Clinical trial results:
A phase III, multi-centre, open study to assess antibody persistence after completion of the 3-dose primary vaccination course with GlaxoSmithKline (GSK) Biologicals' 10-valent pneumococcal conjugate vaccine in study 10PN-PD-DIT-048 (111654) in Singapore as well as the safety, reactogenicity and immunogenicity of GSK Biologicals' 10-valent pneumococcal conjugate vaccine when given as a booster dose at 18-21 months of age.

Summary

EudraCT number	2012-000819-82
Trial protocol	Outside EU/EEA
Global end of trial date	17 February 2011

Results information

Result version number	v1
This version publication date	05 April 2016
First version publication date	28 June 2015

Trial information

Trial identification

Sponsor protocol code	113266

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01119625
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	16 December 2011
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 February 2011
Global end of trial reached?	Yes
Global end of trial date	17 February 2011
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the antibody persistence induced by the GSK Biologicals' 10-valent pneumococcal conjugate vaccine (commercial lot versus phase III clinical lot), when co-administered with DTPa-IPV/Hib 13-16 months after completion of the 3-dose primary vaccination course in study 10PN-PD-DIT-048 (111654)

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	12 July 2010
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	Singapore: 238
Worldwide total number of subjects	238
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)	238
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:

This booster study was conducted in Singapore only where the primary vaccination phase (NCT00808444) was conducted in Singapore and Malaysia.

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	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Synflorix™ Commercial-Commercial + Infanrix™-IPV/Hib Group

Arm description:

Children primed with 3 doses of commercial lot of Synflorix™ co-administered with Rotarix™ and Infanrix™-hexa in the primary phase of the study (NCT00808444) and boosted at 18-21 months of age, with commercial lot of Synflorix™ co-administered with Infanrix™-IPV/Hib. The Synflorix™ vaccine (commercial lots) was administered intramuscularly in the right deltoid or anterolateral thigh and the Infanrix™-IPV/Hib vaccine was administered intramuscularly in the left deltoid or anterolateral thigh.

Arm type	Experimental
Investigational medicinal product name	Pneumococcal vaccine GSK1024850A
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

One dose, administered intramuscularly in the right deltoid or anterolateral thigh.

Investigational medicinal product name	Infanrix-IPV/Hib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

One dose, administered intramuscularly in the left deltoid or anterolateral thigh.

Arm title	Synflorix™ Clinical-Commercial + Infanrix™-IPV/Hib Group

Arm description:

Children primed with 3 doses of clinical lot of Synflorix™ + Rotarix™ co-administered with Infanrix™-hexa in the primary phase of the study (NCT00808444) and boosted at 18-21 months of age, with commercial lot of Synflorix™ co-administered with Infanrix™-IPV/Hib. The Synflorix™ vaccine (clinical and commercial lots) was administered intramuscularly in the right deltoid or anterolateral thigh and the Infanrix™-IPV/Hib vaccine was administered intramuscularly in the left deltoid or anterolateral thigh.

Arm type	Active comparator

Investigational medicinal product name	Pneumococcal vaccine GSK1024850A
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

One dose, administered intramuscularly in the right deltoid or anterolateral thigh.

Investigational medicinal product name	Infanrix-IPV/Hib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

One dose, administered intramuscularly in the left deltoid or anterolateral thigh.

Number of subjects in period 1	Synflorix™ Commercial-Commercial + Infanrix™-IPV/Hib Group	Synflorix™ Clinical-Commercial + Infanrix™-IPV/Hib Group
Started	118	120
Completed	115	116
Not completed	3	4
Consent withdrawn by subject	2	1
out of window period	-	1
Lost to follow-up	1	2

Baseline characteristics

Reporting groups

Reporting group title	Synflorix™ Commercial-Commercial + Infanrix™-IPV/Hib Group

Reporting group description:

Children primed with 3 doses of commercial lot of Synflorix™ co-administered with Rotarix™ and Infanrix™-hexa in the primary phase of the study (NCT00808444) and boosted at 18-21 months of age, with commercial lot of Synflorix™ co-administered with Infanrix™-IPV/Hib. The Synflorix™ vaccine (commercial lots) was administered intramuscularly in the right deltoid or anterolateral thigh and the Infanrix™-IPV/Hib vaccine was administered intramuscularly in the left deltoid or anterolateral thigh.

Reporting group title	Synflorix™ Clinical-Commercial + Infanrix™-IPV/Hib Group

Reporting group description:

Children primed with 3 doses of clinical lot of Synflorix™ + Rotarix™ co-administered with Infanrix™-hexa in the primary phase of the study (NCT00808444) and boosted at 18-21 months of age, with commercial lot of Synflorix™ co-administered with Infanrix™-IPV/Hib. The Synflorix™ vaccine (clinical and commercial lots) was administered intramuscularly in the right deltoid or anterolateral thigh and the Infanrix™-IPV/Hib vaccine was administered intramuscularly in the left deltoid or anterolateral thigh.

Reporting group values	Synflorix™ Commercial-Commercial + Infanrix™-IPV/Hib Group	Synflorix™ Clinical-Commercial + Infanrix™-IPV/Hib Group	Total
Number of subjects	118	120	238
Age categorical			
Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Units: months			
arithmetic mean	18.8	18.9	
standard deviation	± 0.84	± 0.87	-
Gender categorical			
Units: Subjects			
Female	62	49	111
Male	56	71	127

End points

End points reporting groups

Reporting group title	Synflorix™ Commercial-Commercial + Infanrix™-IPV/Hib Group

Reporting group description:

Children primed with 3 doses of commercial lot of Synflorix™ co-administered with Rotarix™ and Infanrix™-hexa in the primary phase of the study (NCT00808444) and boosted at 18-21 months of age, with commercial lot of Synflorix™ co-administered with Infanrix™-IPV/Hib. The Synflorix™ vaccine (commercial lots) was administered intramuscularly in the right deltoid or anterolateral thigh and the Infanrix™-IPV/Hib vaccine was administered intramuscularly in the left deltoid or anterolateral thigh.

Reporting group title	Synflorix™ Clinical-Commercial + Infanrix™-IPV/Hib Group

Reporting group description:

Children primed with 3 doses of clinical lot of Synflorix™ + Rotarix™ co-administered with Infanrix™-hexa in the primary phase of the study (NCT00808444) and boosted at 18-21 months of age, with commercial lot of Synflorix™ co-administered with Infanrix™-IPV/Hib. The Synflorix™ vaccine (clinical and commercial lots) was administered intramuscularly in the right deltoid or anterolateral thigh and the Infanrix™-IPV/Hib vaccine was administered intramuscularly in the left deltoid or anterolateral thigh.

Primary: Concentrations of antibodies against vaccine pneumococcal serotypes.

End point title	Concentrations of antibodies against vaccine pneumococcal serotypes.[1]

End point description:

Vaccine pneumococcal serotypes assessed were serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F. Concentrations were expressed as geometric mean concentrations (GMCs) in microgram per millilitre (µg/mL). Pneumococcal serotype specific total imunoglobuline G (IgG) antibodies were measured by 22F-inhibition Enzyme-linked immunosorbent assay (ELISA). The cut-off of the assay was 0.05 µg/mL.

End point type	Primary

End point timeframe:

Before booster vaccination at Month 0

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	Synflorix™ Commercial-Commercial + Infanrix™-IPV/Hib Group	Synflorix™ Clinical-Commercial + Infanrix™-IPV/Hib Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	111	112		
Units: µg/mL				
geometric mean (confidence interval 95%)				
Anti-1 [Pre-booster] (N=111;112)	0.48 (0.4 to 0.57)	0.35 (0.3 to 0.41)		
Anti-4 [Pre-booster] (N=107;106)	0.56 (0.48 to 0.67)	0.48 (0.4 to 0.58)		
Anti-5 [Pre-booster] (N=103;103)	0.76 (0.65 to 0.89)	0.54 (0.47 to 0.63)		
Anti-6B [Pre-booster] (N=103;102)	0.34 (0.29 to 0.4)	0.32 (0.25 to 0.41)		
Anti-7F [Pre-booster] (N=104;105)	0.88 (0.75 to 1.03)	0.91 (0.78 to 1.07)		

Anti-9V [Pre-booster] (N=105;102)	0.9 (0.77 to 1.06)	0.73 (0.62 to 0.85)		
Anti-14 [Pre-booster] (N=105;100)	1.06 (0.86 to 1.31)	0.91 (0.75 to 1.11)		
Anti-18C [Pre-booster] (N=109;108)	0.83 (0.69 to 1.01)	0.78 (0.65 to 0.93)		
Anti-19F [Pre-booster] (N=103;103)	1.1 (0.87 to 1.4)	0.96 (0.82 to 1.13)		
Anti-23F [Pre-booster] (N=108;106)	0.66 (0.51 to 0.84)	0.47 (0.38 to 0.58)		

Statistical analyses

No statistical analyses for this end point

Primary: Concentrations of antibodies against protein D (PD).

End point title	Concentrations of antibodies against protein D (PD).[2]

End point description:

Anti-PD antibodies were determined using an ELISA assay. Concentration of specific PD antibodies was determined, using a standard reference serum. The cut-off of the assay is 100 ELISA units per millilitre (EU/mL).

End point type	Primary

End point timeframe:

Before booster vaccination at Month 0

Notes:

[2] - 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	Synflorix™ Commercial-Commercial + Infanrix™-IPV/Hib Group	Synflorix™ Clinical-Commercial + Infanrix™-IPV/Hib Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	116	118		
Units: EU/mL				
geometric mean (confidence interval 95%)				
Anti-PD [pre-booster]	801.6 (693.1 to 927.1)	619.7 (530.1 to 724.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reporting any and grade 3 solicited local adverse events (AEs).

End point title	Number of subjects reporting any and grade 3 solicited local adverse events (AEs).

End point description:

Solicited AEs = AEs to be recorded as endpoints in the clinical study. The presence/occurrence/intensity of these events is actively solicited from the subject or an observer during a specified post-vaccination follow-up period. Solicited local symptoms assessed were pain, redness and swelling. Any = occurrence of any local symptom regardless of intensity grade. Grade 3 pain = cried when limb was moved/spontaneously painful. Grade 3 redness/swelling = redness/swelling above 30 millimetre (mm).

End point type	Secondary

End point timeframe:

Within 4 days (Days 0-3) after booster vaccination.

End point values	Synflorix™ Commercial-Commercial + Infanrix™-IPV/Hib Group	Synflorix™ Clinical-Commercial + Infanrix™-IPV/Hib Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	117	117		
Units: Subjects				
Any pain	61	70		
Grade 3 pain	8	13		
Any redness	66	61		
Grade 3 redness	0	0		
Any swelling	45	49		
Grade 3 swelling	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reporting any, grade 3 and related solicited general adverse events (AEs).

End point title	Number of subjects reporting any, grade 3 and related solicited general adverse events (AEs).

End point description:

Solicited general symptoms assessed were drowsiness, irritability, loss of appetite and fever (= axillary temperature equal to or above 37.5 degrees Celsius (°C)). Any= occurrence of any general symptom regardless of intensity grade or relationship to vaccination Grade 3 drowsiness = drowsiness which prevented normal activity. Grade 3 irritability = crying that could not be comforted/ prevented normal activity. Grade 3 loss of appetite = not eating at all. Grade 3 fever = temperature >39.5°C. Related = solicited symptom assessed by the investigator as causally related to study vaccination.

End point type	Secondary

End point timeframe:

Within 4 days (Days 0-3) after booster vaccination.

