Clinical trial results:
A phase IIIb, randomized, double-blind, placebo-controlled study to explore the existence of horizontal transmission of the RIX4414 vaccine strain between twins within a family.

Summary

EudraCT number	2015-001542-29
Trial protocol	Outside EU/EEA
Global end of trial date	13 February 2008

Results information

Result version number	v2 (current)
This version publication date	03 March 2018
First version publication date	15 July 2015
Version creation reason	• Correction of full data set Align with US Results Summary updated as per NIH PRS comments

Trial information

Trial identification

Sponsor protocol code	106260

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00396630
WHO universal trial number (UTN)	-
Other trial identifiers	US NIH Grant Number: BB-IND #9231

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	24 December 2008
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 January 2008
Global end of trial reached?	Yes
Global end of trial date	13 February 2008
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Estimate the rate of transmission of the HRV vaccine strain to twin receiving placebo using RV detection by ELISA and vaccine strain identification using appropriate molecular technique.

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 vaccines.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	23 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	Dominican Republic: 200
Worldwide total number of subjects	200
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 months)	200
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:

Within each pair of twins enrolled in the study, one subject was assigned to the Rotarix Group and one to the Placebo Group.

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, Assessor

Blinding implementation details:

An open-label dose of HRV vaccine was administered at Visit 3 to all subjects in each group who were aged less than 6 months at Visit 3 as a benefit to the placebo group for participation in the study. Visits 1, 2, 3 and 4 corresponded to Day 0, Week 7, Week 13 and Week 17.

Arms

Are arms mutually exclusive?	Yes
Arm title	Rotarix Group

Arm description:

All subjects received 2 oral doses of Rotarix vaccine at Day 0 (Visit 1) and Week 7 (Visit 2).
Subjects aged less than 6 months at Visit 3 received one complimentary Rotarix vaccine dose at Week 13 (Visit 3).

Arm type	Experimental
Investigational medicinal product name	Rotarix
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for 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 at Day 0 (Visit 1) and Week 7 (Visit 2). Subjects aged less than 6 months at Visit 3 received one complimentary Rotarix vaccine dose at Week 13 (Visit 3).

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for 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	100	100
Completed	95	95
Not completed	5	5
Not vaccinated at Visit 3	3	3
Consent withdrawn by subject	1	1
Lost to follow-up	1	1

Baseline characteristics

Reporting groups	
Reporting group title	Rotarix Group
Reporting group description:	
All subjects received 2 oral doses of Rotarix vaccine at Day 0 (Visit 1) and Week 7 (Visit 2). Subjects aged less than 6 months at Visit 3 received one complimentary Rotarix vaccine dose at Week 13 (Visit 3).	
Reporting group title	Placebo Group
Reporting group description:	
All subjects received 2 oral doses of placebo at Day 0 (Visit 1) and Week 7 (Visit 2). Subjects aged less than 6 months at Visit 3 received one complimentary Rotarix vaccine dose at Week 13 (Visit 3).	

Reporting group values	Rotarix Group	Placebo Group	Total
Number of subjects	100	100	200
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			
arithmetic mean	8.2	8.2	
standard deviation	± 1.8	± 1.8	-
Gender categorical			
Units: Subjects			
Female	56	49	105
Male	44	51	95

End points

End points reporting groups

Reporting group title	Rotarix Group

Reporting group description:

All subjects received 2 oral doses of Rotarix vaccine at Day 0 (Visit 1) and Week 7 (Visit 2). Subjects aged less than 6 months at Visit 3 received one complimentary Rotarix vaccine dose at Week 13 (Visit 3).

Reporting group title	Placebo Group

Reporting group description:

All subjects received 2 oral doses of placebo at Day 0 (Visit 1) and Week 7 (Visit 2). Subjects aged less than 6 months at Visit 3 received one complimentary Rotarix vaccine dose at Week 13 (Visit 3).

Primary: Presence of rotavirus vaccine strain in any stool sample from twin receiving placebo.

End point title	Presence of rotavirus vaccine strain in any stool sample from twin receiving placebo.[1][2]

End point description:

Number of subjects in the Placebo Group with rotavirus vaccine strain in at least one stool sample. This outcome measure concerns subjects in the Placebo Group only.

End point type	Primary

End point timeframe:

On the day of each vaccine/placebo dose, then three times weekly for 6 consecutive weeks starting after each vaccine/placebo dose and on the day of Visit 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.
[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This outcome measure concerns subjects in the Placebo Group only.

End point values	Placebo Group			
Subject group type	Reporting group			
Number of subjects analysed	80			
Units: Subjects				
Subjects with RV in at least one stool sample	15			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of human rotavirus (HRV) shedding per study group.

End point title	Duration of human rotavirus (HRV) shedding per study group.

End point description:

Duration of shedding in the Placebo Group= number of days between first and last stool sample positive (+) for rotavirus (RV) antigen and in the Rotarix Group= number of days between the day of vaccination and the date of last stool sample + for RV antigen.

End point type	Secondary

End point timeframe:

From Day 0 up to Week 13

End point values	Rotarix Group	Placebo Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: Number of days				
median (inter-quartile range (Q1-Q3))				
After Dose 1 (n=11; 9)	17 (11 to 19)	7 (3 to 13)		
After Dose 2 (n=9; 7)	13 (5 to 17)	1 (1 to 1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Anti-rotavirus immunoglobulin A (IgA) antibody seroconversion.

End point title	Anti-rotavirus immunoglobulin A (IgA) antibody seroconversion.

End point description:

Number of initially seronegative subjects with anti-rotavirus IgA antibody concentration ≥ 20 Units/milliliter (U/mL), 1 month after the second dose.

End point type	Secondary

End point timeframe:

At Visit 3 (Week 13)

End point values	Rotarix Group	Placebo Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	80	80		
Units: Subjects				
Anti-rotavirus immunoglobulin A (IgA) antibody	50	17		

Statistical analyses

No statistical analyses for this end point

Secondary: Anti-rotavirus IgA antibody concentration.

End point title	Anti-rotavirus IgA antibody concentration.

End point description:

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

End point type	Secondary

End point timeframe:

At Visit 3 (Week 13)

End point values	Rotarix Group	Placebo Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	80	80		
Units: U/mL				
geometric mean (confidence interval 95%)				
Anti-rotavirus IgA antibody concentration	78.6 (50.6 to 122.2)	20.5 (14.5 to 28.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with gastroenteritis (GE) and rotavirus gastroenteritis (RV GE) episodes.

End point title	Number of subjects with gastroenteritis (GE) and rotavirus gastroenteritis (RV GE) episodes.

End point description:

GE episodes were defined as diarrhea (passage of three or more looser than normal stools within a day) with or without vomiting. RV GE episodes were defined as GE episodes for which the stool sample temporally closest to the onset day of the GE episode was positive for rotavirus by Enzyme Linked Immunosorbent Assay (ELISA).

End point type	Secondary

End point timeframe:

Until Visit 4 (Week 17) for GE and until Visit 3 (Week 13) for RV GE

End point values	Rotarix Group	Placebo Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	100	100		
Units: Subjects				
GE episodes	32	31		
RV GE episodes	10	6		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reporting unsolicited Adverse Events (AEs).

End point title	Number of subjects reporting unsolicited Adverse Events (AEs).

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 dose.

End point values	Rotarix Group	Placebo Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	100	100		
Units: Subjects				
Any AE(s)	69	71		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reporting any Serious Adverse Events (SAEs).

End point title	Number of subjects reporting any Serious Adverse Events (SAEs).

End point description:

A serious adverse event (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:

Up to Visit 4

End point values	Rotarix Group	Placebo Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	100	100		
Units: Subjects				
SAEs	5	6		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of genetic variation differences detected by sequencing of genomic mutations in the HRV vaccine strain after transmission.

End point title	Number of genetic variation differences detected by sequencing of genomic mutations in the HRV vaccine strain after transmission.

End point description:

Dissimilar amino acid substitutions in the HRV vaccine strain isolated from the twin receiving placebo, when compared to the genetic variation of HRV vaccine strain isolated from the Rotarix vaccine recipients, were counted as genetic variation differences.

End point type	Secondary

End point timeframe:

During the entire study period (up to Visit 4, Week 17).

End point values	Rotarix Group	Placebo Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: Genetic variation difference				
number (not applicable)	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Live viral vaccine load in the stool of the twin receiving placebo in case of transmission.

End point title	Live viral vaccine load in the stool of the twin receiving placebo in case of transmission.[3]

End point description:

Number of subjects in the Placebo Group with live virus identified in at least one stool sample in case of transmission.

End point type	Secondary

End point timeframe:

During the entire study period (up to Visit 4, Week 17).

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This outcome measure concerns subjects in the Placebo Group only.

End point values	Placebo Group			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: Subjects				
number (not applicable)	3			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Unsolicited Adverse Events: within 31 days after any doses (Day 0-30) and Serious adverse events: during the entire study period (Day 0 to Week 17).

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	11.1

Reporting groups

Reporting group title	Rotarix Group

Reporting group description:

All subjects received 2 oral doses of Rotarix vaccine at Day 0 (Visit 1) and Week 7 (Visit 2). Subjects aged less than 6 months at Visit 3 received one complimentary Rotarix vaccine dose at Week 13 (Visit 3).

Reporting group title	Placebo Group

Reporting group description:

All subjects received 2 oral doses of placebo at Day 0 (Visit 1) and Week 7 (Visit 2). Subjects aged less than 6 months at Visit 3 received one complimentary Rotarix vaccine dose at Week 13 (Visit 3).

Serious adverse events	Rotarix Group	Placebo Group	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 100 (5.00%)	6 / 100 (6.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Infections and infestations			
Bronchiolitis			
subjects affected / exposed	3 / 100 (3.00%)	3 / 100 (3.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	2 / 100 (2.00%)	1 / 100 (1.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial sepsis			

subjects affected / exposed	1 / 100 (1.00%)	0 / 100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	0 / 100 (0.00%)	1 / 100 (1.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 100 (0.00%)	1 / 100 (1.00%)	
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	69 / 100 (69.00%)	71 / 100 (71.00%)	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	32 / 100 (32.00%)	32 / 100 (32.00%)	
occurrences (all)	32	32	
Irritability			
subjects affected / exposed	4 / 100 (4.00%)	5 / 100 (5.00%)	
occurrences (all)	4	5	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	49 / 100 (49.00%)	49 / 100 (49.00%)	
occurrences (all)	49	49	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 August 2006	This amendment was implemented in order to comply with a request from the MOH in the Dominican Republic reviewing the study protocol. They specifically requested that subjects allocated to the placebo group receive Rotarix vaccination at study end. Given the upper age limit to administer Rotarix vaccination, it has been agreed to give a single open-label Rotarix dose before 6 months of age. To facilitate the study amendment design it has been proposed to give all subjects a dose of Rotarix at Visit 3 given the fact that three-dose regimens have been explored previously and shown to be safe. As an additional study benefit for all subjects Prevnar vaccination will be offered to all study participants at the discretion of the investigator.
23 May 2007	This amendment was implemented in order to comply with a request from the MOH in the Dominican Republic reviewing the study protocol. They specifically requested that subjects allocated to the placebo group receive Rotarix™ vaccination at study end. Given the upper age limit to administer Rotarix™ vaccination, it has been agreed to give a single open-label Rotarix™ dose before 6 months of age. To facilitate the study amendment design it has been proposed to give all subjects a dose of Rotarix™ at Visit 3 given the fact that three-dose regimens have been explored previously and shown to be safe. As an additional study benefit for all subjects Prevnar™ vaccination will be offered to all study participants at the discretion of the investigator.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported