Clinical trial results:
A phase IIIb, double blind, randomised, placebo–controlled, multi–country, multicentre study to assess the safety, reactogenicity and immunogenicity of two doses of GlaxoSmithKline (GSK) Biologicals' oral live attenuated Human Rotavirus (HRV) Vaccine in pre–term infants.

Summary

EudraCT number	2006-003762-33
Trial protocol	FR PT ES
Global end of trial date	31 March 2008

Results information

Result version number	v1
This version publication date	11 May 2016
First version publication date	18 December 2014

Trial information

Trial identification

Sponsor protocol code	106481

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00420745
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 Trials Call Center, GlaxoSmithKline Biologicals, 044 2089904466, GSKClinicalSupportHD@gsk.com
Scientific contact	Clinical Trials Call Center, GlaxoSmithKline Biologicals, 044 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?	Yes
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	31 March 2008
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 March 2008
Global end of trial reached?	Yes
Global end of trial date	31 March 2008
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the safety of GSK Biologicals' HRV vaccine in terms of occurrence of serious adverse events (SAEs), throughout the study period in pre–term infants receiving HRV vaccine versus pre–term infants receiving placebo.

Protection of trial subjects:

The subjects were observed closely for at least 30 minutes, with appropriate medical treatment readily available in case of a rare anaphylactic reaction following the administration of vaccine.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	25 January 2007
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 435
Country: Number of subjects enrolled	Portugal: 142
Country: Number of subjects enrolled	Spain: 354
Country: Number of subjects enrolled	France: 78
Worldwide total number of subjects	1009
EEA total number of subjects	1009

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 months)	0
Children (2-11 years)	1009
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, Monitor

Arms

Are arms mutually exclusive?	Yes
Arm title	Rotarix Group

Arm description:

All subjects received 2 oral doses of Rotarix vaccine, 1 dose at Day 0 and 1 dose at Month 1 or 2 depending on the country.

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

Dosage and administration details:

Two-dose oral vaccination.

Arm title	Placebo Group

Arm description:

All subjects received 2 oral doses of placebo, 1 dose at Day 0 and 1 dose at Month 1 or 2 depending on the country.

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

Dosage and administration details:

Two-dose oral administration.

Number of subjects in period 1	Rotarix Group	Placebo Group
Started	670	339
Completed	655	333
Not completed	15	6
Physician decision	1	1
Adverse event, non-fatal	2	2
Recurrent pneumonia & bronchitis	-	1
Lost to follow-up	10	2
Protocol deviation	1	-
Age limit exceeded for Dose 2	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Rotarix Group
Reporting group description:	
All subjects received 2 oral doses of Rotarix vaccine, 1 dose at Day 0 and 1 dose at Month 1 or 2 depending on the country.	
Reporting group title	Placebo Group
Reporting group description:	
All subjects received 2 oral doses of placebo, 1 dose at Day 0 and 1 dose at Month 1 or 2 depending on the country.	

Reporting group values	Rotarix Group	Placebo Group	Total
Number of subjects	670	339	1009
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: weeks			
geometric mean	8.5	8.5	
standard deviation	± 1.77	± 1.78	-
Gender categorical			
Units: Subjects			
Female	327	167	494
Male	343	172	515

End points

End points reporting groups

Reporting group title	Rotarix Group

Reporting group description:

All subjects received 2 oral doses of Rotarix vaccine, 1 dose at Day 0 and 1 dose at Month 1 or 2 depending on the country.

Reporting group title	Placebo Group

Reporting group description:

All subjects received 2 oral doses of placebo, 1 dose at Day 0 and 1 dose at Month 1 or 2 depending on the country.

Primary: Number of Subjects Reporting Any Serious Adverse Events (SAEs).

End point title	Number of Subjects Reporting Any Serious Adverse Events (SAEs).[1]

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	Primary

End point timeframe:

From Day 0 up to 1 month after Dose 2 of Rotarix vaccine/Placebo

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	670	339		
Units: Subjects				
(SAEs)	34	23		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Reporting Unsolicited Adverse Events (AEs), According to Medical Dictionary for Regulatory Activities (MedDRA) Classification

End point title	Number of Subjects Reporting Unsolicited Adverse Events (AEs), According to Medical Dictionary for Regulatory Activities (MedDRA) Classification

End point description:

An AE is any untoward medical occurrence in a clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

End point type	Secondary

End point timeframe:

Within 31 days after any Rotarix vaccine/Placebo dose.

End point values	Rotarix Group	Placebo Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	670	339		
Units: Subjects	196	138		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects for whom each type of solicited symptom was reported.

End point title	Number of subjects for whom each type of solicited symptom was reported.

End point description:

Solicited symptoms included Diarrhea (3 or more looser than normal stools/day), Fever (axillary temperature ≥ 37.5 degrees Celsius (°C)), Irritability, Loss of appetite, and Vomiting

End point type	Secondary

End point timeframe:

Within 15 days after each Rotarix vaccine/Placebo dose.

End point values	Rotarix Group	Placebo Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	203	100		
Units: Subjects				
Diarrhea	9	5		
Fever	54	29		
Irritability	133	66		
Loss of appetite	81	45		
Vomiting	52	27		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects for whom presence of rotavirus (RV) gastroenteritis (GE) was detected in stools.

End point title	Number of subjects for whom presence of rotavirus (RV) gastroenteritis (GE) was detected in stools.

End point description:

Gastroenteritis (GE): diarrhoea with or without vomiting. Rotavirus (RV) GE: A GE episode was a RV GE if a stool sample taken during or not later than 7 days after the episode was RV positive by Enzyme Linked Immunosorbent Assay.

End point type	Secondary

End point timeframe:

From Dose 1 up to 1 month after Dose 2 of Rotarix vaccine/Placebo

End point values	Rotarix Group	Placebo Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	670	339		
Units: Subjects				
Number of subjects with RV	3	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Seroconversion to anti-rotavirus Immunoglobulin A (IgA) antibody.

End point title	Seroconversion to anti-rotavirus Immunoglobulin A (IgA) antibody.

End point description:

Number of subjects with anti-rotavirus IgA antibody concentration ≥ 20 Units/milliliter (U/mL).

End point type	Secondary

End point timeframe:

At Visit 3, 1 month after Dose 2 of Rotarix vaccine/Placebo

End point values	Rotarix Group	Placebo Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	147	81		
Units: Subjects				
Seroconversion to anti-rotavirus IgA	126	13		

Statistical analyses

No statistical analyses for this end point

Secondary: Serum anti–rotavirus IgA antibody concentration.

End point title	Serum anti–rotavirus IgA antibody concentration.

End point description:

Anti-rotavirus IgA antibody concentrations are given as geometric mean concentrations (GMC) with 95%

Confidence Intervals, calculated on all subjects.

End point type	Secondary

End point timeframe:

At Visit 3, 1 month after Dose 2 of Rotarix vaccine/Placebo

End point values	Rotarix Group	Placebo Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	147	81		
Units: U/mL				
geometric mean (confidence interval 95%)				
Serum anti–rotavirus IgA	202.2 (153.1 to 267.1)	0 (0 to 0)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Serious Adverse events (SAE) = During the entire study period. Solicited local and general symptoms = Within 15 days (Day 0–Day 14) after each HRV vaccine/placebo dose. Unsolicited AEs = Within 31 days (Day 0–Day 30) after any HRV vaccine/placebo dose.

Adverse event reporting additional description:

The number of occurrences reported for solicited symptoms, adverse events, and serious adverse events were not available for posting. The number of subjects affected by each specific event was indicated as the number of occurrences.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	11

Reporting groups

Reporting group title	Rotarix Group

Reporting group description:

All subjects received 2 oral doses of Rotarix vaccine, 1 dose at Day 0 and 1 dose at Month 1 or 2 depending on the country.

Reporting group title	Placebo Group

Reporting group description:

All subjects received 2 oral doses of placebo, 1 dose at Day 0 and 1 dose at Month 1 or 2 depending on the country.

Serious adverse events	Rotarix Group	Placebo Group	
Total subjects affected by serious adverse events			
subjects affected / exposed	34 / 670 (5.07%)	23 / 339 (6.78%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Congenital, familial and genetic disorders			
Coarctation of the aorta			
subjects affected / exposed	1 / 670 (0.15%)	0 / 339 (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			
Anaemia			
subjects affected / exposed	0 / 670 (0.00%)	2 / 339 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			

Pyrexia			
subjects affected / exposed	4 / 670 (0.60%)	3 / 339 (0.88%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	2 / 670 (0.30%)	0 / 339 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea haemorrhagic			
subjects affected / exposed	0 / 670 (0.00%)	1 / 339 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspepsia			
subjects affected / exposed	0 / 670 (0.00%)	2 / 339 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	1 / 670 (0.15%)	0 / 339 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	6 / 670 (0.90%)	1 / 339 (0.29%)	
occurrences causally related to treatment / all	0 / 6	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 670 (0.15%)	1 / 339 (0.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	0 / 670 (0.00%)	2 / 339 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			

subjects affected / exposed	1 / 670 (0.15%)	0 / 339 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Apnoea			
subjects affected / exposed	1 / 670 (0.15%)	0 / 339 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchial obstruction			
subjects affected / exposed	1 / 670 (0.15%)	0 / 339 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cough			
subjects affected / exposed	0 / 670 (0.00%)	1 / 339 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	0 / 670 (0.00%)	1 / 339 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 670 (0.00%)	1 / 339 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchiolitis			
subjects affected / exposed	3 / 670 (0.45%)	4 / 339 (1.18%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	4 / 670 (0.60%)	2 / 339 (0.59%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Bronchopneumonia			
subjects affected / exposed	4 / 670 (0.60%)	1 / 339 (0.29%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dacryocystitis			
subjects affected / exposed	1 / 670 (0.15%)	0 / 339 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis adenovirus			
subjects affected / exposed	0 / 670 (0.00%)	1 / 339 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis rotavirus			
subjects affected / exposed	0 / 670 (0.00%)	1 / 339 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis media acute			
subjects affected / exposed	0 / 670 (0.00%)	1 / 339 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periorbital cellulitis			
subjects affected / exposed	1 / 670 (0.15%)	0 / 339 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pertussis			
subjects affected / exposed	1 / 670 (0.15%)	0 / 339 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	4 / 670 (0.60%)	2 / 339 (0.59%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			

subjects affected / exposed	0 / 670 (0.00%)	1 / 339 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	2 / 670 (0.30%)	0 / 339 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory syncytial virus bronchiolitis			
subjects affected / exposed	2 / 670 (0.30%)	3 / 339 (0.88%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	0 / 670 (0.00%)	1 / 339 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 670 (0.15%)	0 / 339 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 670 (0.15%)	0 / 339 (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			
Dehydration			
subjects affected / exposed	1 / 670 (0.15%)	0 / 339 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	0 / 670 (0.00%)	1 / 339 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypernatraemia			

subjects affected / exposed	1 / 670 (0.15%)	0 / 339 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
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	133 / 670 (19.85%)	66 / 339 (19.47%)	
General disorders and administration site conditions			
Fever			
alternative assessment type: Systematic			
subjects affected / exposed[1]	54 / 203 (26.60%)	29 / 100 (29.00%)	
occurrences (all)	54	29	
Irritability			
alternative assessment type: Systematic			
subjects affected / exposed[2]	133 / 203 (65.52%)	66 / 100 (66.00%)	
occurrences (all)	133	66	
Pyrexia			
subjects affected / exposed[3]	28 / 203 (13.79%)	25 / 100 (25.00%)	
occurrences (all)	28	25	
Gastrointestinal disorders			
Diarrhoea			
alternative assessment type: Systematic			
subjects affected / exposed[4]	9 / 203 (4.43%)	5 / 100 (5.00%)	
occurrences (all)	9	5	
Vomiting			
alternative assessment type: Systematic			
subjects affected / exposed[5]	52 / 203 (25.62%)	27 / 100 (27.00%)	
occurrences (all)	52	27	
Metabolism and nutrition disorders			
Loss of appetite			
alternative assessment type: Systematic			
subjects affected / exposed[6]	81 / 203 (39.90%)	45 / 100 (45.00%)	
occurrences (all)	81	45	

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: The number of subjects exposed to the adverse event may differ from the total number of subjects exposed for the reporting group as subjects who missed reporting symptoms were treated as subjects without symptoms.
[2] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: The number of subjects exposed to the adverse event may differ from the total number of subjects exposed for the reporting group as subjects who missed reporting symptoms were treated as subjects without symptoms.
[3] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: The number of subjects exposed to the adverse event may differ from the total number of subjects exposed for the reporting group as subjects who missed reporting symptoms were treated as subjects without symptoms.
[4] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: The number of subjects exposed to the adverse event may differ from the total number of subjects exposed for the reporting group as subjects who missed reporting symptoms were treated as subjects without symptoms.
[5] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: The number of subjects exposed to the adverse event may differ from the total number of subjects exposed for the reporting group as subjects who missed reporting symptoms were treated as subjects without symptoms.
[6] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: The number of subjects exposed to the adverse event may differ from the total number of subjects exposed for the reporting group as subjects who missed reporting symptoms were treated as subjects without symptoms.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 June 2007	Amendment 3 The present study will be conducted to evaluate the safety, reactogenicity and immunogenicity of the HRV vaccine when used in pre-term infants aged between 6 and 14 weeks at the time of first dose in Portugal, France and Poland and in preterm infants aged between 6 and 12 weeks at the time of first dose in Spain. The study will be performed in four European countries (France, Poland, Portugal and Spain). (Amendment 3:11 June 2007)

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported