



## Clinical trial results:

**A Phase IV, double-blind, randomised, placebo-controlled study to evaluate immunogenicity, reactogenicity and safety of GlaxoSmithKline (GSK) Biologicals' oral live attenuated HRV vaccine in healthy infants previously uninfected with HRV.**

### Summary

EudraCT number	2015-001545-81
Trial protocol	Outside EU/EEA
Global end of trial date	23 July 2010

### Results information

Result version number	v1
This version publication date	20 April 2016
First version publication date	22 July 2015

### Trial information

#### Trial identification

Sponsor protocol code	112269
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#### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00969228
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, 44 2089904466, GSKClinicalSupportHD@gsk.com
Scientific contact	Clinical Trials 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:

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**Results analysis stage**

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Analysis stage	Final
Date of interim/final analysis	28 December 2010
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 July 2010
Global end of trial reached?	Yes
Global end of trial date	23 July 2010
Was the trial ended prematurely?	No

Notes:

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**General information about the trial**

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Main objective of the trial:

To demonstrate at least 40% increase in seroconversion rate, in the HRV vaccine group at Visit 3 (i.e. one month post-Dose 2) as compared to Placebo group.

Criteria: the primary objective will be met if the lower limit of the two-sided asymptotic standardised 95% CI (Confidence interval) for treatment difference (HRV minus placebo) is  $\geq 40\%$ .

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 or placebo.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	25 August 2009
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

Country: Number of subjects enrolled	Korea, Republic of: 684
Worldwide total number of subjects	684
EEA total number of subjects	0

Notes:

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**Subjects enrolled per age group**

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In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	684
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	Investigator, Carer, Assessor, Subject

Blinding implementation details:

The study was conducted in a double-blind manner with respect to the Rotarix <sup>TM</sup> vaccine and placebo. The parents/guardians of the subjects, the study personnel and the investigator were unaware of the study vaccine administered (Rotarix <sup>TM</sup> vaccine or placebo).

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Rotarix Group

Arm description:

Subjects received 2 oral doses of Rotarix according to a 0, 1 or 2-month schedule.

Arm type	Experimental
Investigational medicinal product name	Rotarix <sup>TM</sup>
Investigational medicinal product code	
Other name	HRV
Pharmaceutical forms	Powder and solvent for oral suspension
Routes of administration	Oral use

Dosage and administration details:

Subjects received 2 oral doses of Rotarix according to a 0, 1 or 2-month schedule.

<b>Arm title</b>	Placebo Group
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Arm description:

Subjects received 2 oral doses of placebo according to a 0, 1 or 2-month schedule.

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:

Subjects received 2 oral doses of placebo according to a 0, 1 or 2-month schedule.

<b>Number of subjects in period 1</b>	Rotarix Group	Placebo Group
Started	508	176
Completed	465	162
Not completed	43	14
Consent withdrawn by subject	4	-
Adverse event, non-fatal	1	-
Porcine circovirus detection in vaccine	38	14

## Baseline characteristics

### Reporting groups

Reporting group title	Rotarix Group
Reporting group description:	
Subjects received 2 oral doses of Rotarix according to a 0, 1 or 2-month schedule.	
Reporting group title	Placebo Group
Reporting group description:	
Subjects received 2 oral doses of placebo according to a 0, 1 or 2-month schedule.	

Reporting group values	Rotarix Group	Placebo Group	Total
Number of subjects	508	176	684
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	8.8	8.9	
standard deviation	± 1.25	± 1.26	-
Gender categorical Units: Subjects			
Female	231	79	310
Male	277	97	374

## End points

### End points reporting groups

Reporting group title	Rotarix Group
Reporting group description: Subjects received 2 oral doses of Rotarix according to a 0, 1 or 2-month schedule.	
Reporting group title	Placebo Group
Reporting group description: Subjects received 2 oral doses of placebo according to a 0, 1 or 2-month schedule.	

### Primary: Number of subjects seroconverted for anti-rotavirus immunoglobulin A

End point title	Number of subjects seroconverted for anti-rotavirus immunoglobulin A
End point description: Seroconversion is defined as the appearance of antibodies with concentrations greater than or equal to 20 units per milliliter (U/mL) in the serum of subjects seronegative before vaccination.	
End point type	Primary
End point timeframe: One month after the second vaccine dose	

End point values	Rotarix Group	Placebo Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	318	114		
Units: Subjects	280	5		

### Statistical analyses

Statistical analysis title	To demonstrate increase in seroconversion rate
Statistical analysis description: To demonstrate at least 40% increase in seroconversion rate, in the HRV Group at Visit 3 (i.e. one month post-dose 2) as compared to the Placebo Group. The increase in seroconversion rate was concluded if the lower limit of the two-sided asymptotic standardised 95% confidence interval (CI) for treatment difference (HRV minus placebo) was $\geq 40\%$ .	
Comparison groups	Rotarix Group v Placebo Group
Number of subjects included in analysis	432
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in seroconversion rate
Point estimate	83.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	77.26
upper limit	87.98

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**Secondary: Serum anti-rotavirus immunoglobulin A antibody concentrations**

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End point title	Serum anti-rotavirus immunoglobulin A antibody concentrations
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End point description:

Concentrations are given as Geometric Mean Concentrations (GMCs). Note: In the Placebo Group the value was below the assay cut-off (20 units per milliliter).

End point type	Secondary
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End point timeframe:

One month after the second vaccine dose

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End point values	Rotarix Group	Placebo Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	280	114		
Units: U/mL				
geometric mean (confidence interval 95%)	208.5 (174.2 to 249.5)	20 (20 to 20)		

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**Statistical analyses**

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No statistical analyses for this end point

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**Secondary: Number of subjects reporting solicited symptoms**

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End point title	Number of subjects reporting solicited symptoms
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End point description:

During the 8-day (Day 0 – Day 7) follow-up period after each vaccine dose.

End point type	Secondary
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End point timeframe:

Solicited symptoms assessed include cough, diarrhoea, irritability, loss of appetite , fever and vomiting.

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End point values	Rotarix Group	Placebo Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	508	176		
Units: Subjects				
Cough	180	66		
Diarrhoea	20	7		
Irritability	290	106		
Loss of appetite	174	60		
Fever	67	18		
Vomiting	95	36		

## 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)
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End point description:

Unsolicited AE covers any AE reported in addition to those solicited during the clinical study and any solicited symptom with onset outside the specified period of follow-up for solicited symptoms.

End point type	Secondary
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End point timeframe:

During the 31-day (Day 0 – Day 30) follow-up period after each vaccine dose

End point values	Rotarix Group	Placebo Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	508	176		
Units: Subjects	148	59		

## 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)
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End point description:

SAEs assessed include medical occurrences that result in death, are life threatening, require hospitalization or prolongation of hospitalization, result in disability/incapacity or are a congenital anomaly/birth defect in the offspring of a study subject.

End point type	Secondary
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End point timeframe:

Throughout the study period (2-3 months).



<b>End point values</b>	Rotarix Group	Placebo Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	508	176		
Units: Subjects	17	13		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of subjects reporting rotavirus gastroenteritis episode(s)

End point title	Number of subjects reporting rotavirus gastroenteritis episode(s)
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End point description:

End point type	Secondary
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End point timeframe:

From Dose 1 up to 1 month after Dose 2.

<b>End point values</b>	Rotarix Group	Placebo Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	508	176		
Units: Subjects	0	0		

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Solicited symptoms: during the 8-day follow-up period after each dose of vaccine. Unsolicited adverse events: during the 31-day follow-up after any dose of Rotarix vaccine or placebo. Serious adverse events: during the entire study period (2-3 months)

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
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	13.1
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### Reporting groups

Reporting group title	Rotarix Group
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Reporting group description:

Subjects received 2 oral doses of Rotarix according to a 0, 1 or 2-month schedule.

Reporting group title	Placebo Group
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Reporting group description:

Subjects received 2 oral doses of placebo according to a 0, 1 or 2-month schedule.

Serious adverse events	Rotarix Group	Placebo Group	
Total subjects affected by serious adverse events			
subjects affected / exposed	17 / 508 (3.35%)	13 / 176 (7.39%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lymphoma			
subjects affected / exposed	1 / 508 (0.20%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Solitary kidney			
subjects affected / exposed	0 / 508 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			

subjects affected / exposed	4 / 508 (0.79%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Gastrointestinal disorders</b>			
Abdominal pain			
subjects affected / exposed	0 / 508 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	1 / 508 (0.20%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Respiratory, thoracic and mediastinal disorders</b>			
Pneumonia aspiration			
subjects affected / exposed	0 / 508 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Infections and infestations</b>			
Bronchiolitis			
subjects affected / exposed	6 / 508 (1.18%)	5 / 176 (2.84%)	
occurrences causally related to treatment / all	0 / 6	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	5 / 508 (0.98%)	4 / 176 (2.27%)	
occurrences causally related to treatment / all	0 / 5	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	2 / 508 (0.39%)	2 / 176 (1.14%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 508 (0.20%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Bronchopneumonia			
subjects affected / exposed	2 / 508 (0.39%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia urinary tract infection			
subjects affected / exposed	0 / 508 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis viral			
subjects affected / exposed	0 / 508 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis externa			
subjects affected / exposed	1 / 508 (0.20%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis media			
subjects affected / exposed	1 / 508 (0.20%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis			
subjects affected / exposed	1 / 508 (0.20%)	0 / 176 (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	0 / 508 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	1 / 508 (0.20%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			

subjects affected / exposed	0 / 508 (0.00%)	1 / 176 (0.57%)	
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 %

<b>Non-serious adverse events</b>	Rotarix Group	Placebo Group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	290 / 508 (57.09%)	106 / 176 (60.23%)	
General disorders and administration site conditions			
Cough			
alternative assessment type: Systematic			
subjects affected / exposed	180 / 508 (35.43%)	66 / 176 (37.50%)	
occurrences (all)	180	66	
Irritability			
alternative assessment type: Systematic			
subjects affected / exposed	290 / 508 (57.09%)	106 / 176 (60.23%)	
occurrences (all)	290	106	
Loss of appetite			
alternative assessment type: Systematic			
subjects affected / exposed	174 / 508 (34.25%)	60 / 176 (34.09%)	
occurrences (all)	174	60	
Fever			
alternative assessment type: Systematic			
subjects affected / exposed	67 / 508 (13.19%)	18 / 176 (10.23%)	
occurrences (all)	67	18	
Vomiting			
alternative assessment type: Systematic			
subjects affected / exposed	95 / 508 (18.70%)	36 / 176 (20.45%)	
occurrences (all)	95	36	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	29 / 508 (5.71%)	17 / 176 (9.66%)	
occurrences (all)	29	17	



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 July 2009	<p>The contact details for reporting of SAEs &amp; the emergency code break have been clarified. As of now:</p> <ul style="list-style-type: none"><li>• two fax numbers will be used as back-up for the safety contact for reporting SAEs</li><li>• two mobile numbers (one for the US/Canada &amp; one for the rest of the world) will be used for the safety contact for code break (emergency unblinding) depending on the region the study is conducted.</li></ul>

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported