**

Analysis of Demography

Demographic characteristics on age at Dose 1 and Dose 2 of HRV vaccine/placebo, height and weight at Visit 1,racial and gender composition were tabulated by group. The increase in height and weight of the subjects from Visit 1 to Visit 3 was tabulated by group. Summary of feeding practices on the day of each study vaccination was presented by group. The summary of concomitant vaccinations administered from Dose 1 of HRV/placebo up to Visit 3 were summarised by group. The percentage of subjects in the below mentioned three concomitant vaccination categories were calculated for each group

- without concomitant vaccinations. category (i.e. subjects with no vaccination administered within 13 days of both doses of HRV/placebo, excluding subjects who might have been administered with OPV (as per the government immunisation programme) within 13 days of HRV/placebo doses)
- with concomitant vaccinations. category (i.e. subjects with at least one vaccination administered within 13 days of at least one dose of HRV/placebo, excluding the unknown OPV administration (as per the government immunisation programme))
- with unknown concomitant vaccinations. (i.e. subjects who do not belong to .With concomitant vaccination. or .Without concomitant vaccination. i.e. subject who might have been administered with OPV (as per the government immunisation programme) within 13 days of at least one dose of HRV/placebo and without vaccination administered within 13 days of both doses of HRV/placebo)

Analysis of Immunogenicity

Anti-RV IgA antibody seropositivity/seroconversion rates and GMCs (also calculated on seropositive subjects) with their 95% confidence interval (CI) were tabulated.

As per protocol, a minimum interval of two weeks between the administration of the study vaccine and the administration of concomitant vaccines was to be observed. However, approximately one third of enrolled subjects received routine vaccinations in this forbidden interval and for some subjects OPV administration was unknown. Therefore, the above mentioned analyses were also explored by three concomitant vaccination categories. The distribution of the ratio of post- over pre-vaccination for anti-rotavirus IgA antibody concentrations in subjects seropositive at prevaccination was explored by group.

Analysis of Safety

The percentage of doses and of subjects with any symptom (solicited or unsolicited) reported during the 8-day (Day 0 to Day 7) follow-up period and with each solicited general symptom reported during the 8-day solicited follow-up period was tabulated by group with their exact 95% CIs.

The percentage of doses and of subjects with unsolicited AEs classified by Medical Dictionary for Regulatory Activities (MedDRA) system reported during the 31-day (Day 0 to Day 30) follow-up period after any HRV vaccine or placebo dose were tabulated by group with their exact 95% CIs. The same calculations were done for symptoms rated as grade "3" in intensity and for those assessed as causally related to vaccination. The percentage of subjects with GE and RV (vaccine strain or wild-type RV) GE from Dose 1 of HRV vaccine or placebo to Visit 3 was tabulated by group with their exact 95% CIs.

SAEs reported during the study period and withdrawals due to AEs or SAEs were described. Difference between groups was explored using the two-sided Fisher.s exact test for the following endpoints:

- percentage of subjects reporting each individual solicited general symptom within 8-day (Day 0 toDay 7) follow-up period after any dose,
- percentage of subjects reporting each individual solicited general symptom graded 3 intensity within 8-day (Day 0 to Day 7) follow-up period after any dose,
- percentage of subjects reporting each individual solicited general symptom assessed as related to vaccination within 8-day (Day 0 to Day 7) follow-up period after any dose.

p-values less than 0.05 were used as an indicator of a possible difference between groups. However, since p-values were not adjusted for multiplicity of comparisons, statistically significant findings were to be interpreted with caution and also taking into account clinically relevant difference.

➢ **Results**

Demography

In the ATP cohort for immunogenicity, the demographic profile of the two groups at study entry was similar with respect to mean age, height, weight and BMI. All subjects were Indian.

Number of subjects:	Total	Group HRV	Group Placebo
Planned	360	180	180
Enrolled	363	182	181
Completed	344	173	171
Total vaccinated cohort	363	182	181
According to protocol (ATP) cohort for safety	253	127	126
ATP cohort for immunogenicity	227	115	112

Immunogenicity

Analysis was performed on the ATP cohort for immunogenicity (primary analysis) and on the Total vaccinated cohort. Included in the ATP cohort were all subjects who received concomitant vaccinations in the forbidden interval but who complied with other study criteria.

At Visit 3:

- The anti-rotavirus IgA antibody seroconversion rates were 58.3% [95% CI: 48.7%; 67.4%] in the HRV Group. Similar seroconversion rates were observed in subjects without concomitant vaccination (55.7% [95% CI: 43.3%; 67.6%]), in subjects with concomitant vaccination (65.7% [95% CI: 47.8%; 80.9%]) and for subjects with unknown concomitant vaccination (50% [95% CI: 18.7%; 81.3%])
- The seroconversion rates were 6.3% [95% CI: 2.5%; 12.5%] in the Placebo Group, indicating natural infection with wild type RV had occurred in these subjects.
- GMCs calculated on subjects seropositive for anti-rotavirus IgA was 153.9U/ml [95% CI: 113.3 U/ml; 209.0 U/ml] in the HRV Group and 81.6 U/ml [95% CI: 27.4 U/ml; 242.8 U/ml] in the Placebo Group.
- The lower limit of the two sided asymptotic standardised 95% CI for the difference in the percentage of subjects who seroconverted for anti-rotavirus IgA antibody at Visit 3 between the HRV vaccine Group and (minus) the Placebo Group was 41.46% indicating that the seroconversion rate was significantly higher in the HRV vaccine group as compared to that in the Placebo Group.

Table 6: Anti-rotavirus IgA antibody GMC and seroconversion rates (ATP cohort for immunogenicity)

Group	Timing	N	≥ 20 U/ml				GMC		
			n	%	95% CI		U/ml	95% CI	
					LL	UL		LL	UL
HRV	PRE	115	0	0.0	0.0	3.2	<20	-	-
	PII (M2)	115	67	58.3	48.7	67.4	49.2	36.2	66.8
Placebo	PRE	112	0	0.0	0.0	3.2	<20	-	-
	PII (M2)	112	7	6.3	2.5	12.5	<20	-	-

GMC = geometric mean antibody concentration calculated on all subjects
N = number of subjects with available results; n (%) = number (percentage) of subjects with anti-RV Ig A antibody concentration ≥ 20U/ml; 95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PRE = Pre-vaccination blood sample; PII (M2) = one month after the second dose (Visit 3)

Table 7: Difference between groups in percentage of subjects who seroconverted at Visit 3 for serum antirotavirus IgA antibody (ATP cohort for immunogenicity)

Group	N	%	Group	N	%	Difference in seroconversion rate			
						Difference	%	95 % CI	
								LL	UL
HRV	115	58.3	Placebo	112	6.3	HRV - Placebo	52.01	41.46	61.50
N = number of subjects with available results; % = percentage of subjects who seroconverted at Visit 3 95% CI = asymptotic standardised 95% confidence interval; LL = Lower Limit, UL = Upper Limit									

- **Safety results**

Analysis was performed on Total vaccinated cohort (primary analysis) and on ATP cohort for safety.

Any symptom:

- The percentage of subjects reporting any, grade 3 symptoms and symptoms causally related to vaccination (solicited or unsolicited) during the 8-day (Day 0 to Day 7) follow-up period after any dose was similar between both groups. The incidence of any symptoms was similar after Dose 1 and Dose 2 in both groups indicating no increase in symptoms with subsequent doses.

Solicited general symptoms:

- The percentage of subjects for who solicited general symptom was reported during the 8-day follow-up period after vaccination was similar in both groups. Cough/runny nose were the most commonly reported symptoms. Statistically significant differences were not detected between the two groups with respect to the percentage of subjects reporting any individual solicited general symptom including those rated as grade 3 in intensity and those assessed as causally related to vaccination during the 8-day followup period after any HRV vaccine or placebo dose (p-value > 0.05, two-sided Fisher.s exact test).

Unsolicited symptoms:

- The percentage of subjects for whom at least one unsolicited symptom was reported within the 31-day follow-up period after any vaccination was similar in both groups: 19.8 % [95% CI: 14.3%; 26.3%] of subjects in the HRV Group and 17.7% [95% CI: 12.4%; 24.0%] of subjects in the Placebo Group.

Rotavirus in stool samples collected during GE episodes:

- Of all the GE episodes reported from Dose 1 of HRV vaccine or placebo up to Visit 3, stool samples were not available from 30.4% of the GE episodes in the HRV Group and from 15.4% of the GE episodes in the Placebo Group.
- The percentage of subjects reporting GE episodes from Dose 1 of HRV vaccine or placebo up to Visit 3 was 12.6% [95% CI: 8.2%; 18.4%] in the HRV Group and 13.3% [95% CI: 8.7%; 19.1%] in the Placebo Group.
- RV was not isolated from any of the tested stool samples collected in case of GE episodes up to Visit 3

Serious adverse events:

Five subjects (three in the HRV Group and two in the Placebo Group) reported non-fatal SAEs. None of these were considered by the investigator to be causally related to vaccination. All SAEs resolved. No deaths or intussusception cases occurred during the study.

Withdrawals due to adverse events/serious adverse events:

One subject (n□□203) in the HRV Group withdrew from the study due to diarrhoea (non-serious adverse event).

Concomitant medications:

The percentage of subjects who started taking at least one concomitant medication from Day 0 to Day 7 after any vaccination was similar in both groups. The percentage of subjects who started taking any antipyretic or any antibiotic from Day 0 to Day 7 after any vaccination was similar in both groups. None of the subjects started taking prophylactic antipyretic medication from Day 0 to Day 7 after any vaccination.

➢ **Conclusions:**

- The immune response in the ATP cohort for immunogenicity in terms of anti-rotavirus seroconversion rates in the group receiving HRV vaccine was 58.3% [95% CI: 48.7%; 67.4%] which was significantly higher than the seroconversion observed in the Placebo Group (6.3% [95% CI: 2.5%; 12.5%]). The results observed from the analysis for the total vaccinated cohort were consistent with the results observed with the ATP cohort for immunogenicity.
- The HRV vaccine was well tolerated and the reactogenicity profile of the HRV vaccine was similar when compared to the reactogenicity profile of placebo. No SAEs causally related to vaccination were reported.
- RV was not isolated from any of the tested stool samples collected in case of GE episodes up to Visit 3

> ***Assessor's comment:*** *Study 103792 investigated the seroconversion rate in children vaccinated with Rotarx using a twofold administration versus placebo. The primary endpoint was easily met, with the vaccinated cohort showing a more or less ten times higher seroconversion rate versus the placebo. Safety and reactogenity of the vaccine was also shown to be good, and rota-virus was undetectable in any of the stool samples taken from patients presenting with gastro-enteritis during the trial. The MAH's conclusions drawn from the results are thus corroborated.*

Study 103992

- **General**

A phase II, randomised, double-blind, placebo-controlled study to evaluate the immunogenicity, reactogenicity and safety of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine (RIX4414 at 106.5 CCID50) when given concomitantly with OPV (Oral Polio Vaccine) *versus* when given alone (HRV vaccine dose given 15 days after the OPV dose) in healthy infants in Bangladesh.

- **Objective(s)**

Primary:

- To assess immunogenicity of GSK Biologicals' HRV vaccine in terms of anti-rotavirus IgA antibody seroconversion at Visit 6 in the group receiving HRV vaccine concomitantly with OPV *versus* placebo group.

Secondary:

- To assess immunogenicity of GSK Biologicals' HRV vaccine in terms of anti-rotavirus IgA antibody seroconversion at Visit 6 in the group receiving HRV vaccine alone versus placebo group.
- To assess vaccine immunogenicity of GSK Biologicals' HRV vaccine in terms of anti-rotavirus IgA antibody seroconversion at Visit 6 in group receiving HRV vaccine concomit antly withOPV versus group receiving HRV vaccine alone (HRV vaccine dose given 15 days after the OPV dose).
- To assess vaccine take at Visit 6 in groups receiving GSK Biologicals' HRV vaccine concomitantly with OPV versus group receiving GSK Biologicals' HRV vaccine alone (HRV vaccine dose given 15 days after the OPV dose) in a subset of subjects.
- To assess immunogenicity of GSK Biologicals' HRV vaccine in terms of Geometric Mean Concentration (GMC) at Visit 6.
- To assess rotavirus (RV) shedding in stool samples collected at pre-determined timepoints in a subset of subjects.
- To assess the presence of RV in diarrhoeal stools collected from Visit 3 until Visit 6.
- To assess the immunogenicity of the poliovirus antigens at Visit 6 in each of the HRV vaccine groups versus placebo group.
- To assess the safety and reactogenicity of each dose of GSK Biologicals' HRV vaccine versus placebo.

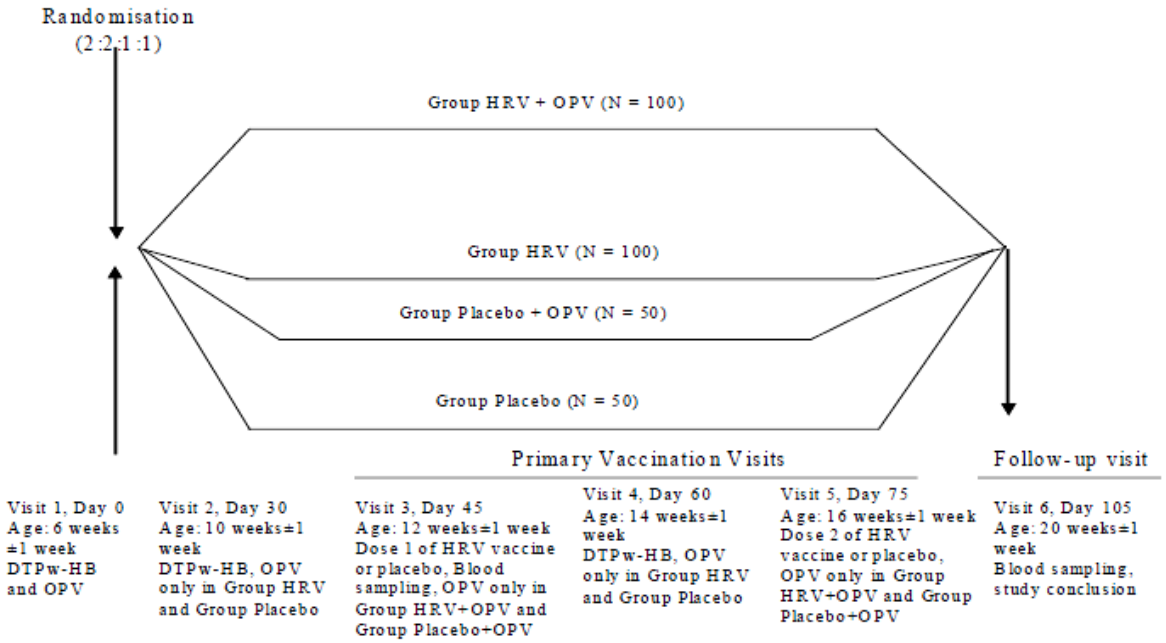
- **Study design**

Randomised (2:2:1:1 ratio), placebo-controlled, study with four parallel groups.

- Group HRV+OPV: receiving 2 doses of HRV given concomitantly with OPV
- Group HRV: receiving 2 doses of HRV given alone (HRV vaccine dose given 15 days after the OPV dose)
- Group Placebo+OPV: receiving 2 doses of placebo for HRV vaccine given concomitantly with OPV
- Group Placebo: Group receiving 2 doses of placebo for HRV vaccine (HRV placebo dose given 15)

The study was conducted in a double-blind manner with respect to HRV vaccine and placebo. Hepatitis B, BCG and OPV vaccinations at birth are allowed according to local EPI schedule and were to be documented in the case report form (CRF). BCG at Visit 1 was allowed and was to be documented in the CRF.

Following the EPI recommendation in Bangladesh, routine DTPw-HB vaccine was to be administered at 6, 10 and 14 weeks of age (at Visits 1, 2 and 4).



N = number of subjects planned to be enrolled

- **Study population / Sample size**

Inclusion criteria

- Subjects who the investigator believed that their parents/guardians could and would comply with the requirements of the protocol (e.g., completion of the diary cards, return for follow-up visits) were to be enrolled in the study.
- A male or female between, and including, 6 weeks +/- 1 week of age at the time of Visit 1.
- Written informed consent obtained from the parent or guardian of the subject.
- Free of obvious health problems as established by medical history and clinical examination before entering into the study.

Exclusion criteria

- Use of any investigational or non-registered product (drug or vaccine) other than the study vaccine(s) within 30 days preceding the first dose of study vaccine, or planned use during the study period.
- Planned administration of a vaccine not foreseen by the study protocol within 14 days before each dose of study vaccine(s) and ending 14 days after.
- Chronic administration (defined as more than 14 days) of major immunosuppressants (equivalent to prednisone 1mg/kg/day) since birth. (Topical steroids were allowed.)
- Malnutrition (< -3Z score weight for age).
- History of/or intercurrent polio disease.
- Previous confirmed occurrence of RV GE.
- History of use of experimental RV vaccine.
- Previous routine vaccination except BCG, HBV and OPV vaccination at birth (were to be documented in the CRF).
- Any clinically significant history of chronic gastrointestinal disease including any uncorrected congenital malformation of the gastrointestinal tract, intussusception or other medical condition determined to be serious by the investigator.

- Any confirmed or suspected immunosuppressive or immunodeficient condition, including human immunodeficiency virus (HIV) infection.
- History of allergic disease or reaction likely to be exacerbated by any component of the vaccine.
- Acute disease at the time of enrolment. (Acute disease was defined as the presence of a moderate or severe illness with or without fever. All vaccines could be administered to infants with a minor illness such as mild upper respiratory infection with or without low-grade febrile illness, i.e. oral temperature <37.5°C (99.5°F) / axillary temperature <37.5°C (99.5°F) / rectal temperature <38°C (100.4°F).)
- A family history of congenital or hereditary immunodeficiency.
- Administration of immunoglobulins and/or blood products since birth or planned administration during the study period.
- History of any neurologic disorders or seizures.
- Acute or chronic, clinically significant pulmonary, cardiovascular, hepatic or renal functional abnormality, as determined by physical examination or laboratory screening tests.

Elimination criteria

- Up to Visit 3, previous confirmed occurrence of RV GE.
- GE (diarrhoea) within 7 days preceding the study vaccine administration (warranted deferral of the vaccination).
- Use of any investigational or non-registered product (drug or vaccine) other than the study vaccine(s) during the study period.
- Chronic administration (defined as more than 14 days) of immunosuppressants during the study period. (Topical steroids were allowed.)
- Administration of a vaccine not foreseen by the study protocol during the period starting from 14 days before each dose of study vaccine(s) and ending 14 days after.
- Administration of immunoglobulins and/or any blood products during the study period.
- Any confirmed or suspected immunosuppressive or immunodeficient condition, including HIV infection.

- **Endpoints**

Primary endpoint

- Percentage of subjects who seroconverted at Visit 6 (percentage of subjects with titre ≥ assay cut-off in subjects who were negative for RV before vaccination).

Secondary endpoints

- Serum anti-RV IgA antibody concentration expressed as Geometric Mean concentration (GMC) at Visit 6.
- Percentage of subjects with anti-poliovirus type 1, 2 and 3 antibody titre □□8 at Visit 6.
- Antibody titres for anti-polio type 1, anti-polio type 2, anti-polio type 3 at Visit 6.
- RV shedding in a subset of subjects (at the day of or 1 day prior to each dose, and on Day 4 +/- 1 and Day 7 +/- 1 after each dose of HRV vaccine or placebo).
- Presence of RV in diarrhoeal stools collected from Dose 1 of HRV vaccine or placebo (Visit 3) up to Visit 6.
- Percentage of subjects with vaccine take at Visit 6 in a subset of subjects.
- Occurrence of any grade 2 or grade 3 fever, vomiting or diarrhoea within the 8-day (Day 0 - Day 7) solicited follow-up period after each dose of HRV vaccine or placebo.
- For each type of solicited symptoms, occurrence of the symptom within the 8-day (Day 0 - Day 7) solicited follow-up period after each dose of HRV vaccine or placebo.

- Occurrence of unsolicited adverse events within 31 days (Day 0- Day 30) after each dose of HRV vaccine or placebo according to Medical Dictionary for Regulatory Activities (MedDRA) classification.
- Occurrence of serious adverse events throughout the study period.
- **Statistical Methods**

Analysis of Demography

Demographic characteristics (descriptive statistics on age at Visit 1, Dose 1 and Dose 2 of HRV vaccine or placebo, height and weight at Visit 1 and gender and race distribution) were tabulated for each group. Increase in height and weight from Visit 1 to Visit 3, Visit 5 and Visit 6 was summarised by group.

Analysis of Immunogenicity

Immunogenicity analysis was performed on the (ATP) cohort for immunogenicity (primary analysis) and the total vaccinated cohort.

All subjects:

At each time point that serum antibody response to a given antigen was measured, seroprotection/seroconversion/seropositivity rates and their exact 95% CI were calculated by group and for pooled placebo groups. GMCs/GMTs and their 95% CI were calculated by group and for pooled placebo groups. GMCs and their 95% CI were also calculated on the subjects who had seroconverted to anti-rotavirus IgA antibody.

The asymptotic standardised 95% CI for difference between the two HRV groups and between each HRV group and the pooled placebo group was computed for each of the following endpoints separately.

- the percentage of subjects who seroconverted for anti-rotavirus IgA antibody; the corresponding one-sided asymptotic standardised P-value was also computed

- seroprotection rates for each anti-polio type 1, 2 and 3 antibodies

Stool analysis subset:

The percentage of subjects with presence of RV in stool samples collected at pre-determined time points (shedding) was tabulated by group and for pooled placebo groups. The percentage of subjects with vaccine take at Visit 6 was calculated by group and for pooled placebo groups with its exact 95% CI.

Analysis of Safety

The safety analysis was performed on the total vaccinated cohort (primary analysis) and the ATP cohort for safety. The percentages of doses and of subjects with any symptom (solicited or unsolicited) reported during the 8-day follow-up period and with specific solicited symptoms reported during the 8-day (Day 0 to Day 7) solicited follow-up period were tabulated by group with their exact 95% CI. The percentages of doses and of subjects with unsolicited adverse events classified by MedDRA system reported during the 31-day follow-up period after any HRV vaccine or placebo dose were tabulated by group with their exact 95% CI. The same calculations were done for symptoms rated as grade "3" in intensity and for those assessed as related to vaccination.

Differences between the two HRV groups and between each HRV group and pooled placebo groups were explored using two-sided Fisher Exact test for each individual solicited symptom (any, grade "3", related) reported within the 8-day follow-up period after any HRV vaccine or placebo dose. Due to multiple endpoints analysed without multiplicity adjustment, statistically significant differences (Pvalue < 0.05) should be interpreted cautiously and the differences observed in this study could occur by chance alone.

The percentages of subjects with gastroenteritis (GE) and RV (vaccine strain or wild-type RV) GE from Dose 1 of HRV vaccine or placebo to Visit 6 were tabulated by group with their exact 95% CI. SAEs /withdrawals due to AE/SAEs were described.

- **Results**

Demography

The demographic profile of the four groups at study entry (Visit 1) was similar with respect to mean age, gender, racial distribution, height and weight. All subjects were of Bangladeshi origin. The mean age of subjects was 12.3 weeks at the time of the first HRV vaccine or placebo dose, 16.7 weeks at the time of the second HRV vaccine or placebo dose. The mean increase in height and weight were similar between the groups after the full vaccination course. The intended duration of the study, per subject, was approximately 3.5 months.

Number of subjects:	Total	HRV + OPV group	HRV group	Placebo + OPV group	Placebo group
Planned	300	100	100	50	50
Enrolled	300	100	100	50	50
Vaccinated	294	99	97	50	48
Completed	290	98	95	49	48
TVC cohort for safety	294	99	97	50	48
ATP cohort for immunogenicity	214	70	71	37	36

Immunogenicity

Analysis was performed on the ATP cohort for immunogenicity (primary analysis).

- Table 8 presents the anti-rotavirus IgA antibody GMC and seroconversion rates. Approximately one month after Dose 2 of HRV vaccine, the anti-rotavirus IgA antibody seroconversion rate was 56.5% [95% CI: 44.0%; 68.4%] in group HRV+OPV and 66.7% [95% CI: 54.0%; 77.8%] in group HRV.
- The 18.6 % of seroconversion observed in the pooled placebo group at Visit 6 indicated that natural infection with wild type RV had occurred during the study. The presence of wild type RV was confirmed by RT-PCR analysis of the diarrhoeal stool samples.
- Table 9 presents inferential analysis on anti-rotavirus IgA antibody seroconversion rates at Visit 6. A statistically significant increase was detected in group HRV+OPV and in group HRV as compared to the pooled placebo group in terms of seroconversion rate at Visit 6 (P-value < 0.05; one-sided asymptotic standardised test).
- Although the seroconversion rate at Visit 6 was somewhat lower in the HRV+OPV group, a statistically significant decrease was not detected in the HRV+OPV group when compared to the HRV group (P-value > 0.05; one-sided asymptotic standardised test) (Table 2).
- In the stool analysis subset, RV shedding was observed at Day 4 and Day 7 after Dose 1 and Dose 2 of HRV vaccine. The percentage of subjects with RV shedding at combined time points was 17.6% [95% CI: 6.8%; 34.5%] in group HRV+OPV and 31.0% [95% CI: 17.6%; 47.1%] in group HRV. RV shedding at combined time points was also detected in 10.5% [95% CI: 2.9%; 24.8%] subjects in group pooled placebo.
- The percentage of subjects with vaccine take at Visit 6 was 51.5% [95% CI: 33.5%; 69.2%] in group HRV+OPV, 73.7% [95% CI: 56.9%; 86.6%] in group HRV and 19.4% [95% CI: 8.2%; 36.0%] in the pooled placebo group.
- The seroprotection rate observed against poliovirus type 3 in Bangladesh appeared to be lower than seroprotection rates observed in previous South African studies but are in line with seroprotection rates observed in other countries using the EPI schedule.
- Statistically significant differences were not detected between each HRV group and the pooled placebo group, and between the two HRV groups in terms of anti-poliovirus types 1, type 2 and type 3 seroprotection rates and GMTs at Visit 6, except for anti-poliovirus type 2 antibody GMT between the 2 HRV groups (in favour of the HRV+OPV group).

Table 8: Anti-rotavirus IgA antibody GMC and seroconversion rates (ATP cohort for immunogenicity)

			≥ 20 U/ml				GMC (U/ml)		
					95% CI			95% CI	
Group	Timing	N	n	%	LL	UL	Value	LL	UL
HRV+OPV	Pre	69	0	0.0	0.0	5.2	< 20	-	-
	PII(D105)	69	39	56.5	44.0	68.4	46.6	30.3	71.7
HRV	Pre	70	0	0.0	0.0	5.1	< 20	-	-
	PII(D105)	66	44	66.7	54.0	77.8	75.3	47.5	119.4
Placebo+OPV	Pre	34	0	0.0	0.0	10.3	< 20	-	-
	PII(D105)	36	7	19.4	8.2	36.0	< 20	-	-
Placebo	Pre	36	0	0.0	0.0	9.7	< 20	-	-
	PII(D105)	34	6	17.6	6.8	34.5	< 20	-	-
Placebo pooled	Pre	70	0	0.0	0.0	5.1	< 20	-	-
	PII(D105)	70	13	18.6	10.3	29.7	< 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
Pre = Pre-vaccination blood sample (taken before Dose 1 of HRV vaccine or placebo at Visit 3)
PII(D105) = Post-vaccination blood sample (taken approximately one month after Dose 2 of HRV vaccine or placebo at Day 105 at Visit 6)

Table 9: Difference between groups in percentage of subjects who seroconverted at Visit 6 for serum anti-rotavirus IgA antibody (ATP cohort for immunogenicity)

						Difference in seroconversion rate at Visit 6				
								95 % CI		
Group	N	%	Group	N	%	Difference	%	LL	UL	P
HRV+ OPV	69	56.5	Placebo pooled	70	18.6	HRV+OPV minus Placebo pooled	37.95	22.38	51.77	<0.001
HRV	66	66.7	Placebo pooled	70	18.6	HRV minus Placebo pooled	48.10	32.43	61.29	<0.001
HRV	66	66.7	HRV+ OPV	69	56.5	HRV minus HRV+OPV	10.14	-6.27	26.00	0.113

N = number of subjects with available results; % = percentage of subjects with anti-rotavirus IgA antibody concentration ≥ 20 U/ml; 95% CI = 95% asymptotic standardised confidence interval; LL = lower limit, UL = upper limit; P = one-sided asymptotic standardised P-value for the null hypothesis that there is no increase in proportion with the HRV vaccine as compared to pooled placebo groups, or that there is no decrease in proportion with group HRV+OPV as compared to group HRV

Table 10: Seroprotection rates and GMTs for anti-poliovirus types 1, 2 and 3 antibodies (ATP cohort HRV+OPV for immunogenicity)

			≥ 8 ED50				GMT		
					95 % CI			95 % CI	
Group	Timing	N	n	%	L.L	U.L	value	LL	UL
Anti-poliovirus type 1									
HRV+OPV	PII(D105)	66	57	86.4	75.7	93.6	404.1	224.2	728.4
HRV	PII(D105)	69	64	92.8	83.9	97.6	442.5	256.2	764.3
Placebo+OPV	PII(D105)	35	33	94.3	80.8	99.3	840.0	427.2	1651.6
Placebo	PII(D105)	36	31	86.1	70.5	95.3	376.2	179.5	788.5
Placebo pooled	PII(D105)	71	64	90.1	80.7	95.9	559.0	339.5	920.3
Anti-poliovirus type 2									
HRV+OPV	PII(D105)	68	67	98.5	92.1	100	839.3	550.5	1279.6
HRV	PII(D105)	70	65	92.9	84.1	97.6	454.6	302.5	683.3
Placebo+OPV	PII(D105)	34	33	97.1	84.7	99.9	621.4	352.9	1094.1
Placebo	PII(D105)	36	35	97.2	85.5	99.9	517.0	316.0	845.8
Placebo pooled	PII(D105)	70	68	97.1	90.1	99.7	565.3	392.5	814.1
Anti-poliovirus type 3									
HRV+OPV	PII(D105)	69	48	69.6	57.3	80.1	65.4	38.7	110.3
HRV	PII(D105)	68	50	73.5	61.4	83.5	59.3	36.9	95.3
Placebo+OPV	PII(D105)	36	22	61.1	43.5	76.9	59.8	25.3	141.1
Placebo	PII(D105)	36	27	75.0	57.8	87.9	67.2	35.0	129.0
Placebo pooled	PII(D105)	72	49	68.1	56.0	78.6	63.4	37.5	107.3

N = number of subjects with available results; n/% = number/percentage of subjects with titre above the cut-off
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PII(D105) = Post-dose II vaccination blood sample at Day 105 (Visit 6)

- **Safety results**

Analysis was performed on the Total Vaccinated Cohort.

- The percentage of subjects with symptoms (solicited or unsolicited) reported within the 8-day (Day 0 to Day 7) follow-up period after HRV vaccine or placebo dose including those rated as grade "3" were similar in all the groups. None were assessed as related to vaccination.
- Table 11 presents percentage of subjects reporting each solicited general symptoms and those graded “3” in intensity during the 8-day (Day 0 to Day 7) follow-up period after any HRV vaccine or placebo dose. Irritability was the most frequently recorded solicited general symptom in all groups. Reports of solicited symptoms rated grade 3 in intensity were infrequent in all groups. None of the solicited symptoms were considered to be related to vaccination.
- Statistically significant differences were not detected for the comparison between the two HRV groups and between each HRV group and the pooled placebo group with respect to the incidence of subjects reporting any individual solicited general symptom and those rated grade 3 in intensity during the 8-day follow-up period after any HRV vaccine or placebo dose (P-value > 0.05, two-sided Fisher’s exact test), except for grade 3 vomiting between HRV group and the pooled placebo group (P-value = 0.029 in favour of the pooled placebo group). On the contrary, there was no significant difference in grade 3 vomiting between the HRV+OPV group and the pooled placebo group suggesting that the observed difference with the HRV group was likely to be a chance finding due to the number of endpoints analysed and to the fact that no multiplicity adjustment was done.
- The percentages of subjects with report of at least one unsolicited symptom within the 31-day follow-up period after any vaccination were similar in all groups. None of the unsolicited symptoms were determined to have a causal relationship to vaccination.

- RV was isolated in stool samples from seven subjects reporting GE between Dose 1 of HRV vaccine or placebo up to Visit 6 (two subjects in group HRV+OPV, one subject in group HRV, three subjects in group placebo+OPV and one subject in group placebo). No subject had more than one episode of RV GE. Of these seven RV GE episodes, G2P[4] was isolated in 2 GE stool samples and G12P[6] was isolated in 5 GE stool samples.
- SAEs: One SAE was reported during the study: A fatal SAE (Case ID B0399127A) assessed as not related to vaccination (severe pneumonia leading to cardio respiratory and renal failure) was reported in one subject from group HRV on Day 16 after Dose 1 of HRV vaccine. No intussusception cases were reported during the study.
- Withdrawal due to AE/SAE: One discontinuation from the study took place due to the fatal SAE described above.

Table 11: Percentage of subjects reporting each solicited general symptoms and those graded "3" in intensity during the 8-day (Day 0 to Day 7) follow-up period, for all doses (TVC)

		HRV+OPV					HRV					Placebo+OPV					Placebo				
					95 % CI					95 % CI					95 % CI					95 % CI	
Symptom	Type	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
Overall/subject																					
Diarrhoea	All	99	4	4.0	1.1	10.0	97	1	1.0	0.0	5.6	50	3	6.0	1.3	16.5	48	1	2.1	0.1	11.1
	Grade 3	99	3	3.0	0.6	8.6	97	1	1.0	0.0	5.6	50	3	6.0	1.3	16.5	48	1	2.1	0.1	11.1
Fever	All	99	17	17.2	10.3	26.1	97	13	13.4	7.3	21.8	50	7	14.0	5.8	26.7	48	11	22.9	12.0	37.3
	Grade 3	99	0	0.0	0.0	3.7	97	2	2.1	0.3	7.3	50	0	0.0	0.0	7.1	48	0	0.0	0.0	7.4
Irritability	All	99	47	47.5	37.3	57.8	97	46	47.4	37.2	57.8	50	15	30.0	17.9	44.6	48	18	37.5	24.0	52.6
	Grade 3	99	0	0.0	0.0	3.7	97	1	1.0	0.0	5.6	50	0	0.0	0.0	7.1	48	0	0.0	0.0	7.4
Loss of appetite	All	99	35	35.4	26.0	45.6	97	37	38.1	28.5	48.6	50	9	18.0	8.6	31.4	48	17	35.4	22.2	50.5
	Grade 3	99	0	0.0	0.0	3.7	97	0	0.0	0.0	3.7	50	0	0.0	0.0	7.1	48	0	0.0	0.0	7.4
Vomiting	All	99	15	15.2	8.7	23.8	97	21	21.6	13.9	31.2	50	9	18.0	8.6	31.4	48	7	14.6	6.1	27.8
	Grade 3	99	1	1.0	0.0	5.5	97	5	5.2	1.7	11.6	50	0	0.0	0.0	7.1	48	0	0.0	0.0	7.4

N= number of subjects with at least one administered dose; n/%= number/percentage of subjects reporting at least once the specified symptom; All = any occurrence of the specified symptom, irrespective of intensity grade and relationship to vaccination; Grade 3 = any occurrence of the specified symptom rated as grade 3
95%CI= Exact 95% confidence interval; LL = lower limit, UL = upper limit

➢ **Conclusions:**

- The immune response in terms of anti-rotavirus IgA seroconversion rates in the group receiving HRV vaccine concomitantly with OPV and in the group receiving HRV vaccine alone (HRV vaccine dose given 15 days after the OPV dose) was of 56.5% and 66.7% respectively which is significantly higher than the seroconversion rate observed in the placebo groups. A statistically significant decrease was not detected in the HRV+OPV group when compared to the HRV group.
- Shedding (17.6% versus 31.0%) and vaccine take rates (51.5% versus 73.7%) tended to be somewhat lower in the group receiving HRV vaccine concomitantly with OPV compared to the group receiving HRV vaccine alone (HRV vaccine dose given 15 days after the OPV dose).
- There was no interference observed with co-administration of OPV with GSK Biologicals' HRV vaccine on the immune response to poliovirus types 1, 2 and 3.
- The reactogenicity profile of the group receiving HRV vaccine concomitantly with OPV was similar to group receiving HRV vaccine alone (HRV vaccine dose given 15 days after the OPV dose). The reactogenicity profile of the HRV vaccine groups was similar to the placebo groups.
- No SAEs related to vaccination were reported.

Assessor's comment: *Study 103992 was set up as an investigation to compare immunogenicity and safety of Rotarix vaccination, both alone and concomitantly with oral polio vaccine, versus placebo using a four arm study design (HRV vs. HRV+OPV vs. placebo vs. placebo+OPV). Immunogenicity results showed a clear superiority of the HRV treatment groups versus the placebo groups in anti-rotavirus IgA seroconversion. Although a 10% difference was*

noted between the HRV and HRV+OPV groups, this difference was shown to be statistically non-significant. There was neither decrease nor increase noted in the OPV immune response.

Safety and reactogenicity was similar in all four study arms. The results of this trial thus confirm the efficacy and safety of Rotarix when concomitantly administered with OPV.

Study 107531

➢ **General**

A phase III randomized multi-center study to assess the immunogenicity of three doses of Pediarix, Prevnar and ActHIB given to healthy infants at 2, 4 and 6 months of age when administered with GlaxoSmithKline (GSK) Biologicals two-dose oral live attenuated human rotavirus (HRV) vaccine given during the same vaccination visit (at 2 and 4 months of age) or given separately (at 3 and 5 months of age).

- **Objective(s)**

Primary:

- To demonstrate that the co-administration with GSK Biologicals HRV vaccine does not impair the immune response to all antigens contained in each of the routine infant vaccines (Pediarix, Prevnar and ActHIB).

  For this comparison the criteria for non-inferiority 1 month after Dose 3 of routine infant vaccines at Visit 6 were specified as follows:

  Lower limit of the standardized asymptotic 95% confidence interval (CI) on the difference (HRV co-administration group minus HRV separate group) in the percentage of subjects with anti-polyribosyl ribitol phosphate (PRP) antibody concentration ≥1.0 µg/mL is ≥ -10% (clinical limit for non-inferiority).

  and

  Lower limits of the 95% CIs on the geometric mean antibody concentration (GMC) ratios (HRV co-administration group divided by HRV separate group) for each of the anti-pertussis toxoid (PT), anti-filamentous haemagglutinin (FHA) and anti-pertactin (PRN) antibodies are ≥0.67 (clinical limit for non-inferiority).

  and

  Lower limit of the standardized asymptotic 95% CI on the difference (HRV co-administration group minus HRV separate group) in the percentage of subjects with seroprotective concentration (≥10 mIU/mL) for anti-Hepatitis B surface antigen (HBsAg) antibodies is ≥ -10% (clinical limit for non-inferiority).

  and

  Lower limits of the 95% CIs on the GMC ratios (HRV co-administration group divided by HRV separate group) for each of the seven S. pneumoniae (Pn) serotypes are ≥0.5 (clinical limit for non-inferiority).

  and

  Lower limits of the standardized asymptotic 95% CIs on the differences (HRV co- administration group minus HRV separate group) in the percentage of subjects with seroprotective titers (≥1:8) for each of anti-poliovirus serotypes 1, 2 and 3 antibodies are ≥ -10% (clinical limit for non-inferiority).

  and

  Lower limits of the standardized asymptotic 95% CIs on the differences (HRV co-administration group minus HRV separate group) in the percentage of subjects with seroprotective concentrations (≥0.1 IU/mL) for each of anti-diphtheria and anti-tetanus antibodies are ≥ - 10% (clinical limit for non-inferiority).

Secondary:

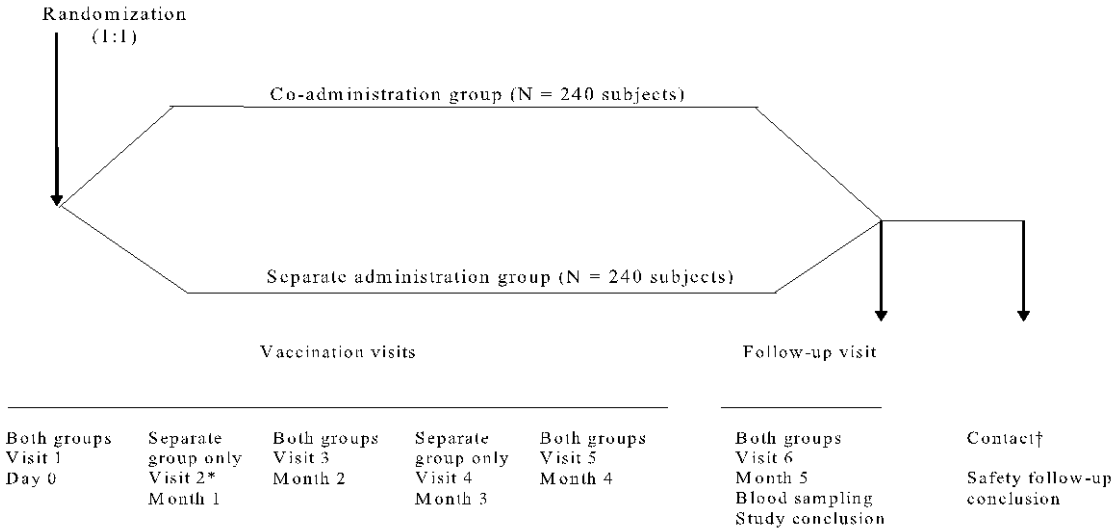
- To assess the immunogenicity of GSK Biologicals' HRV vaccine in terms of serum anti- rotavirus immunoglobulin A (IgA) antibody seropositivity (≥20 U/mL) at 2 to 3 months after Dose 2 of HRV vaccine (Visit 6).

- **Study design**

Open-label, randomized (1:1), multi-center study with two parallel groups.

- Co-administration group (henceforth referred to as co-ad group) received Pediarix, Prevnar and ActHIB at 2, 4 and 6 months of age and HRV vaccine during the same vaccination visit at 2 and 4 months of age.
- Separate administration group (henceforth referred to as sep-ad group) received Pediarix, Prevnar and ActHIB at 2, 4 and 6 months of age and HRV vaccine separately at 3 and 5 months of age.

Fluzone vaccine was to be offered to subjects at 6 months (Visit 5) and 7 months (Visit 6) of age. Administration of this vaccine was optional at the investigator's and subject's parents/guardians discretion. Blood samples were to be drawn from all subjects at Visit 6. Safety was to be assessed in all subjects during the entire study period inclusive of the Extended Safety Follow-up Phase (from Day 0 up to 5 months after the 3rd dose of Pediarix, Prevnar and ActHIB or within 7 months following the last dose of Pediarix, Prevnar and ActHIB in case the 3rd dose was not given).



N = number of subjects planned to be enrolled
*Visit 2 was to take place before 17 weeks of age
Subjects in both groups received a dose of *Pediarix*, *Prevnar* and *ActHIB* at Visit 1, Visit 3 and Visit 5
Subjects in the co-ad group received a dose of HRV vaccine at Visit 1 and Visit 3
Subjects in the sep-ad group received a dose of HRV vaccine at Visit 2 and Visit 4. †Contact (by telephone call or any other convenient procedure) 120 – 150 days after Visit 5 for safety follow-up.

- **Study population**

Inclusion criteria

- Subjects who the investigator believed that their parents/guardians would comply with the requirements of the protocol (e.g. return for follow-up visits) were enrolled in the study.
- A male or female between, and including, 6 and 12 weeks of age at the time of the first vaccination.
- Written informed consent obtained from the parent or guardian of the subject.
- Healthy subjects as established by medical history and clinical examination before entering into the study.

- Infants who had not received a previous dose of hepatitis B vaccine or those who had received only one dose of hepatitis B vaccine administered at least 30 days prior to enrolment.

Exclusion criteria

- Use of any investigational or non-registered product (drug or vaccine) within 30 days preceding the first dose of any of the study vaccines, or planned use during the study period.
- Chronic administration (defined as more than 14 days) of immunosuppressants since birth (topical steroids were allowed).
- Planned administration/administration of a vaccine not foreseen by the study protocol within 30 days of the first dose of vaccine.
- Concurrently participating in another clinical study, at any time during the study period, in which the subject had been or was exposed to an investigational or a non- investigational product (pharmaceutical product or device).
- History of diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis, Hib, and/or S. pneumoniae disease.
- Previous vaccination against RV.
- Previous vaccination against diphtheria, tetanus, pertussis, poliovirus, Hib or S. pneumoniae.
- Any confirmed or suspected immunosuppressive or immunodeficient condition, based on medical history and physical examination (no laboratory testing was required).
- A family history of congenital or hereditary immunodeficiency.
- History of allergic disease or reactions likely to be exacerbated by any component of the vaccine(s).
- Major congenital defects or serious chronic illness.
- History of any neurologic disorders or seizures.
- History of thrombocytopenia or any other coagulation disorders.
- Acute disease at the time of enrolment. (Acute disease was defined as the presence of a moderate or severe illness with or without fever. All vaccines could be administered to persons with a minor illness such as diarrhea, mild upper respiratory infection with or without low-grade febrile illness, i.e. oral temperature <99.5°F/ axillary temperature <99.5°F/rectal temperature <100.4°F/tympanic temperature on oral setting <99.5°F/tympanic temperature on rectal setting <100.4°F). A temperature greater than or equal to these cut-offs warranted deferral of the vaccination pending recovery of the subject.
- Administration of immunoglobulins and/or any blood products since birth or planned administration during the study period.

Eliminiation criteria

- Use of any investigational or non-registered product (drug or vaccine) other than the investigational vaccine (HRV vaccine) during the study period.
- Chronic administration (defined as more than 14 days) of immunosuppressants during the study period (Topical steroids were allowed).
- Administration of a vaccine not foreseen by the study protocol during the study period.
- Administration of immunoglobulins and/ or any blood products during the study period.
- Any confirmed or suspected immunosuppressive or immunodeficient condition based on medical history and physical examination (no laboratory testing was required).
- **Endpoints**

Primary endpoint

- Immunogenicity of routine infant vaccines at 1 month after Dose 3 of routine infant vaccines (Visit 6):

- anti-PRP antibody concentration ≥ 1.0 µg/mL (seroprotection)
- anti-PT, anti-FHA, anti-PRN antibody concentrations
- anti-HBsAg antibody concentration ≥ 10 mIU/mL (seroprotection)
- concentrations of antibodies to S. pneumoniae serotypes 4, 6B, 9V, 14, 18C, 19F, 23F
- anti-poliovirus serotypes 1, 2 and 3 antibody titer ≥ 1:8 (seroprotection)
- anti-diphtheria and anti-tetanus antibody concentrations ≥ 0.1 IU/mL, (seroprotection)

Secondary endpoints

- Serum anti-rotavirus IgA antibody seropositivity rate (≥20 U/mL) at 2 to 3 months after Dose 2 of HRV vaccine (Visit 6).
- Serum anti-rotavirus IgA antibody concentration at 2 to 3 months after Dose 2 of HRV vaccine (Visit 6).
- Seropositivity status:
  - anti-PT antibody concentration □□□EL.U/mL
  - anti-FHA antibody concentration □□□EL.U/mL
  - anti-PRN antibody concentration □□□EL.U/mL
  - concentrations of antibodies to S. pneumoniae serotypes 4, 6B, 9V, 14, 18C, 19F, 23F □□□□□□µg/mL
- Serum concentrations/ titers for anti-PRP, anti-diphtheria, anti-tetanus, anti-HBsAg, anti-poliovirus serotypes 1, 2 and 3 antibodies.
- **Statistical Methods**

Analysis of Demography

The distributions of subjects enrolled by center were tabulated by group. The number of subjects who dropped out at Visit 6 was tabulated by group according to the reason for drop- out. The median, mean, range and standard deviation (SD) of age at each study vaccine dose (in weeks) were computed by group. The median, mean and SD of height in centimeter (cm) and weight in kilograms (kg) at Visit 1 were computed by group. The Body Mass Index (BMI) at Visit 1 was also computed as weight (in kg) / height2 (in meters). The median, mean and SD of the gestation period (in weeks) and weight at birth (in kg) were computed by group. The racial and gender composition were also presented. The number of doses of HRV vaccine, Prevnar, Pediarix and ActHIB administered was tabulated per group. The percentage of subjects who received a dose of hepatitis B vaccine before Dose 1 of routine vaccination at Visit 1 was tabulated per group.

Analysis of Immunogenicity

Within group analysis

For each treatment group and each antigen:

- Seropositivity/seroprotection rates, as applicable, were calculated with exact 95% CI
- GMC/geometric mean titers (GMTs) with 95% CIs were tabulated. Calculation of the GMC/GMTs was performed by taking the anti-log of the mean of the log concentration/ titer transformations. Antibody concentrations/ titers below the cut-off of the assay were given an arbitrary value of half the cut-off for the purpose of GMC/GMT calculation
- The distribution of antibody concentrations/ titers was presented using reverse cumulative curves (RCC). For anti-HBsAg antibodies, seroprotection rates and GMC, with 95% CIs, were also computed according to whether subjects received a dose of hepatitis B vaccine or not before Dose 1 of routine vaccination at Visit 1.

Between groups analysis

For each antigen:

- The two-sided asymptotic standardized 95% CIs for the difference between group (co-ad group minus sep-ad group) in seropositivity/seroprotection rates, as applicable, were computed
- The 95% CIs of GMC/GMT ratios between groups (co-ad group divided by sep-ad group) were computed using an analysis of variance (ANOVA) model on the logarithm10 transformation of the concentrations/titers. The ANOVA model included the vaccine group as only fixed effect. For anti-HBsAg antibodies, the ANOVA included the previous hepatitis B vaccination status as an additional fixed effect
- The criteria for non-inferiority were only pre-specified for the response to routine vaccines

Analysis of Safety

Preliminary safety data on SAEs occurring in study Rota-060 from study initiation up to the data lock point of 23 April 2007 and recorded in the GSK SAE database is provided as a tabular summary. SAEs reported in clinical studies are also recorded in the clinical study database. The GSK SAE database and the clinical study database will undergo a final reconciliation upon completion of the Extended Safety Follow-up Phase.

➢ **Results**

Demography

The analysis was performed on the ATP Cohort for immunogenicity and on the TVC.

The demographic profiles of the two groups of subjects in the ATP Cohort for immunogenicity were comparable with respect to mean weight, mean height, gender and BMI at Visit 1. The mean age of the subjects in the co-ad group was 8.7 weeks at the time of the first dose of HRV vaccine and the routine infant vaccines and 17.4 weeks at the time of the second dose of HRV vaccine and the routine infant vaccines. The mean age of the subjects in the sep-ad group was 8.8 weeks at the time of the first dose of the routine vaccination and 17.6 weeks at the time of the second dose of the routine vaccination.The mean age of the subjects in the sep-ad group was 12.8 weeks at the time of the first dose of the HRV vaccine and 21.5 weeks at the time of the second dose of the HRV vaccine. The demographic characteristics were similar for the ATP Cohort for immunogenicity and the TVC.

Number of Subjects	Total	Co-ad group	Sep-ad group
Planned	480	240	240
Enrolled and vaccinated [Total Vaccinated Cohort (TVC)]	484	249	235
Completed Active Phase of the study up to Visit 6	417	223	194
According To Protocol (ATP) cohort for immunogenicity	317	180	137

Immunogenicity

Primary endpoints

- The co-ad group was statistically non-inferior to the sep-ad group in terms of seroprotection rates to anti-PRP, anti-HBsAg, anti-poliovirus types 1, 2 and 3, anti-diphtheria and anti-tetanus antibodies as the lower limits of the standardized asymptotic 95% CI for the treatment difference (co-ad group minus sep-ad group) were ≥ -10% (pre-specified clinical limit for non-inferiority).
- The co-ad group was statistically non-inferior to the sep-ad group in terms of GMCs to anti-PT, anti-FHA, anti-PRN antibodies and antibodies to each of the seven S. pneumoniae serotypes as the lower limits of the 95% CIs on the ratios of GMC (co-ad group divided by sep-ad group) were ≥0.67 for anti-PT, anti-FHA and anti-PRN antibody GMCs and ≥0.5 for each of the seven S. pneumoniae serotypes antibody GMCs (pre-specified clinical limits for non-inferiority).

Table 12: Difference between groups in seroprotection rates for anti-PRP, anti-HBsAg, anti-poliovirus 1, 2 and 3, anti-diphtheria and anti-tetanus antibodies one month post-Dose 3 of routine childhood vaccination (ATP Cohort for immunogenicity)

							Difference in seroprotection rate			
									95% CI	
Antibody	**Group**	**N**	**%**	**Group**	**N**	**%**	**Difference**	**%**	**LL**	**UL**
Anti-PRP	Co-Ad	180	89.4	Sep-Ad	137	88.3	**Co-Ad - Sep-Ad**	1.12	-5.81*	8.60
Anti-HBsAg	Co-Ad	169	100	Sep-Ad	126	100	**Co-Ad - Sep-Ad**	0.00	-2.22*	2.96
Anti-Poliovirus 1	Co-Ad	128	100	Sep-Ad	91	100	**Co-Ad - Sep-Ad**	0.00	-2.91*	4.05
Anti-Poliovirus 2	Co-Ad	139	100	Sep-Ad	95	97.9	**Co-Ad - Sep-Ad**	2.11	-0.62*	7.35
Anti-Poliovirus3	Co-Ad	146	100	Sep-Ad	105	100	**Co-Ad - Sep-Ad**	0.00	-2.56*	3.53
Anti-Diphtheria	Co-Ad	178	100	Sep-Ad	136	100	**Co-Ad - Sep-Ad**	0.00	-2.11*	2.75
Anti-Tetanus	Co-Ad	178	100	Sep-Ad	136	100	**Co-Ad - Sep-Ad**	0.00	-2.11*	2.75

Group Co-Ad = *Pediarix*, *Prevnar* and *ActHIB* at 2, 4 and 6 months of age and HRV vaccine co-administered at 2 and 4 months of age.
Group Sep-Ad = *Pediarix*, *Prevnar* and *ActHIB* at 2, 4 and 6 months of age and HRV vaccine administered separately at 3 and 5 months of age.
N = number of subjects with available results
% = percentage of subjects who are seroprotected one month after Dose 3 of routine childhood vaccination (Visit 6)
95% CI = asymptotic standardized 95% confidence interval; LL = lower limit; UL = upper limit
Seroprotection level for anti-PRP antibody = ≥1.0 µg/mL
Seroprotection level for anti-HBsAg antibody = ≥10 mIU/mL
Seroprotection level for anti-poliovirus serotypes 1, 2 and 3 antibodies = ≥1:8
Seroprotection level for anti-diphtheria and anti-tetanus antibodies = ≥0.1 IU/mL
*Lower limits of the 95% CI ≥--10% (the pre-specified clinical limit for non-inferiority)

Table 13: Ratio of GMCs for anti-PT, anti-FHA, anti-PRN and each of the seven S. pneumoniae serotypes antibodies between groups, one month post-Dose 3 of routine childhood vaccination (ATP Cohort for immunogenicity)

						GMC ratio				
									95 % CI	
Antibody	**Group**	**N**	**GMC**	**Group**	**N**	**GMC**	**Ratio order**	**Value**	**LL**	**UL**
Anti-PT	Co-Ad	179	58.9	Sep-Ad	137	60.9	**Co-Ad/Sep-Ad**	0.97	0.85*	1.10
Anti-FHA	Co-Ad	179	270.9	Sep-Ad	137	265.0	**Co-Ad/Sep-Ad**	1.02	0.89*	1.17
Anti-PRN	Co-Ad	179	105.7	Sep-Ad	137	118.6	**Co-Ad/Sep-Ad**	0.89	0.72*	1.10
Anti-PN 4	Co-Ad	178	1.96	Sep-Ad	136	2.19	**Co-Ad/Sep-Ad**	0.90	0.75**	1.07
Anti-PN 6B	Co-Ad	179	1.42	Sep-Ad	135	1.42	**Co-Ad/Sep-Ad**	1.00	0.75**	1.33
Anti-PN 9V	Co-Ad	179	2.60	Sep-Ad	136	2.65	**Co-Ad/Sep-Ad**	0.98	0.81**	1.19
Anti-PN 14	Co-Ad	180	4.84	Sep-Ad	136	5.35	**Co-Ad/Sep-Ad**	0.90	0.75**	1.09
Anti-PN 18C	Co-Ad	180	2.44	Sep-Ad	136	2.97	**Co-Ad/Sep-Ad**	0.82	0.68**	1.00
Anti-PN 19F	Co-Ad	180	1.99	Sep-Ad	137	1.92	**Co-Ad/Sep-Ad**	1.03	0.87**	1.23
Anti-PN 23F	Co-Ad	178	2.15	Sep-Ad	136	2.55	**Co-Ad/Sep-Ad**	0.84	0.67**	1.06

Group Co-Ad = *Pediarix*, *Prevnar* and *ActHIB* at 2, 4 and 6 months of age and HRV vaccine co-administered at 2 and 4 months of age.
Group Sep-Ad = *Pediarix*, *Prevnar* and *ActHIB* at 2, 4 and 6 months of age and HRV vaccine administered separately at 3 and 5 months of age.
N = number of subjects with available results
95% CI = 95% confidence interval for the GMC ratio (Anova model - pooled variance across the 2 groups);
LL = lower limit, UL = upper limit
*Lower limit of the 95% CI ≥0.67 (the pre-specified clinical limit for non-inferiority)
**Lower limit of the 95% CI ≥0.5 (the pre-specified clinical limit for non-inferiority)

Secondary endpoints

- Antibody response to HRV vaccine:
  - The seropositivity rate for anti-rotavirus IgA antibody at 3 months after Dose 2 of the HRV vaccine dose in the co-ad group was 78.8% [95% CI: 71.8%; 84.8%] and at 2 months after Dose 2 of the HRV vaccine dose in the sep-ad group was 86.0% [95% CI: 78.5%; 91.6%].
  - The anti-rotavirus IgA GMC was 110.0 U/mL [95% CI: 85.8; 141.1] at 3 months after Dose 2 of the HRV vaccine dose in the co-ad group and was 188.2 U/mL [95% CI: 139.6; 253.5] at 2 months after Dose 2 of the HRV vaccine dose in the sep-ad group.

- **Safety results**

Preliminary Safety Results up to the data lock point of 23 April 2007

No deaths were reported up to the data lock point. SAEs were reported by the investigators for 28 subjects up to the data lock point of 23 April 2007. Of these, 10 SAEs were reported within the 31-day post-vaccination period. All SAEs reported within 31 days of an HRV vaccine dose (either co-administered or given separately with the routine infant vaccines) were resolved. One subject in the sep-ad group withdrew due to an unrelated SAE (malignant brain neoplasm) from the Active Phase of the study. One case of intussusception was reported in study Rota-060 up to the data lock point of 23 April 2007. A 39-week old female subject from the sep-ad group experienced intussusception 90 days after the third dose of routine vaccines. The intussusception was reduced by surgery. The event resolved after 6 days.

Assessor's comment: *The final safety data was provided in the annex report of the Extended Safety Follow-up Phase. Please see further down this AR.*

➢ **Conclusions:**

- By meeting the pre-specified criteria for non-inferiority, study Rota-060 has demonstrated that co- administration of the HRV vaccine with licensed routine infant vaccines recommended in the US (Pediarix, Prevnar and ActHIB) does not negatively impact the immune response to any of the antigens (PRP, HBsAg, poliovirus serotypes 1, 2 and 3, diphtheria, tetanus, PT, FHA, PRN and S. pneumoniae serotypes 4, 6B, 9V, 14, 18C, 19F and 23F) that are currently included in the Centers for Disease Control and Prevention is schedule, Advisory Committee on Immunization Practices (ACIP), American Academy of Pediatrics (AAP) and in the American Academy of Family Physician (AAFP) schedules of recommended immunizations for infants in the US. The primary objective of this study was met.
- Two doses of the HRV vaccine (at least $10^{6.0}$ $CCID_{50}$ per dose) were immunogenic in US infants, with anti-rotavirus IgA seropositivity rates of 78.8% [95% CI: 71.8%; 84.8%] at 3 months after the 2nd HRV vaccine dose in the co-ad group and 86.0% [95% CI: 78.5%; 91.6%] at 2 months after the 2nd HRV vaccine dose in the sep-ad group.
- There are no clinical concerns raised based on the preliminary safety data from study Rota-060.

Assessor's comment: *Study 107531 sought to investigate the potential impact of Rotarix vaccination on the immunogenicity of routine infant vaccinations (as recommended in the US) when said vaccination was given concomitantly. The study design thus compromised two arms: one where HRV was given at the same time as the first two routine vaccinations and one were the two HRV administrations were done separately.*

Non-inferiority between the both study arms in respect to immune responses to the routine vaccinations was attained, and neither was HRV immunogenicity impacted due to co-administration.

Safety was to be assessed in a prolonged safety follow-up report, but preliminary data gathered in this trial did not point towards worrisome trends or issues of particular interest. Only one case of intussusception, which was dealt with by surgery, was reported in all of the groups.

From this trial it can be gathered that co-administration of HRV with routine child vaccinations, as done in the US, has no appreciable impact on the immunogenicity of either of the vaccines.

Study 107531 – Annex report: Extended Safety Follow-up Phase

- **General**

A phase III randomized multi-center study to assess the immunogenicity of three doses of Pediarix, Prevnar and ActHIB given to healthy infants at 2, 4 and 6 months of age when administered with GlaxoSmithKline (GSK) Biologicals two-dose oral live attenuated human rotavirus (HRV) vaccine given during the same vaccination visit (at 2 and 4 months of age) or given separately (at 3 and 5 months of age).

- **Objective(s)**

Safety:

To assess the safety of two doses of GSK Biologicals HRV vaccine given concomitantly or separately with routine infant vaccinations in terms of serious adverse events (SAEs) and specific adverse events (AEs) from Day 0 (i.e. Day of administration of Dose 1 of the routine infant vaccines) up to 5 months after the 3rd dose of Pediarix, Prevnar and ActHIB or within the 7 months following the last dose of Pediarix, Prevnar and ActHIB in case the 3rd dose is not given.

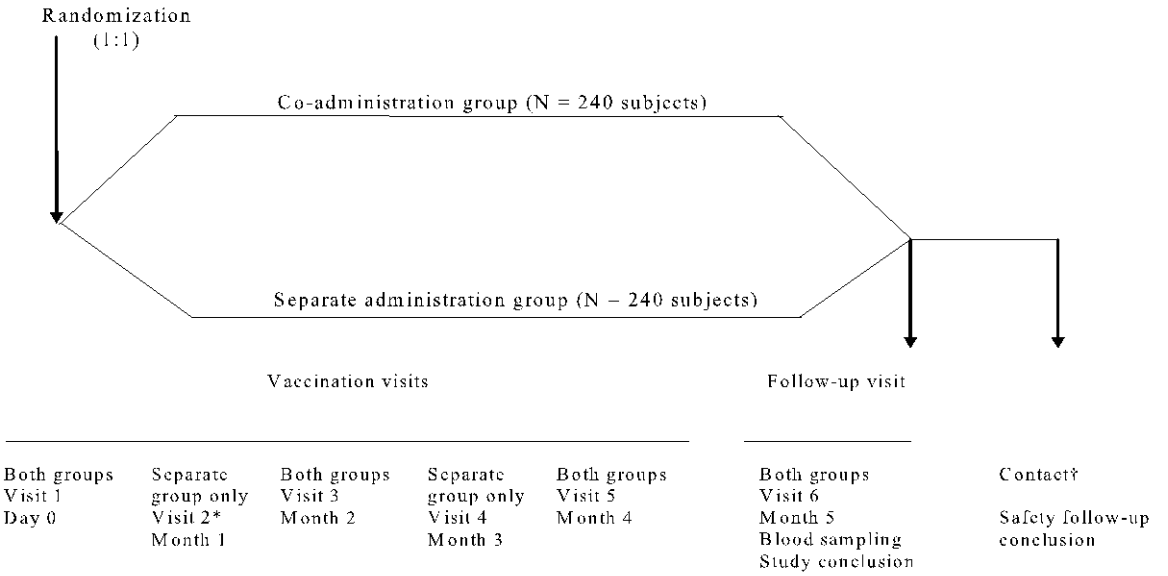
- **Study design**

Open-label, randomized (1:1), multi-center study with two parallel groups.

- Co-administration group (henceforth referred to as co-ad group) received Pediarix, Prevnar and ActHIB at 2, 4 and 6 months of age and HRV vaccine during the same vaccination visit at 2 and 4 months of age.
- Separate administration group (henceforth referred to as sep-ad group) received Pediarix, Prevnar and ActHIB at 2, 4 and 6 months of age and HRV vaccine separately at 3 and 5 months of age.

Fluzone vaccine was to be offered to subjects at 6 months (Visit 5) and 7 months (Visit 6) of age. Administration of this vaccine was optional at the investigator's and subject's parents/guardians discretion. Blood samples were to be drawn from all subjects at Visit 6. Safety was to be assessed in all subjects during the entire study period inclusive of the Extended Safety Follow-up Phase (from Day 0 up to 5 months after the 3rd dose of Pediarix, Prevnar and ActHIB or within 7 months following the last dose of Pediarix, Prevnar and ActHIB in case the 3rd dose was not given).

Active Phase included the period starting from Day 0 up to final study visit (Visit 6) for post-vaccination blood sampling at approximately one month after Dose 3 of the routine vaccines. Extended safety follow-up phase included the period starting from the day after Visit 6 up to the contact at Month 9.



N = number of subjects planned to be enrolled
*Visit 2 was to take place before 17 weeks of age
Subjects in both groups received a dose of *Pediarix, Prevnar* and *ActHIB* at Visit 1, Visit 3 and Visit 5
Subjects in the co-ad group received a dose of HRV vaccine at Visit 1 and Visit 3
Subjects in the sep-ad group received a dose of HRV vaccine at Visit 2 and Visit 4. †Contact (by telephone call or any other convenient procedure) 120 – 150 days after Visit 5 for safety follow-up.

- **Study population**

Inclusion criteria

Healthy infants between 6 and 12 weeks of age at the time of the first vaccination with written informed consent obtained from the parent or guardian of the subject, and those who had not received a previous dose of hepatitis B vaccine or those who had received only one dose of hepatitis B vaccine administered at least 30 days prior to enrolment were included in the study. All vaccinated subjects were to be followed for safety during the entire study period (Day 0 up to 5 months after the 3rd dose of Pediarix, Prevnar and ActHIB or within 7 months following the last dose of Pediarix, Prevnar and ActHIB in case the 3rd dose was not given).

- **Endpoints**

SAEs and specific AEs [new onset of chronic illness(es) that are not congenital anomalies (e.g. autoimmune disorders, asthma, type I diabetes and allergies) and conditions prompting ER visits] during the entire study period (from Day 0 up to 5 months after the 3rd dose of Pediarix, Prevnar and ActHIB or within the 7 months following the last dose of Pediarix, Prevnar and ActHIB in case the 3rd dose was not given).

- **Statistical Methods**

Analysis of Safety

The safety analysis was performed on the TVC (primary analysis) and on the ATP cohort for safety. Specific AEs and SAEs were analyzed separately. Specific AEs include only non-serious AEs.

- Percentage of subjects with specific AEs classified by Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term (PT) from Day 0 up to the last study contact of the extended safety follow-up phase was computed along with exact 95% confidence interval (CI). The same calculations were done for specific AEs with causal relationship to vaccination, for specific AEs rated as Grade 3, specific AEs leading to ER visit and specific AEs that did not result in an ER visit.
- Percentage of subjects reporting SAEs classified by MedDRA SOC and PT from Day 0 up to the last study contact of the extended safety follow-up was computed along with exact 95% CI.

- The percentage of subjects who took at least one concomitant medication by type, during the active phase of the study was tabulated with exact 95% CI for each group.

Exploratory comparisons between groups for the percentage of subjects reporting specific AEs (any intensity, related, grade 3, those leading to ER visit and those that did not result in an ER visit) and subjects reporting SAEs from Day 0 up to the last study contact of the extended safety follow-up were performed using two-sided asymptotic standardized 95% CIs for group difference and the two-sided asymptotic score test for the null hypothesis of identical incidence in both groups (significance level of alpha = 0.05).

P-values less than 0.05 were used as an aid to highlight potential imbalance between groups.

➢ **Results**

Demography

The analysis was performed on the TVC, which included 484 subjects who received at least one dose of the study vaccines (Pediarix, Prevnar, ActHIB and HRV vaccine). Of these 484 subjects, 25 subjects in the sep-ad group dropped out before Visit 2 without having received any HRV vaccine. Hence, only 459 subjects received at least one dose of the HRV vaccine.

Number of Subjects	Total	Co-ad group	Sep-ad group
Planned	480	240	240
Enrolled and vaccinated [Total Vaccinated Cohort (TVC)]	484	249	235
Completed Active Phase of the study (up to Visit 6)	417	223	194
According To Protocol (ATP) cohort for safety	423	214	209
ATP cohort for immunogenicity	317	180	137
Number of subjects completed the extended safety follow-up phase	432	227	205

- **Safety results**

Table 14 presents the percentage of subjects reporting AEs from Day 0 up to the last study contact.

Table 14: Percentage of subjects reporting adverse events from Day 0 up to the last study contact -TVC

	Co-ad N = 249				Sep-ad N = 235			
			95%CI				95%CI	
	n	%	LL	UL	n	%	LL	UL
Number of subjects with at least one specific# AE or SAE*	39	15.7	11.4	20.8	42	17.9	13.2	23.4
Number of subjects with at least one SAE	15	6.0	3.4	9.7	14	6.0	3.3	9.8
Number of subjects with at least one specific AE leading to ER visit (excluding SAE)	21	8.4	5.3	12.6	21	8.9	5.6	13.3
Number of subjects with at least one specific AE excluding SAE and ER visit	6	2.4	0.9	5.2	11**	4.7	2.4	8.2

N = Number of subjects with at least one administered dose; n (%) = number (percentage) of subjects reporting at least once the specified symptom; 95% CI = exact 95% confidence interval, LL = lower limit, UL = upper limit
*one subject may be counted in more than one category
#new onset of chronic illness(es) that are not congenital anomalies (e.g. autoimmune disorders, asthma, type I diabetes and allergies) and conditions prompting ER visits. Specific AEs include only non-serious AEs.
**One subject with missing information for the day of onset for the AE was not counted (Subject No: 807 in the sep-ad group experienced allergy for which medical advice was sought)

specific AE incidences:

- The percentage of subjects with at least one specific AE from Day 0 up to the last study contact was similar in both groups (10.8% in the co-ad group and 12.8% in the sep-ad group) (p-value = 0.512).
- A potential imbalance between groups was noted for only one specific AE 'Gastroesophageal reflux' (5 subjects (2.1%) in the sep-ad group and none in the co-ad group) (p-value = 0.021). None of the cases were considered by the investigator to be related to vaccination. One case

resulted in an ER visit. None of the subjects had a prior medical history of 'Gastroesophageal reflux'. This potential imbalance is likely due to a chance observation.

- The percentage of subjects with at least one specific AE leading to ER visit from Day 0 up to the last study contact was 8.4% in the co-ad group and 8.9% in the sep-ad group (p-value = 0.844).
- The percentage of subjects with at least one specific AE not leading to an ER visit from Day 0 up to the last study contact was 2.4% in the co-ad group and 4.7% in the sep-ad group (p-value = 0.175)
- One subject in the sep-ad group reported a specific AE (pyrexia) that was assessed as related to vaccination. This subject experienced pyrexia one day after receiving the first dose of the routine infant vaccines. The duration of this AE was two days and the subject recovered.

SAE incidences:

- From Day 0 up to the last study contact, at least one SAE was reported by 15 (6.0%) subjects in the co-ad group and 14 (6.0%) subjects in the sep-ad group (p-value = 0.975).
- When SAEs were classified by MedDRA SOC and PT, no potential imbalance between groups were noted for any of the SAEs reported during the entire study period (p-value >0.05 for all comparisons).
- One subject in the co-ad group experienced rotavirus gastroenteritis 108 days after the third dose of routine infant vaccines. This subject was hospitalized and laboratory demonstrated rotavirus antigen in stool (serotype not investigated). This SAE resolved and was not considered by the investigator to be causally related to vaccination.
- All subjects recovered from the SAEs except one subject in the sep-ad group with malignant brain neoplasm. This SAE was not considered to be causally related to vaccination by the investigator. This subject was withdrawn from the study before receiving any dose of the HRV vaccine.
- One case of intussusception was reported during the study. A 39-week old female subject (n° 92) from the sep-ad group experienced intussusception 90 days after the third dose of routine vaccines (125 days after the second dose of HRV vaccine). The intussusception was reduced by surgery. The event resolved after 6 days.
- One SAE ('Fever' with PT 'Viral Infection') was considered by the investigator to be causally related to vaccination. The subject in the co-ad group developed fever 9 days after receiving the first dose of the HRV vaccine co-administered with routine infant vaccines and was hospitalized. The fever lasted for 3 days and the subject recovered.
- There were no fatal events reported in this study.

Withdrawals due to adverse events/serious adverse events:

Withdrawals due to AE/SAE were assessed only during the active phase of the study. The parents/guardians of subject number 50 in the sep-ad group withdrew their child from the study after administration of the routine vaccinations at Visit 1 due to an unrelated SAE (atypical rhabdoid tumor). This subject did not receive any dose of the HRV vaccine. This SAE was not considered by the investigator to be causally related to vaccination.

➢ **Conclusions:**

- Two doses of the HRV vaccine, when co-administered with licensed routine infant vaccines recommended in the US (Pediarix, Prevnar and ActHIB) or given separately, have a similar safety profile.
- There are no clinical concerns raised based on the available safety data.

> ***Assessor's comment:*** *The extended safety follow-up of Study 107531 included all patients whom were vaccinated in the active phase of the study, and was meant to investigate the safety of HRV vaccination in combination with routine (US) childhood vaccinations, whether administered concomitantly or separately.*
>
> *The data gathered in this follow-up showed that the safety profile between both groups (concomitant versus separate administration) was similar, and that no administration-specific safety signals were detectable. It is agreed with the MAH that none of the observations made in this safety follow-up are a reason for concern.*

III. OVERALL DISCUSSION ON CLINICAL ASPECTS

The four Rotarix studies (+ extended safety follow-up annex) submitted in the framework of the P45 resolution aimed to a) compare the vaccine's immunogenicity and safety compared to placebo with or without routine pediatric co-vaccines in children aged from 6 weeks to 12 weeks of age and b) investigate non-inferiority and non-negative-impact bearing of concomitant vaccination with OPV and vaccines used within the US routine pediatric vaccination schedule.

All study outcomes confirmed the good immunogenicity and safety profiles of the Rotarix vaccine in the study populations, and it was clearly established that concomitant vaccination within the routine pediatric vaccination schedule did not bring about any negative effects on these or the other vaccine's established immunogenicity and safety profiles.

No new issues that would warrant regulatory actions were found to exist in any of the study results provided, and results were in agreement with the already established knowledge on Rotarix safety and immunogenicity.

This submission is thus hereby considered fulfilled.

IV. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

➢ **Overall conclusion**

This submission is considered fulfilled, and no further regulatory action is required.

➢ **Recommendation**

☒ **Fulfilled –**

No further action required

☐ **Not fulfilled:**

V. ADDITIONAL CLARIFICATIONS REQUESTED

Not applicable