Clinical trial results:
A phase III, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy and safety of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants.

Summary

EudraCT number	2015-001541-92
Trial protocol	Outside EU/EEA
Global end of trial date	07 July 2008

Results information

Result version number	v1
This version publication date	13 April 2016
First version publication date	02 August 2015

Trial information

Trial identification

Sponsor protocol code	444563/028/029/030,107070,72,76

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00329745
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	GlaxoSmithKline Biologicals
Sponsor organisation address	Rue de l'Institut 89, Rixensart, Belgium, B-1330
Public contact	Clinical Trails Call Center, GlaxoSmithKline Biologicals, 44 2089904466, GSKClinicalSupportHD@gsk.com
Scientific contact	Clinical Trails Call Center, GlaxoSmithKline Biologicals, 44 2089904466, GSKClinicalSupportHD@gsk.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	19 January 2009
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 July 2008
Global end of trial reached?	Yes
Global end of trial date	07 July 2008
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

•In all subjects, to determine if two doses of GSK Biologicals' HRV vaccine given concomitantly with routine vaccinations* can prevent severe rotavirus gastroenteritis (RV GE) caused by the circulating wild-type RV strains during the period starting from 2 weeks after Dose 2 until 2 years of age.
(*Whenever Oral Polio Vaccination (OPV) is used a minimum 2-week interval should be observed between HRV vaccine and OPV doses.)
•In all subjects, to assess the safety of HRV vaccine with respect to definite intussusception (IS) within 31 days (Day 0-Day 30) after each HRV vaccine dose.

Protection of trial subjects:

All subjects were supervised closely for at least 30 minutes following vaccination with appropriate medical treatment readily available. Vaccines were administered by qualified and trained personnel. Vaccines were administered only to eligible subjects that had no contraindications to any components of the vaccines. Subjects were followed-up from the time the subject consents to participate in the study until she/he is discharged.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	08 December 2003
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Hong Kong: 2954
Country: Number of subjects enrolled	Taiwan: 1084
Country: Number of subjects enrolled	Singapore: 4649
Worldwide total number of subjects	8687
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23	8687

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

During the screening the following steps occurred: check for inclusion/exclusion criteria, contraindications/precautions, medical history of the subjects and signing informed consent forms.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer

Arms

Are arms mutually exclusive?	Yes
Arm title	Rotarix Group

Arm description:

During the primary study (NCT00197210) subjects received two oral doses of Rotarix™ vaccine.

Arm type	Experimental
Investigational medicinal product name	Rotarix™
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Oral use

Dosage and administration details:

Oral administration, 2 doses

Arm title	Placebo Group

Arm description:

During the primary study (NCT00197210) subjects received two oral doses of placebo.

Arm type	Active comparator
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Oral use

Dosage and administration details:

Oral administration, 2 doses

Number of subjects in period 1	Rotarix Group	Placebo Group
Started	4359	4328
Completed	4272	4226
Not completed	87	102
Consent withdrawn by subject	-	1
Migrated/moved from study area	1	4
Lost to follow-up	85	97
Protocol deviation	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Rotarix Group
Reporting group description:	
During the primary study (NCT00197210) subjects received two oral doses of Rotarix™ vaccine.	
Reporting group title	Placebo Group
Reporting group description:	
During the primary study (NCT00197210) subjects received two oral doses of placebo.	

Reporting group values	Rotarix Group	Placebo Group	Total
Number of subjects	4359	4328	8687
Age categorical			
Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Units: months			
arithmetic mean	35.4	35.4	
standard deviation	± 1.18	± 1.26	-
Gender categorical			
Units: Subjects			
Female	2108	2097	4205
Male	2251	2231	4482

End points

End points reporting groups

Reporting group title	Rotarix Group
Reporting group description:	
During the primary study (NCT00197210) subjects received two oral doses of Rotarix™ vaccine.	
Reporting group title	Placebo Group
Reporting group description:	
During the primary study (NCT00197210) subjects received two oral doses of placebo.	

Primary: Number of subjects with severe rotavirus gastroenteritis (RV GE) caused by the circulating wild-type rotavirus strains

End point title	Number of subjects with severe rotavirus gastroenteritis (RV GE) caused by the circulating wild-type rotavirus strains[1]
End point description:	
Severe RV GE is an episode of severe GE in which rotavirus other than vaccine strain was identified in a GE stool sample. Note that this outcome measure is secondary in the study protocol. We have reported it here as primary outcome measure, since none of the primary outcome measures in the study protocol pertain to the time point (Year 3 follow-up) presented in this summary.	
End point type	Primary
End point timeframe:	
From Year 2 up to Year 3	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The analysis of the primary endpoint was descriptive i.e. no statistical hypothesis test was performed.

End point values	Rotarix Group	Placebo Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4222	4185		
Units: Subjects				
Severe rotavirus gastroenteritis (RV GE)	0	13		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reporting serious adverse events (SAEs)

End point title	Number of subjects reporting serious adverse events (SAEs)
End point description:	
An SAE is any untoward medical occurrence that: results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in disability/incapacity, is a congenital anomaly/birth defect in the offspring of a study subject, or may evolve into one of the outcomes listed above.	
End point type	Secondary
End point timeframe:	
From the end of the primary study up to Year 3	

End point values	Rotarix Group	Placebo Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4359	4328		
Units: Subjects				
SAEs	10	11		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

The occurrence of reported AEs (all/related) was not available and is encoded as equal to the number of subjects affected.

Adverse event reporting additional description:

Adverse events were not systematically followed up in this study. Only the adverse events (and serious adverse events) leading to subject withdrawal or drop-out were collected.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	11.1

Reporting groups

Reporting group title	Rotarix Group

Reporting group description:

During the primary study (NCT00197210) subjects received two oral doses of Rotarix™ vaccine.

Reporting group title	Placebo Group

Reporting group description:

During the primary study (NCT00197210) subjects received two oral doses of placebo.

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: No non-serious adverse events were reported during the course of the study as per the protocol.

Serious adverse events	Rotarix Group	Placebo Group	
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 4359 (0.23%)	11 / 4328 (0.25%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Burns third degree			
subjects affected / exposed	1 / 4359 (0.02%)	0 / 4328 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Croup infectious			
subjects affected / exposed	0 / 4359 (0.00%)	1 / 4328 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overdose			

subjects affected / exposed	0 / 4359 (0.00%)	1 / 4328 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Febrile convulsion			
subjects affected / exposed	1 / 4359 (0.02%)	0 / 4328 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Idiopathic thrombocytopenic purpura			
subjects affected / exposed	0 / 4359 (0.00%)	2 / 4328 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphadenitis			
subjects affected / exposed	1 / 4359 (0.02%)	1 / 4328 (0.02%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Intussusception			
subjects affected / exposed	2 / 4359 (0.05%)	1 / 4328 (0.02%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	1 / 4359 (0.02%)	1 / 4328 (0.02%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Dermatitis atopic			
subjects affected / exposed	1 / 4359 (0.02%)	0 / 4328 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Gastroenteritis			

subjects affected / exposed	3 / 4359 (0.07%)	2 / 4328 (0.05%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract			
subjects affected / exposed	0 / 4359 (0.00%)	3 / 4328 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epyema			
subjects affected / exposed	0 / 4359 (0.00%)	1 / 4328 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Kawasaki's disease			
subjects affected / exposed	1 / 4359 (0.02%)	0 / 4328 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydratation			
subjects affected / exposed	0 / 4359 (0.00%)	1 / 4328 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	0 / 4359 (0.00%)	1 / 4328 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Rotarix Group	Placebo Group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 4359 (0.00%)	0 / 4328 (0.00%)	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 June 2003	Rationale: Evaluated the safety of GSK Biologicals' HRV vaccine, administration of OPV will be deferred from the study vaccine administration by minimum 2 weeks. (1, 2) Interim analysis of an ongoing study (rota-021) in Latin America did not establish the non-inferiority of the all-in-one formulation planned to be used in study 023 as compared to the initial formulation. The initial formulation was therefore used instead of all-in-one formulation.
24 February 2004	Unlike planned, Malaysia and Thailand did not participate in this study, for logistical and internal organizational reasons. This led to reduction of the sample size. The power was recalculated for the reduced sample size. Because of the overall reduction in sample size, it was decided that all subjects will be followed for efficacy and safety until they reach 2 years of age, instead of only a subset. The method for power computation for the primary safety objective and the statistical analysis section on safety was adapted to reflect a recommendation from the statistician from the IDMC. An exclusion criterion was added to exclude infants who could have rare underlying congenital abnormalities caused by consanguinity.
26 April 2005	An interim analysis on the safety and immunogenicity data was performed in June 2005. Unblinding at the level of individual data was restricted to the Statistician and database administration until the study end. An interim study report was written for this time point.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported