



## Clinical trial results:

**A phase III, randomized, open-label, multicentre study to assess the immunogenicity, safety and reactogenicity of GlaxoSmithKline Biologicals' combined DTPa-IPV/Hib vaccine administered as a three-dose primary vaccination course at 2-4-6 months of age in healthy infants in South Korea.**

Due to a system error, the data reported in v1 is not correct and has been removed from public view.

## Summary

EudraCT number	2012-004137-16
Trial protocol	Outside EU/EEA
Global end of trial date	24 February 2012

## Results information

Result version number	v2
This version publication date	08 July 2016
First version publication date	02 July 2015
Version creation reason	<ul style="list-style-type: none"><li>• Correction of full data set</li></ul> Data correction due to a system error in EudraCT – Results

## Trial information

### Trial identification

Sponsor protocol code	114260
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### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01309646
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:

### Results analysis stage

Analysis stage	Final
Date of interim/final analysis	21 March 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	24 February 2012
Global end of trial reached?	Yes
Global end of trial date	24 February 2012
Was the trial ended prematurely?	No

Notes:

### General information about the trial

Main objective of the trial:

To demonstrate that the immunogenicity of GSK Biologicals' DTPa-IPV/Hib vaccine administered at 2, 4 and 6 months of age is non-inferior to that of the concomitant administration of GSK Biologicals' DTPa-IPV and Hib vaccines, in terms of immune response to all vaccine antigens, one month after the third dose of the primary vaccination.

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 for one month (minimum 30 days) following administration of the last dose of study vaccines.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	04 March 2011
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	Korea, Republic of: 454
Worldwide total number of subjects	454
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)	454
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 period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Infanrix-IPV+Hib Group

Arm description:

Subjects aged between, and including, 42 and 69 days at the time of first vaccination received 3 doses of Infanrix-IPV+Hib at 2, 4 and 6 months of age, 3 doses of Synflorix at 6 weeks, 3.5 and 5.5 months of age and 2 doses of Rotarix at 6 weeks and 3.5 months of age. The Infanrix-IPV+Hib was administered intramuscularly in the right thigh, the Synflorix vaccine was administered intramuscularly in the left thigh and the Rotarix vaccine was administered orally.

Arm type	Experimental
Investigational medicinal product name	Infanrix-IPV+Hib
Investigational medicinal product code	
Other name	DTPa-IPV/Hib
Pharmaceutical forms	Powder and suspension for suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Intramuscular, 3 doses at 2,4 and 6 months of age.

Investigational medicinal product name	Synflorix
Investigational medicinal product code	
Other name	10Pn-PD-DiT
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Intramuscular, 3 doses at 6 weeks, 3.5 and 5.5 months of age.

Investigational medicinal product name	Rotarix
Investigational medicinal product code	
Other name	HRV
Pharmaceutical forms	Powder and solvent for oral suspension
Routes of administration	Oral use

Dosage and administration details:

Oral, 2 doses at 6 weeks and 3.5 months of age.

<b>Arm title</b>	Infanrix IPV Group
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Arm description:

Subjects aged between, and including, 42 and 69 days at the time of first vaccination received 3 doses of Infanrix IPV and Hiberix co-administered at separate injection sites at 2, 4 and 6 months of age, 3 dose of Synflorix at 6 weeks, 3.5 and 5.5 months of age and 2 doses of Rotarix at 6 weeks and 3.5 months of age. The Infanrix IPV was administered intramuscularly in the right thigh, the Synflorix and Hiberix vaccines were administered intramuscularly in the left thigh and the Rotarix vaccine was

administered orally.

Arm type	Active comparator
Investigational medicinal product name	Infanrix IPV
Investigational medicinal product code	
Other name	DTPa-IPV
Pharmaceutical forms	Powder and suspension for suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Intramuscular, 3 doses co-administered at 2, 4 and 6 months of age with Hiberix™.

Investigational medicinal product name	Hiberix
Investigational medicinal product code	
Other name	Hib
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Intramuscular, 3 doses co-administered at 2, 4 and 6 months of age with Infanrix™ IPV.

Investigational medicinal product name	Synflorix
Investigational medicinal product code	
Other name	10Pn-PD-DiT
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Intramuscular, 3 doses at 6 weeks, 3.5 and 5.5 months of age.

Investigational medicinal product name	Rotarix
Investigational medicinal product code	
Other name	HRV
Pharmaceutical forms	Powder and solvent for oral suspension
Routes of administration	Oral use

Dosage and administration details:

Oral, 2 doses at 6 weeks and 3.5 months of age.

<b>Number of subjects in period 1</b>	Infanrix-IPV+Hib Group	Infanrix IPV Group
Started	226	228
Completed	224	227
Not completed	2	1
Consent withdrawn by subject	1	-
Protocol Violation	1	1

## Baseline characteristics

### Reporting groups

Reporting group title	Infanrix-IPV+Hib Group
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Reporting group description:

Subjects aged between, and including, 42 and 69 days at the time of first vaccination received 3 doses of Infanrix-IPV+Hib at 2, 4 and 6 months of age, 3 doses of Synflorix at 6 weeks, 3.5 and 5.5 months of age and 2 doses of Rotarix at 6 weeks and 3.5 months of age. The Infanrix-IPV+Hib was administered intramuscularly in the right thigh, the Synflorix vaccine was administered intramuscularly in the left thigh and the Rotarix vaccine was administered orally.

Reporting group title	Infanrix IPV Group
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Reporting group description:

Subjects aged between, and including, 42 and 69 days at the time of first vaccination received 3 doses of Infanrix IPV and Hiberix co-administered at separate injection sites at 2, 4 and 6 months of age, 3 dose of Synflorix at 6 weeks, 3.5 and 5.5 months of age and 2 doses of Rotarix at 6 weeks and 3.5 months of age. The Infanrix IPV was administered intramuscularly in the right thigh, the Synflorix and Hiberix vaccines were administered intramuscularly in the left thigh and the Rotarix vaccine was administered orally.

Reporting group values	Infanrix-IPV+Hib Group	Infanrix IPV Group	Total
Number of subjects	226	228	454
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	8.8	
standard deviation	± 1.1	± 1.09	-
Gender categorical Units: Subjects			
Female	98	116	214
Male	128	112	240

## End points

### End points reporting groups

Reporting group title	Infanrix-IPV+Hib Group
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Reporting group description:

Subjects aged between, and including, 42 and 69 days at the time of first vaccination received 3 doses of Infanrix-IPV+Hib at 2, 4 and 6 months of age, 3 doses of Synflorix at 6 weeks, 3.5 and 5.5 months of age and 2 doses of Rotarix at 6 weeks and 3.5 months of age. The Infanrix-IPV+Hib was administered intramuscularly in the right thigh, the Synflorix vaccine was administered intramuscularly in the left thigh and the Rotarix vaccine was administered orally.

Reporting group title	Infanrix IPV Group
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Reporting group description:

Subjects aged between, and including, 42 and 69 days at the time of first vaccination received 3 doses of Infanrix IPV and Hiberix co-administered at separate injection sites at 2, 4 and 6 months of age, 3 dose of Synflorix at 6 weeks, 3.5 and 5.5 months of age and 2 doses of Rotarix at 6 weeks and 3.5 months of age. The Infanrix IPV was administered intramuscularly in the right thigh, the Synflorix and Hiberix vaccines were administered intramuscularly in the left thigh and the Rotarix vaccine was administered orally.

### Primary: Number of seroprotected subjects for anti-diphtheria (anti-D) and anti-tetanus (anti-T) antibodies

End point title	Number of seroprotected subjects for anti-diphtheria (anti-D) and anti-tetanus (anti-T) antibodies
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End point description:

A seroprotected subject was defined as a vaccinated subject who had an anti-D and anti-T antibody concentration greater to or above ( $\geq$ ) 0.1 international units per milliliter (IU/mL). The Month 5 results are the primary outcome variables.

End point type	Primary
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End point timeframe:

At Month 0 and Month 5

End point values	Infanrix-IPV+Hib Group	Infanrix IPV Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	213	217		
Units: Subjects				
Anti-D at Month 0	29	30		
Anti-D at Month 5	213	217		
Anti-T at Month 0	64	76		
Anti-T at Month 5	213	217		

### Statistical analyses

Statistical analysis title	Difference in seroprotection rates for anti-D
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Statistical analysis description:

To demonstrate that the immunogenicity of the Infanrix™-IPV+Hib vaccine administered at 2, 4 and 6 months of age was non-inferior to that of the concomitant administration of the Infanrix™ IPV and Hiberix™ vaccines, in terms of immune response to all vaccine antigens, one month after the third dose

of the primary vaccination.

Comparison groups	Infanrix IPV Group v Infanrix-IPV+Hib Group
Number of subjects included in analysis	430
Analysis specification	Pre-specified
Analysis type	non-inferiority <sup>[1]</sup>
Parameter estimate	Difference in seroprotection rate
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.74
upper limit	1.78

Notes:

[1] - UL of the standardized asymptotic 95% CI on the group difference [Infanrix-IPV+Hib Group minus Infanrix IPV Group] in percentage of seroprotected subjects  $\leq 10\%$

<b>Statistical analysis title</b>	Difference in seroprotection rates for anti-T
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Statistical analysis description:

To demonstrate that the immunogenicity of the Infanrix™-IPV+Hib vaccine administered at 2, 4 and 6 months of age was non-inferior to that of the concomitant administration of the Infanrix™ IPV and Hiberix™ vaccines, in terms of immune response to all vaccine antigens, one month after the third dose of the primary vaccination.

Comparison groups	Infanrix-IPV+Hib Group v Infanrix IPV Group
Number of subjects included in analysis	430
Analysis specification	Pre-specified
Analysis type	non-inferiority <sup>[2]</sup>
Parameter estimate	Difference in seroprotection rate
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.74
upper limit	1.78

Notes:

[2] - UL of the standardized asymptotic 95% CI on the group difference [Infanrix-IPV+Hib Group minus Infanrix IPV Group] in percentage of seroprotected subjects  $\leq 10\%$

### **Primary: Number of seroprotected subjects for anti-polyribosyl-ribitol-phosphate (anti-PRP) antibodies**

End point title	Number of seroprotected subjects for anti-polyribosyl-ribitol-phosphate (anti-PRP) antibodies
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End point description:

A seroprotected subject was defined as a vaccinated subject who had an anti-PRP antibody concentration  $\geq 0.15$  micrograms per milliliter ( $\mu\text{g}/\text{mL}$ ). The Month 5 results are the primary outcome variables.

End point type	Primary
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End point timeframe:

At Month 0 and Month 5

<b>End point values</b>	Infanrix-IPV+Hib Group	Infanrix IPV Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	213	217		
Units: Subjects				
Anti-PRP at Month 0	91	109		
Anti-PRP at Month 5	213	217		

## Statistical analyses

<b>Statistical analysis title</b>	Difference in seroprotection rates for anti-PRP
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Statistical analysis description:

To demonstrate that the immunogenicity of the Infanrix™-IPV+Hib vaccine administered at 2, 4 and 6 months of age was non-inferior to that of the concomitant administration of the Infanrix™ IPV and Hiberix™ vaccines, in terms of immune response to all vaccine antigens, one month after the third dose of the primary vaccination.

Comparison groups	Infanrix-IPV+Hib Group v Infanrix IPV Group
Number of subjects included in analysis	430
Analysis specification	Pre-specified
Analysis type	non-inferiority <sup>[3]</sup>
Parameter estimate	Difference in seroprotection rate
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.74
upper limit	1.78

Notes:

[3] - UL of the standardized asymptotic 95% CI on the group difference [Infanrix-IPV+Hib Group minus Infanrix IPV Group] in percentage of seroprotected subjects ≤ 10%

## Primary: Concentrations for anti-D and anti-T antibodies

End point title	Concentrations for anti-D and anti-T antibodies <sup>[4]</sup>
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End point description:

Concentrations were expressed as geometric mean concentrations (GMCs). The seroprotection cut-off of the assay was 0.1 IU/mL.

End point type	Primary
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End point timeframe:

At Month 0 and Month 5

Notes:

[4] - 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 scope of this primary end point was descriptive, no statistical hypothesis test was performed.

<b>End point values</b>	Infanrix-IPV+Hib Group	Infanrix IPV Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	213	217		
Units: IU/mL				
geometric mean (confidence interval 95%)				

Anti-D at Month 0	0.058 (0.055 to 0.061)	0.06 (0.056 to 0.064)		
Anti-D at Month 5	8.096 (7.52 to 8.717)	8.692 (8.125 to 9.298)		
Anti-T at Month 0	0.081 (0.072 to 0.09)	0.091 (0.08 to 0.103)		
Anti-T at Month 5	10.259 (9.654 to 10.902)	12.421 (11.599 to 13.301)		

## Statistical analyses

No statistical analyses for this end point

### Primary: Number of subjects seroprotected for anti-Polio virus type 1, 2 and 3 antibodies

End point title	Number of subjects seroprotected for anti-Polio virus type 1, 2 and 3 antibodies
End point description:	
End point type	Primary
End point timeframe:	At one month after (POST) Dose 3

End point values	Infanrix-IPV+Hib Group	Infanrix IPV Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	212	216		
Units: Subjects				
Anti-Polio 1, POST [N=212;216]	212	216		
Anti-Polio 2, POST [N=204;211]	204	211		
Anti-polio 3, POST [N=198;199]	197	197		

## Statistical analyses

Statistical analysis title	Difference in seroprotection rates for anti-Polio1
Statistical analysis description:	To demonstrate that the immunogenicity of the Infanrix™-IPV+Hib vaccine administered at 2, 4 and 6 months of age was non-inferior to that of the concomitant administration of GSK Biologicals' Infanrix™ IPV and Hiberix™ vaccines, in terms of immune response to anti-Polio type 1 antibodies, one month after the third dose of the primary vaccination.
Comparison groups	Infanrix IPV Group v Infanrix-IPV+Hib Group

Number of subjects included in analysis	428
Analysis specification	Pre-specified
Analysis type	non-inferiority <sup>[5]</sup>
Parameter estimate	Difference in seroprotection rates
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.75
upper limit	1.78

Notes:

[5] - The upper limits of the standardized asymptotic 95% confidence interval (CI) on the group differences [Infanrix IPV Group minus Infanrix-IPV+Hib Group] in percentages of subjects seroprotected against poliovirus type 1 was  $\leq 10\%$ .

<b>Statistical analysis title</b>	Difference in seroprotection rates for anti-Polio2
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Statistical analysis description:

To demonstrate that the immunogenicity of the Infanrix™-IPV+Hib vaccine administered at 2, 4 and 6 months of age was non-inferior to that of the concomitant administration of GSK Biologicals' Infanrix™ IPV and Hiberix™ vaccines, in terms of immune response to anti-Polio type 2 antibodies, one month after the third dose of the primary vaccination.

Comparison groups	Infanrix-IPV+Hib Group v Infanrix IPV Group
Number of subjects included in analysis	428
Analysis specification	Pre-specified
Analysis type	non-inferiority <sup>[6]</sup>
Parameter estimate	Difference in seroprotection rates
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.79
upper limit	1.85

Notes:

[6] - The upper limits of the standardized asymptotic 95% confidence interval (CI) on the group differences [Infanrix IPV Group minus Infanrix-IPV+Hib Group] in percentages of subjects seroprotected against poliovirus type 2 was  $\leq 10\%$ .

<b>Statistical analysis title</b>	Difference in seroprotection rates for anti-Polio3
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Statistical analysis description:

To demonstrate that the immunogenicity of the Infanrix™-IPV+Hib vaccine administered at 2, 4 and 6 months of age was non-inferior to that of the concomitant administration of GSK Biologicals' Infanrix™ IPV and Hiberix™ vaccines, in terms of immune response to anti-Polio type 3 antibodies, one month after the third dose of the primary vaccination.

Comparison groups	Infanrix IPV Group v Infanrix-IPV+Hib Group
Number of subjects included in analysis	428
Analysis specification	Pre-specified
Analysis type	non-inferiority <sup>[7]</sup>
Parameter estimate	Difference in seroprotection rates
Point estimate	-0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.14
upper limit	1.89

Notes:

[7] - The upper limits of the standardized asymptotic 95% confidence interval (CI) on the group differences [Infanrix IPV Group minus Infanrix-IPV+Hib Group] in percentages of subjects seroprotected against poliovirus type 3 was  $\leq 10\%$ .

**Primary: Anti-pertussis toxoid (PT), anti-filamentous haemagglutinin (FHA) and anti-pertactin (PRN) antibody concentrations**

End point title	Anti-pertussis toxoid (PT), anti-filamentous haemagglutinin (FHA) and anti-pertactin (PRN) antibody concentrations
End point description:	
End point type	Primary
End point timeframe:	
At one month after (POST) Dose 3	

End point values	Infanrix-IPV+Hib Group	Infanrix IPV Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	213	217		
Units: EL.U/mL				
geometric mean (confidence interval 95%)				
Anti-PT [N=213;217]	54.2 (50.4 to 58.3)	56 (51.8 to 60.5)		
Anti-FHA [N=213;217]	125 (115.4 to 135.4)	134.2 (124.2 to 145)		
Anti-PRN [N=213;217]	125.8 (116 to 136.5)	133.4 (123 to 144.6)		

**Statistical analyses**

Statistical analysis title	Difference in GMC ratio for anti-PT
Statistical analysis description:	
To demonstrate that the immunogenicity of the Infanrix™-IPV+Hib vaccine administered at 2, 4 and 6 months of age was non-inferior to that of the concomitant administration of GSK Biologicals' Infanrix™ IPV and Hiberix™ vaccines, in terms of immune response to anti-PT antigens, one month after the third dose of the primary vaccination.	
Comparison groups	Infanrix IPV Group v Infanrix-IPV+Hib Group
Number of subjects included in analysis	430
Analysis specification	Pre-specified
Analysis type	non-inferiority <sup>[8]</sup>
Method	ANCOVA
Parameter estimate	Difference in GMC ratio
Point estimate	1.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.93
upper limit	1.15

Notes:

[8] - The upper limits of the 95% confidence interval (CI) on the group ratio [Infanrix IPV Group divided by Infanrix-IPV+Hib Group] of geometric mean concentrations (GMCs) of antibodies against pertussis toxoid (PT) was  $\leq 1.5$ .

<b>Statistical analysis title</b>	Difference in GMC ratio for anti-FHA
Statistical analysis description:	
To demonstrate that the immunogenicity of the Infanrix™-IPV+Hib vaccine administered at 2, 4 and 6 months of age was non-inferior to that of the concomitant administration of GSK Biologicals' Infanrix™ IPV and Hiberix™ vaccines, in terms of immune response to anti-FHA antigens, one month after the third dose of the primary vaccination.	
Comparison groups	Infanrix-IPV+Hib Group v Infanrix IPV Group
Number of subjects included in analysis	430
Analysis specification	Pre-specified
Analysis type	non-inferiority <sup>[9]</sup>
Method	ANCOVA
Parameter estimate	Difference in GMC ratio
Point estimate	1.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.97
upper limit	1.21

Notes:

[9] - The upper limits of the 95% confidence interval (CI) on the group ratio [Infanrix IPV Group divided by Infanrix-IPV+Hib Group] of geometric mean concentrations (GMCs) of antibodies against filamentous haemagglutinin (FHA) was  $\leq 1.5$ .

<b>Statistical analysis title</b>	Difference in GMC ratio for anti-PRN
Statistical analysis description:	
To demonstrate that the immunogenicity of the Infanrix™-IPV+Hib vaccine administered at 2, 4 and 6 months of age was non-inferior to that of the concomitant administration of GSK Biologicals' Infanrix™ IPV and Hiberix™ vaccines, in terms of immune response to anti-PRN antigens, one month after the third dose of the primary vaccination.	
Comparison groups	Infanrix-IPV+Hib Group v Infanrix IPV Group
Number of subjects included in analysis	430
Analysis specification	Pre-specified
Analysis type	non-inferiority <sup>[10]</sup>
Method	ANCOVA
Parameter estimate	Difference in GMC ratio
Point estimate	1.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.96
upper limit	1.21

Notes:

[10] - The upper limits of the 95% confidence interval (CI) on the group ratio [Infanrix IPV Group divided by Infanrix-IPV+Hib Group] of geometric mean concentrations (GMCs) of antibodies against pertactin (PRN) was  $\leq 1.5$ .

**Primary: Number of subjects with anti-PT, anti-FHA and anti-PRN antibody concentrations equal to or above ( $\geq$ ) the cut-off value of 5 ELISA units per millilitre (EL.U/mL)**

End point title	Number of subjects with anti-PT, anti-FHA and anti-PRN antibody concentrations equal to or above ( $\geq$ ) the cut-off value of 5 ELISA units per millilitre (EL.U/mL) <sup>[11]</sup>
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End point description:

Results for the one month after (POST) Dose 3 vaccination timepoint were the primary outcome.

End point type Primary

End point timeframe:

Prior to vaccination (PRE) and one month after (POST) Dose 3

Notes:

[11] - 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 scope of this primary end point was descriptive, no statistical hypothesis test was performed.

<b>End point values</b>	Infanrix-IPV+Hib Group	Infanrix IPV Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	213	217		
Units: Subjects				
Anti-PT, PRE [N=212;216]	27	34		
Anti-PT, POST [N=213;217]	213	217		
Anti-FHA, PRE [N=211;214]	170	178		
Anti-FHA, POST [N=213;217]	213	217		
Anti-PRN, PRE [N=213;217]	25	30		
Anti-PRN, POST [N=213;217]	213	217		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of subjects with any solicited local symptoms

End point title Number of subjects with any solicited local symptoms

End point description:

Assessed solicited local symptoms were pain, redness and swelling at the injection site. Any = incidence of a particular symptom regardless of intensity grade.

End point type Secondary

End point timeframe:

During the 4-day (Days 0-3) follow-up period after any vaccination with Infanrix™-IPV+Hib or Infanrix™ IPV + Hiberix™

<b>End point values</b>	Infanrix-IPV+Hib Group	Infanrix IPV Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	224	227		
Units: Subjects				
Any Pain	143	146		
Any Redness	177	167		
Any Swelling	130	121		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of subjects with any solicited general symptoms

End point title	Number of subjects with any solicited general symptoms
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End point description:

Assessed solicited general symptoms were drowsiness, irritability/fussiness, loss of appetite and fever [defined as tympanic temperature  $\geq 37.5$  degrees Celsius ( $^{\circ}\text{C}$ )]. Any = incidence of a particular symptom regardless of intensity grade.

End point type	Secondary
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End point timeframe:

During the 4-day (Days 0-3) follow-up period after any vaccination with Infanrix<sup>TM</sup>-IPV+Hib or Infanrix<sup>TM</sup> IPV + Hiberix<sup>TM</sup>

End point values	Infanrix-IPV+Hib Group	Infanrix IPV Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	224	227		
Units: Subjects				
Any Drowsiness	153	147		
Any Irritability/Fussiness	181	182		
Any Loss of appetite	120	103		
Temperature $\geq 37.5^{\circ}\text{C}$	83	81		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of subjects with any unsolicited adverse events (AEs)

End point title	Number of subjects with any 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. Any = any unsolicited AE regardless of intensity or relationship to vaccination.

End point type	Secondary
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End point timeframe:

During the 31-day (Days 0-30) follow-up period after any vaccination with Infanrix<sup>TM</sup>-IPV+Hib or Infanrix<sup>TM</sup> IPV + Hiberix<sup>TM</sup>

<b>End point values</b>	Infanrix-IPV+Hib Group	Infanrix IPV Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	224	227		
Units: Subjects				
Any AEs	130	123		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of subjects with any serious adverse events (SAEs)

End point title	Number of subjects with any serious adverse events (SAEs)
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End point description:

Serious adverse events (SAEs) assessed include medical occurrences that result in death, are life threatening, require hospitalization or prolongation of hospitalization or result in disability/incapacity.

End point type	Secondary
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End point timeframe:

During the entire study period (from Month 0 to Month 5 ½)

<b>End point values</b>	Infanrix-IPV+Hib Group	Infanrix IPV Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	224	227		
Units: Subjects				
Any SAEs	25	21		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Concentrations of anti-PRN antibodies

End point title	Concentrations of anti-PRN antibodies
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End point description:

Concentrations were expressed as geometric mean concentrations (GMCs). The seropositivity cut-off of the assay was 5 EL.U/mL.

End point type	Secondary
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End point timeframe:

At Month 0 and Month 5

<b>End point values</b>	Infanrix-IPV+Hib Group	Infanrix IPV Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	213	217		
Units: EL.U/mL				
geometric mean (confidence interval 95%)				
Anti-PRN at Month 0	2.9 (2.7 to 3)	3.1 (2.8 to 3.3)		
Anti-PRN at Month 5	125.8 (116 to 136.5)	133.4 (123 to 144.6)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Concentrations of anti-PRP antibodies

End point title	Concentrations of anti-PRP antibodies
End point description:	Concentrations were expressed as geometric mean concentrations (GMCs). The seroprotection cut-off of the assay was 0.15 µg/mL.
End point type	Secondary
End point timeframe:	At Month 0 and Month 5

<b>End point values</b>	Infanrix-IPV+Hib Group	Infanrix IPV Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	213	217		
Units: µg/mL				
geometric mean (confidence interval 95%)				
Anti-PRP at Month 0	0.165 (0.143 to 0.191)	0.219 (0.184 to 0.26)		
Anti-PRP at Month 5	8.456 (7.283 to 9.819)	18.7 (16.353 to 21.384)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of subjects with a vaccine response

End point title	Number of subjects with a vaccine response
End point description:	Vaccine response was defined as antibody concentration ≥ 5 EL.U/mL at post vaccination, for initially seronegative subjects, and at least maintenance of antibody concentration from pre to post-vaccination (i.e. antibody concentration at post vaccination ≥ 1 fold the pre-vaccination antibody concentration), for initially seropositive subjects.

End point type	Secondary
End point timeframe:	
At Month 5	

<b>End point values</b>	Infanrix- IPV+Hib Group	Infanrix IPV Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	213	217		
Units: Subjects	213	216		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of seroprotected subjects for anti-Polio type 1, 2 and 3

End point title	Number of seroprotected subjects for anti-Polio type 1, 2 and 3
End point description:	

End point type	Secondary
End point timeframe:	
Prior to vaccination (PRE)	

<b>End point values</b>	Infanrix- IPV+Hib Group	Infanrix IPV Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	211	216		
Units: Subjects				
Anti-Polio 1, PRE [N=211;216]	104	89		
Anti-Polio 2, PRE [N=211;214]	119	108		
Anti-Polio 3, PRE [N=211;216]	41	31		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Anti-Polio type 1, 2 and 3 antibody titers

End point title	Anti-Polio type 1, 2 and 3 antibody titers
End point description:	

End point type	Secondary
End point timeframe:	
Prior to vaccination (PRE) and one month after (POST) Dose 3	

<b>End point values</b>	Infanrix- IPV+Hib Group	Infanrix IPV Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	212	216		
Units: Titers				
geometric mean (confidence interval 95%)				
Anti-Polio 1, PRE [N=211;216]	9.5 (8.3 to 11)	9.4 (8 to 11)		
Anti-Polio 1, POST [N=212;216]	328.8 (289.8 to 373.1)	372.7 (323.8 to 428.9)		
Anti-Polio 2, PRE [N=211;214]	10.8 (9.4 to 12.5)	8.8 (7.7 to 9.9)		
Anti-Polio 2 POST [N=204;211]	340.6 (295.4 to 392.6)	400.2 (347.6 to 460.7)		
Anti-Polio 3, PRE [N=211;216]	5.5 (5 to 6.1)	4.9 (4.5 to 5.3)		
Anti-Polio 3, POST [N=198;199]	377.7 (322.3 to 442.6)	465.3 (390.3 to 554.7)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Anti-PT, anti-FHA and anti-PRN antibody concentrations

End point title	Anti-PT, anti-FHA and anti-PRN antibody concentrations
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End point description:

End point type	Secondary
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End point timeframe:

Prior to vaccination (PRE)

<b>End point values</b>	Infanrix- IPV+Hib Group	Infanrix IPV Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	213	217		
Units: EL.U/mL				
geometric mean (confidence interval 95%)				
Anti-PT, PRE [N=212;216]	3 (2.8 to 3.2)	3.1 (2.9 to 3.3)		
Anti-FHA, PRE [N=211;214]	10.5 (9.3 to 12)	11.7 (10.3 to 13.3)		
Anti-PRN, PRE [N=213;217]	2.9 (2.7 to 3)	3.1 (2.8 to 3.3)		

## Statistical analyses

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

SAE(s): during the entire study period (Month 0 to Month 5 ½); Solicited local/general symptoms: during the 4-day (Days 0-3) follow-up period after any vaccination; Unsolicited AE(s): during the 31-day (Days 0-30) follow-up period after any vaccination.

Assessment type	Non-systematic
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### Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

### Reporting groups

Reporting group title	Infanrix IPV Group
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Reporting group description:

Subjects aged between, and including, 42 and 69 days at the time of first vaccination received 3 doses of Infanrix IPV and Hiberix co-administered at separate injection sites at 2, 4 and 6 months of age, 3 dose of Synflorix at 6 weeks, 3.5 and 5.5 months of age and 2 doses of Rotarix at 6 weeks and 3.5 months of age. The Infanrix IPV was administered intramuscularly in the right thigh, the Synflorix and Hiberix vaccines were administered intramuscularly in the left thigh and the Rotarix vaccine was administered orally.

Reporting group title	Infanrix-IPV+Hib Group
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Reporting group description:

Subjects aged between, and including, 42 and 69 days at the time of first vaccination received 3 doses of Infanrix-IPV+Hib at 2, 4 and 6 months of age, 3 doses of Synflorix at 6 weeks, 3.5 and 5.5 months of age and 2 doses of Rotarix at 6 weeks and 3.5 months of age. The Infanrix-IPV+Hib was administered intramuscularly in the right thigh, the Synflorix vaccine was administered intramuscularly in the left thigh and the Rotarix vaccine was administered orally.

<b>Serious adverse events</b>	Infanrix IPV Group	Infanrix-IPV+Hib Group	
Total subjects affected by serious adverse events			
subjects affected / exposed	21 / 227 (9.25%)	25 / 224 (11.16%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Skull fracture			
subjects affected / exposed	1 / 227 (0.44%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Inguinal hernia			
subjects affected / exposed	1 / 227 (0.44%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			

subjects affected / exposed	0 / 227 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Gastrointestinal haemorrhage</b>			
subjects affected / exposed	1 / 227 (0.44%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Intussusception</b>			
subjects affected / exposed	0 / 227 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Respiratory, thoracic and mediastinal disorders</b>			
<b>Asthma</b>			
subjects affected / exposed	1 / 227 (0.44%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Renal and urinary disorders</b>			
<b>Vesicoureteric reflux</b>			
subjects affected / exposed	1 / 227 (0.44%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Infections and infestations</b>			
<b>Bronchiolitis</b>			
subjects affected / exposed	5 / 227 (2.20%)	7 / 224 (3.13%)	
occurrences causally related to treatment / all	0 / 5	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Urinary tract infection</b>			
subjects affected / exposed	6 / 227 (2.64%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 6	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Pneumonia</b>			
subjects affected / exposed	1 / 227 (0.44%)	5 / 224 (2.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gastroenteritis			
subjects affected / exposed	1 / 227 (0.44%)	4 / 224 (1.79%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	3 / 227 (1.32%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	0 / 227 (0.00%)	2 / 224 (0.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis			
subjects affected / exposed	0 / 227 (0.00%)	2 / 224 (0.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Croup infectious			
subjects affected / exposed	0 / 227 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis			
subjects affected / exposed	0 / 227 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis			
subjects affected / exposed	0 / 227 (0.00%)	1 / 224 (0.45%)	
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	0 / 227 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis chronic			

subjects affected / exposed	1 / 227 (0.44%)	0 / 224 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
<b>Respiratory syncytial virus bronchitis</b>		
subjects affected / exposed	0 / 227 (0.00%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
<b>Sepsis</b>		
subjects affected / exposed	1 / 227 (0.44%)	0 / 224 (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 %

<b>Non-serious adverse events</b>	Infanrix IPV Group	Infanrix-IPV+Hib Group
<b>Total subjects affected by non-serious adverse events</b>		
subjects affected / exposed	220 / 227 (96.92%)	218 / 224 (97.32%)
<b>General disorders and administration site conditions</b>		
<b>Pain</b>		
alternative assessment type: Systematic		
subjects affected / exposed	146 / 227 (64.32%)	143 / 224 (63.84%)
occurrences (all)	146	143
<b>Redness</b>		
alternative assessment type: Systematic		
subjects affected / exposed	167 / 227 (73.57%)	177 / 224 (79.02%)
occurrences (all)	167	177
<b>Swelling</b>		
alternative assessment type: Systematic		
subjects affected / exposed	121 / 227 (53.30%)	130 / 224 (58.04%)
occurrences (all)	121	130
<b>Drowsiness</b>		
alternative assessment type: Systematic		

subjects affected / exposed occurrences (all)	147 / 227 (64.76%) 147	153 / 224 (68.30%) 153	
Irritability/Fussiness alternative assessment type: Systematic			
subjects affected / exposed occurrences (all)	182 / 227 (80.18%) 182	181 / 224 (80.80%) 181	
Loss of appetite alternative assessment type: Systematic			
subjects affected / exposed occurrences (all)	103 / 227 (45.37%) 103	120 / 224 (53.57%) 120	
Temperature (Tympanic) alternative assessment type: Systematic			
subjects affected / exposed occurrences (all)	81 / 227 (35.68%) 81	83 / 224 (37.05%) 83	
Gastrointestinal disorders Diarrhoea			
subjects affected / exposed occurrences (all)	10 / 227 (4.41%) 10	29 / 224 (12.95%) 29	
Infections and infestations Nasopharyngitis			
subjects affected / exposed occurrences (all)	29 / 227 (12.78%) 29	37 / 224 (16.52%) 37	
Upper respiratory tract infection			
subjects affected / exposed occurrences (all)	29 / 227 (12.78%) 29	34 / 224 (15.18%) 34	
Bronchitis			
subjects affected / exposed occurrences (all)	14 / 227 (6.17%) 14	14 / 224 (6.25%) 14	
Bronchiolitis			
subjects affected / exposed occurrences (all)	13 / 227 (5.73%) 13	14 / 224 (6.25%) 14	

## **More information**

### **Substantial protocol amendments (globally)**

Were there any global substantial amendments to the protocol? No

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### **Interruptions (globally)**

Were there any global interruptions to the trial? No

### **Limitations and caveats**

None reported