The study listed may include approved and non-approved uses, formulations or treatment regimens. The results reported in any single study may not reflect the overall results obtained on studies of a product. Before prescribing any product mentioned in this Register, healthcare professionals should consult prescribing information for the product approved in their country.

Study No.: 104480 (Rota-048)

Title: A phase II, double-blind, randomized, placebo controlled study to compare the immunogenicity, reactogenicity and safety of two different formulations of GlaxoSmithKline (GSK) Biologicals' live attenuated human rotavirus (HRV) vaccine given as a two-dose primary vaccination in healthy infants previously uninfected with HRV.

Rationale: The aim of this study was to evaluate the immunogenicity and safety of the liquid formulation of the HRV vaccine compared to the lyophilized formulation of the HRV vaccine.

Phase: II

Study Period: 16 August 2005 to 10 November 2005

Study Design: Double-blind, randomized (4:1:4:1), multi-center study with 4 parallel groups. The study was conducted in a double-blind manner for each HRV vaccine formulation and its respective placebo. Blinding between the 2 different formulations was technically not possible.

Centers: 5 centers in Finland.

Indication: Immunization of healthy infants against HRV disease.

Treatment: The study groups were as follows:

- HRV_LIQ Group: subjects received 2 doses of the liquid formulation of the HRV vaccine
- Pl_LIQ Group: subjects received 2 doses of placebo for liquid formulation
- HRV_LYO Group: subjects received 2 doses of the lyophilized formulation of the HRV vaccine
- Pl_LYO Group : subjects received 2 doses of placebo for lyophilized formulation

All vaccines were administered as an oral dose according to a 0, 1 month schedule. Subjects were 6-12 weeks of age at the time of the first vaccination.
For the analyses, Group Pl_LIQ and Group Pl_LYO were pooled into Placebo Group.
Note: Visits 1, 2 and 3 correspond to Day 0, Month 1 and Month 2 in the schedule.

Objectives: To assess immunogenicity of the liquid formulation of the HRV vaccine compared to the lyophilized formulation of the HRV vaccine, in terms of vaccine take on combined doses.

Primary Outcome/Efficacy Variable:
Percentage of subjects with vaccine take on combined doses.
Vaccine take was defined as appearance of serum Immunoglobulin A (IgA) to rotavirus (RV) in post-vaccination sera at a concentration of $\geq$ 20 U/mL and/or presence of vaccine virus in any stool sample collected from Dose 1 (i.e. Visit 1) to Visit 3 in subjects who were negative for RV before Dose 1.

Secondary Outcome/Efficacy Variable(s):
Immunogenicity:

- Percentage of subjects who seroconverted for anti-RV IgA at each visit. Seroconversion was defined as the appearance of anti-RV IgA antibody concentration $\geq$ 20 U/mL in subjects initially (i.e. prior to the first dose of HRV vaccine or placebo) negative for anti-RV IgA antibody.
- Serum anti-RV IgA antibody concentration at each visit.

Safety:

- For each type of solicited symptoms, occurrence of the symptom within the 15-day (Day 0-14) solicited follow-up period after each dose.
- Occurrence of unsolicited adverse events (AEs) within 31 days (Day 0–30) after any dose according to Medical Dictionary for Regulatory Activities (MedDRA) classification.
- Occurrence of serious adverse events (SAEs) throughout the study period.

Statistical Methods:
The analyses were performed on the According-To-Protocol (ATP) cohort for immunogenicity and the Total Vaccinated cohort.

- The Total Vaccinated cohort included all subjects with at least one vaccine administration documented.
- The ATP cohort for immunogenicity included all subjects
  - who had received at least one dose of study vaccine according to their random assignment,
  - for whom the HRV vaccine or placebo was administered according to protocol (subjects who regurgitated after vaccination were eliminated for this reason),
  - who had not received a replacement vial, except if the appropriate vaccine was administered in "double-blind

replacement",
- for whom the randomization code had not been broken,
- who had not received a vaccine forbidden by or not specified in the protocol,
- who were negative for RV on the day of Dose 1,
- who had not received medication forbidden by the protocol,
- whose underlying medical condition was not forbidden by the protocol,
- with no protocol violation of demographics (unknown age at study entry or outside protocol defined age-interval),
- who complied with vaccination schedule for HRV vaccine or placebo,
- who complied with blood sampling schedule,
- for whom immunogenicity data were available at pre-vaccination time point and at least one post-sampling time point,
- who had no RV other than vaccine strain in gastroenteritis (GE) stool samples collected up to Visit 3,
- who had no concomitant infection unrelated to the vaccine which might influence the immune response.

Analysis of immunogenicity:

The analysis was performed on the ATP cohort for immunogenicity.

The asymptotic standardized 95% confidence interval (CI) for treatment (vaccination) difference between liquid formulation as compared to the lyophilized formulation was computed for the percentage of subjects with vaccine take on the combined doses. A statistically significant decrease would be detected when the p-value was less than 0.05 (one-sided asymptotic standardized test).

For each group, the percentage of subjects with vaccine take after combined doses was calculated with exact 95% CI. At each time point that anti-RV IgA antibodies were measured, seroconversion rates with exact 95% CI and geometric mean concentrations (GMCs) with 95% CI were tabulated for each group.

Analysis of safety:

The analysis was performed on the Total Vaccinated cohort.

For each group, the percentages of subjects with specific solicited symptoms over the 15-day solicited follow-up period (Day 0-14) were calculated with exact 95% CI. The same calculations were done for solicited symptoms rated as grade 3 in intensity and for solicited symptoms assessed as related to vaccination.

For each group, the percentage of subjects with unsolicited AEs during the 31-day follow-up period (Day 0-30) after each vaccination was tabulated according to the MedDRA preferred terms. The occurrence of SAEs during the entire study period was tabulated for each group, according to the MedDRA preferred terms.

Study Population: Male or female infants between, and including, 6 and 12 weeks (42-90 days) of age at the time of the first vaccination, born after a gestation period of 36 to 42 weeks, free of obvious health problems as established by medical history and clinical examination prior to study entry and for whom the investigator believed that their parent(s)/guardian(s) complied with the requirements of the protocol. Written informed consent was obtained from the parent(s)/guardian(s) of each subject before study entry. Subjects with any clinically significant history of chronic gastrointestinal disease including any uncorrected congenital malformation of the gastrointestinal tract or other serious medical condition as determined by the investigator and previously confirmed occurrence of rotavirus GE were excluded.

Number of subjects	HRV_LYO Group	HRV_LIQ Group	Placebo Group
Planned, N	100	100	50
Randomized, N (Total Vaccinated Cohort)	100	100	50
Completed, n (%)	99 (99.0)	96 (96.0)	49 (98.0)
Total Number Subjects Withdrawn, n (%)	1 (1.0)	4 (4.0)	1 (2.0)
Withdrawn due to Adverse Events, n (%)	1 (1.0)	0 (0.0)	0 (0.0)
Withdrawn due to Lack of Efficacy, n (%)	Not applicable	Not applicable	Not applicable
Withdrawn for other reasons, n (%)	0 (0.0)	4 (4.0)	1 (2.0)
Demographics	HRV_LYO Group	HRV_LIQ Group	Placebo Group
N (Total Vaccinated Cohort)	100	100	50
Females:Males	59:41	49:51	23:27
Mean Age, weeks (SD)	9.0 (1.95)	9.3 (1.87)	9.3 (2.04)
White/Caucasian, n (%)	100 (100)	97 (97.0)	49 (98.0)

Primary Efficacy Results:

Difference in percentage of subjects with vaccine take on combined Doses 1 and 2 between HRV_LYO and HRV_LIQ groups (ATP cohort for immunogenicity)

Group	N	%	Group	N	%	Difference in vaccine take rate				P-value
						Group Difference	%	95% CI		
								LL	UL	
HRV_LYO	94	89.4	HRV_LIQ	91	93.4	HRV_LYO minus HRV_LIQ	-4.04	-12.80	4.42	0.836

N = number of subjects with available anti-RV IgA antibody result at Visit 3, or who seroconverted at Visit 2, or with vaccine virus* in stools collected after Visit 1 to Visit 3
% = percentage of subjects who seroconverted at Visit 2 or 3, or with vaccine virus* in stools collected after Visit 1 to Visit 3
95% CI = asymptotic standardized 95% confidence interval; LL = Lower Limit; UL = Upper Limit
*RV in stools collected at pre-determined time points or vaccine virus in stools collected in case of GE episode

Primary Efficacy Results:
Percentage of subjects with vaccine take on combined Doses 1 and 2 at Visit 3 (ATP cohort for immunogenicity)

Group	Vaccine take on combined Doses 1 and 2 at Visit 3				
	N	n	%	95% CI	
				LL	UL
HRV_LYO	94	84	89.4	81.3	94.8
HRV_LIQ	91	85	93.4	86.2	97.5
Placebo	44	0	0.0	0.0	8.0

N = number of subjects with available anti-RV IgA antibody result at Visit 3, or who seroconverted at Visit 2, or with vaccine virus* in stools collected after Visit 1 to Visit 3
n (%) = number (percentage) of subjects who seroconverted at Visits 2 or 3, or with vaccine virus* in stools collected after Visit 1 to Visit 3
95% CI = exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit
*RV in stools collected at pre-determined time points or vaccine virus in stools collected in case of GE episode

Secondary Outcome Variable (s):
Anti-rotavirus IgA antibody GMC and seroconversion rates (ATP cohort for immunogenicity)

Group	Timing	N	≥ 20 U/mL				GMC (U/mL)		
			n	%	95% CI		Value	95% CI	
					LL	UL		LL	UL
HRV_LYO	PRE	94	0	0.0	0.0	3.8	<20	-	-
	PI(M1)	92	66	71.7	61.4	80.6	203.5	129.3	320.5
	PII(M2)	86	72	83.7	74.2	90.8	360.6	236.4	549.8
HRV_LIQ	PRE	93	0	0.0	0.0	3.9	<20	-	-
	PI(M1)	84	64	76.2	65.7	84.8	176.3	113.7	273.3
	PII(M2)	80	72	90.0	81.2	95.6	301.3	205.4	442.0
Placebo	PRE	46	0	0.0	0.0	7.7	<20	-	-
	PI(M1)	42	0	0.0	0.0	8.4	<20	-	-
	PII(M2)	44	0	0.0	0.0	8.0	<20	-	-

N = number of subjects with available results
n (%) = number (percentage) of subjects with antibody concentration above the cut-off
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PRE = pre-vaccination
PI(M1) = blood sampling time point; one month after the first dose (Visit 2)
PII(M2) = blood sampling time point; one month after the second dose (Visit 3)

Secondary Outcome Variable (s):
Percentage of subjects with each solicited general symptom included those graded “3” in intensity and those considered to be related to vaccination, during the solicited 15-day (Day 0-14) follow-up period, for each and any dose (Total Vaccinated cohort)

Symptom	Intensity/ relationship	HRV_LYO Group				HRV_LIQ Group				Placebo Group			
		n	%	95% CI		n	%	95% CI		n	%	95% CI	
				LL	UL			LL	UL			LL	UL
		Dose 1											
		N=100				N=100				N=50			
Cough/ runny nose	Any	36	36.0	26.6	46.2	33	33.0	23.9	43.1	20	40.0	26.4	54.8
	Grade 3	2	2.0	0.2	7.0	0	0.0	0.0	3.6	0	0.0	0.0	7.1
	Related	5	5.0	1.6	11.3	3	3.0	0.6	8.5	2	4.0	0.5	13.7

Diarrhea	Any	7	7.0	2.9	13.9	3	3.0	0.6	8.5	2	4.0	0.5	13.7
	Grade 3	2	2.0	0.2	7.0	0	0.0	0.0	3.6	1	2.0	0.1	10.6
	Related	5	5.0	1.6	11.3	3	3.0	0.6	8.5	1	2.0	0.1	10.6
Fever (rectally)	≥ 38.0°C	3	3.0	0.6	8.5	6	6.0	2.2	12.6	1	2.0	0.1	10.6
	> 39.5°C	0	0.0	0.0	3.6	0	0.0	0.0	3.6	0	0.0	0.0	7.1
	Related	2	2.0	0.2	7.0	3	3.0	0.6	8.5	0	0.0	0.0	7.1
Irritability	Any	69	69.0	59.0	77.9	69	69.0	59.0	77.9	35	70.0	55.4	82.1
	Grade 3	7	7.0	2.9	13.9	5	5.0	1.6	11.3	0	0.0	0.0	7.1
	Related	52	52.0	41.8	62.1	52	52.0	41.8	62.1	21	42.0	28.2	56.8
Loss of appetite	Any	21	21.0	13.5	30.3	20	20.0	12.7	29.2	11	22.0	11.5	36.0
	Grade 3	0	0.0	0.0	3.6	0	0.0	0.0	3.6	0	0.0	0.0	7.1
	Related	15	15.0	8.6	23.5	11	11.0	5.6	18.8	7	14.0	5.8	26.7
Vomiting	Any	24	24.0	16.0	33.6	15	15.0	8.6	23.5	7	14.0	5.8	26.7
	Grade 3	6	6.0	2.2	12.6	1	1.0	0.0	5.4	1	2.0	0.1	10.6
	Related	16	16.0	9.4	24.7	11	11.0	5.6	18.8	3	6.0	1.3	16.5
		Dose 2											
		N=99				N=97				N=49			
Cough/ runny nose	Any	35	35.4	26.0	45.6	44	45.4	35.2	55.8	19	38.8	25.2	53.8
	Grade 3	0	0.0	0.0	3.7	1	1.0	0.0	5.6	0	0.0	0.0	7.3
	Related	5	5.1	1.7	11.4	5	5.2	1.7	11.6	1	2.0	0.1	10.9
Diarrhea	Any	4	4.0	1.1	10.0	1	1.0	0.0	5.6	2	4.1	0.5	14.0
	Grade 3	1	1.0	0.0	5.5	0	0.0	0.0	3.7	0	0.0	0.0	7.3
	Related	4	4.0	1.1	10.0	1	1.0	0.0	5.6	0	0.0	0.0	7.3
Fever (rectally)	≥ 38.0°C	4	4.0	1.1	10.0	6	6.2	2.3	13.0	3	6.1	1.3	16.9
	> 39.5°C	0	0.0	0.0	3.7	0	0.0	0.0	3.7	0	0.0	0.0	7.3
	Related	2	2.0	0.2	7.1	5	5.2	1.7	11.6	0	0.0	0.0	7.3
Irritability	Any	59	59.6	49.3	69.3	64	66.0	55.7	75.3	28	57.1	42.2	71.2
	Grade 3	3	3.0	0.6	8.6	7	7.2	3.0	14.3	0	0.0	0.0	7.3
	Related	41	41.4	31.6	51.8	42	43.3	33.3	53.7	14	28.6	16.6	43.3
Loss of appetite	Any	19	19.2	12.0	28.3	18	18.6	11.4	27.7	11	22.4	11.8	36.6
	Grade 3	0	0.0	0.0	3.7	0	0.0	0.0	3.7	0	0.0	0.0	7.3
	Related	12	12.1	6.4	20.2	9	9.3	4.3	16.9	5	10.2	3.4	22.2
Vomiting	Any	18	18.2	11.1	27.2	13	13.4	7.3	21.8	6	12.2	4.6	24.8
	Grade 3	4	4.0	1.1	10.0	2	2.1	0.3	7.3	1	2.0	0.1	10.9
	Related	9	9.1	4.2	16.6	6	6.2	2.3	13.0	1	2.0	0.1	10.9
		Across doses											
		N=100				N=100				N=50			
Cough/ runny nose	Any	55	55.0	44.7	65.0	58	58.0	47.7	67.8	29	58.0	43.2	71.8
	Grade 3	2	2.0	0.2	7.0	1	1.0	0.0	5.4	0	0.0	0.0	7.1
	Related	8	8.0	3.5	15.2	7	7.0	2.9	13.9	3	6.0	1.3	16.5
Diarrhea	Any	9	9.0	4.2	16.4	4	4.0	1.1	9.9	4	8.0	2.2	19.2
	Grade 3	3	3.0	0.6	8.5	0	0.0	0.0	3.6	1	2.0	0.1	10.6
	Related	8	8.0	3.5	15.2	4	4.0	1.1	9.9	1	2.0	0.1	10.6
Fever (rectally)	≥ 38.0°C	7	7.0	2.9	13.9	11	11.0	5.6	18.8	4	8.0	2.2	19.2
	> 39.5°C	0	0.0	0.0	3.6	0	0.0	0.0	3.6	0	0.0	0.0	7.1
	Related	4	4.0	1.1	9.9	8	8.0	3.5	15.2	0	0.0	0.0	7.1
Irritability	Any	79	79.0	69.7	86.5	82	82.0	73.1	89.0	39	78.0	64.0	88.5
	Grade 3	10	10.0	4.9	17.6	11	11.0	5.6	18.8	0	0.0	0.0	7.1
	Related	64	64.0	53.8	73.4	64	64.0	53.8	73.4	26	52.0	37.4	66.3
Loss of appetite	Any	30	30.0	21.2	40.0	33	33.0	23.9	43.1	18	36.0	22.9	50.8
	Grade 3	0	0.0	0.0	3.6	0	0.0	0.0	3.6	0	0.0	0.0	7.1
	Related	24	24.0	16.0	33.6	18	18.0	11.0	26.9	11	22.0	11.5	36.0
Vomiting	Any	28	28.0	19.5	37.9	20	20.0	12.7	29.2	10	20.0	10.0	33.7
	Grade 3	8	8.0	3.5	15.2	3	3.0	0.6	8.5	1	2.0	0.1	10.6
	Related	19	19.0	11.8	28.1	13	13.0	7.1	21.2	4	8.0	2.2	19.2

N : number of subjects with a documented dose
n (%): number (percentage) of subjects for whom the specified symptom was reported at least once
Any: any occurrence of the specified symptom irrespective of intensity grade and relationship to vaccination
Any Diarrhea: ≥ 3 looser than normal stools/day
Any Vomiting: ≥ 1 episode of vomiting/day
Grade 3 Irritability: crying that could not be comforted/ prevented normal activity
Grade 3 Cough/runny nose: cough/runny nose which prevented daily activity
Grade 3 Loss of appetite: not eating at all
Grade 3 Diarrhea: ≥ 6 looser than normal stools/day
Grade 3 Vomiting: ≥ 3 episodes of vomiting/day
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

Safety Results: Number (%) of subjects with unsolicited adverse events (Total Vaccinated cohort)

Most Frequent Adverse Events - On-Therapy- (occurring within Day 0-30 following vaccination)	HRV_LYO Group N = 100	HRV_LIQ Group N = 100	Placebo Group N = 50
Subjects with any AE(s), n (%)	53 (53.0)	58 (58.0)	28 (56.0)
Rhinitis	13 (13.0)	14 (14.0)	6 (12.0)
Conjunctivitis	6 (6.0)	10 (10.0)	7 (14.0)
Cough	6 (6.0)	9 (9.0)	3 (6.0)
Pyrexia	7 (7.0)	6 (6.0)	4 (8.0)
Upper respiratory tract infection	4 (4.0)	8 (8.0)	3 (6.0)
Irritability	4 (4.0)	8 (8.0)	1 (2.0)
Otitis media	5 (5.0)	5 (5.0)	2 (4.0)
Nasal congestion	3 (3.0)	4 (4.0)	1 (2.0)
Constipation	2 (2.0)	1 (1.0)	3 (6.0)
Eye infection	4 (4.0)	1 (1.0)	1 (2.0)
Gastroenteritis	2 (2.0)	2 (2.0)	2 (4.0)
Regurgitation of food	1 (1.0)	5 (5.0)	0 (0.0)
Crying	3 (3.0)	2 (2.0)	0 (0.0)
Flatulence	2 (2.0)	2 (2.0)	1 (2.0)
Gastrointestinal disorder	1 (1.0)	3 (3.0)	0 (0.0)
Rash	4 (4.0)	0 (0.0)	0 (0.0)
Dermatitis atopic	1 (1.0)	1 (1.0)	1 (2.0)
Fatigue	1 (1.0)	1 (1.0)	1 (2.0)
Rhinorrhea	0 (0.0)	1 (1.0)	2 (4.0)
Teething	2 (2.0)	0 (0.0)	1 (2.0)
Dermatitis diaper	1 (1.0)	0 (0.0)	1 (2.0)
Restlessness	0 (0.0)	1 (1.0)	1 (2.0)
Vomiting	1 (1.0)	0 (0.0)	1 (2.0)
Bronchitis	0 (0.0)	0 (0.0)	1 (2.0)
Eczema	0 (0.0)	0 (0.0)	1 (2.0)

Safety Results: Number (%) of subjects with Serious Adverse Events (SAEs) (Total Vaccinated cohort)

Serious adverse event, n (%) [n considered by the investigator to be related to study medication]

All SAEs	HRV_LYO Group N = 100	HRV_LIQ Group N = 100	Placebo Group N = 50
Subjects with any SAE(s), n (%) [n related]	1 (1.0) [0]	2 (2.0) [0]	0 (0.0) [0]
Otitis media	1 (1.0) [0]	1 (1.0) [0]	0 (0.0) [0]
Respiratory tract infection	1 (1.0) [0]	1 (1.0) [0]	0 (0.0) [0]
Bronchiolitis	0 (0.0) [0]	1 (1.0) [0]	0 (0.0) [0]
Fatal SAEs	**HRV_LYO Group N = 100**	**HRV_LIQ Group N = 100**	**Placebo Group N = 50**
Subjects with fatal SAE(s), n (%) [n related]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]

Conclusion: One month after Dose 2, the percentages of subjects with vaccine take on combined doses were 89.4%, 93.4% and 0.0% in the HRV_LYO, HRV_LIQ and Placebo groups, respectively. At the same time point, 83.7%, 90.0%

and 0.0% of subjects had anti-RV IgA antibody concentrations ≥ 20 U/mL in the HRV_LYO, HRV_LIQ and Placebo groups, respectively. Across doses and groups, irritability was the most frequently reported solicited general symptom. Unsolicited AEs were reported for 53 (53.0%), 58 (58.0%) and 28 (56.0%) subjects in the HRV_LYO, HRV_LIQ and Placebo group, respectively. SAEs were reported for 1 (1.0%) subject in the HRV_LYO Group and for 2 (2.0%) subjects in the HRV_LIQ Group. None of these SAEs were considered by the investigators to be related to the study vaccination. No fatal SAEs were reported during the course of the study.
Please refer also to the publication section.

Date updated: 12-December-2013