End point values	Synflorix™ Commercial-Commercial + Infanrix™-IPV/Hib Group	Synflorix™ Clinical-Commercial + Infanrix™-IPV/Hib Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	117	117		
Units: Subjects				
Any drowsiness	38	49		
Grade 3 drowsiness	2	2		
Related drowsiness	38	48		
Fever >= 37.5°C	56	75		
Fever > 39.5°C	1	1		
Related fever	55	72		
Any irritability	51	67		
Grade 3 irritability	3	5		
Related irritability	50	67		
Any loss of appetite	42	49		
Grade 3 loss of appetite	1	1		
Related loss of appetite	41	47		

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:

Unsolicited AEs = Any AE (i.e. any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product) reported in addition to those solicited during the clinical study. Also any "solicited" symptom with onset outside the specified period of follow-up for solicited symptoms was reported as an unsolicited adverse event.

End point type	Secondary

End point timeframe:

Within 31 days (Days 0-30) after booster vaccination

End point values	Synflorix™ Commercial-Commercial + Infanrix™-IPV/Hib Group	Synflorix™ Clinical-Commercial + Infanrix™-IPV/Hib Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	118	120		
Units: Subjects				
Unsolicited AEs	18	25		

Statistical analyses

No statistical analyses for this end point

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

End point title	Number of subjects reporting serious adverse events (SAEs).

End point description:

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

End point type	Secondary

End point timeframe:

During the entire study period, from the booster vaccination, at Month 0, up to the study end, at Month 1

End point values	Synflorix™ Commercial-Commercial + Infanrix™-IPV/Hib Group	Synflorix™ Clinical-Commercial + Infanrix™-IPV/Hib Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	118	120		
Units: Subjects				
SAEs	0	4		

Statistical analyses

No statistical analyses for this end point

Secondary: Concentrations of antibodies against cross-reactive pneumococcal serotypes.

End point title	Concentrations of antibodies against cross-reactive pneumococcal serotypes.

End point description:

Cross-reactive pneumococcal serotypes assessed were serotypes 6A and 19A. Concentrations were expressed as geometric mean concentrations (GMCs) in microgram per millilitre (µg/mL). The antibody concentrations against the cross-reactive pneumococcal serotypes 6A and 19A were determined by 22F-inhibition Enzyme-linked immunosorbent assay (ELISA). The cut-off of the assay was 0.05 µg/mL.

End point type	Secondary

End point timeframe:

Before booster vaccination at Month 0

End point values	Synflorix™ Commercial-Commercial + Infanrix™-IPV/Hib Group	Synflorix™ Clinical-Commercial + Infanrix™-IPV/Hib Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	112	111		
Units: µg/mL				
geometric mean (confidence interval 95%)				
Anti-6A [pre-booster] (N=109;111)	0.23 (0.18 to 0.28)	0.21 (0.16 to 0.26)		
Anti-19A [pre-booster] (N=112;109)	0.18 (0.14 to 0.22)	0.19 (0.15 to 0.24)		

Statistical analyses

No statistical analyses for this end point

Secondary: Concentrations of antibodies against diphtheria and tetanus.

End point title	Concentrations of antibodies against diphtheria and tetanus.

End point description:

Concentrations were expressed as geometric mean concentrations (GMCs) in International units per millilitre (IU/mL). The cut-off of the assay was 0.1 IU/mL.

End point type	Secondary

End point timeframe:

Before booster vaccination at Month 0

End point values	Synflorix™ Commercial-Commercial + Infanrix™-IPV/Hib Group	Synflorix™ Clinical-Commercial + Infanrix™-IPV/Hib Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	49		
Units: IU/mL				
geometric mean (confidence interval 95%)				
Anti-diphtheria [pre-booster] (N=42;49)	0.32 (0.25 to 0.39)	0.3 (0.24 to 0.39)		
Anti-tetanus [pre-booster] (N=43;48)	0.51 (0.43 to 0.61)	0.47 (0.38 to 0.59)		

Statistical analyses

No statistical analyses for this end point

Secondary: Concentrations of antibodies against pertussis toxoid (PT), filamentous

haemagglutinin (FHA) and pertactin (PRN).

End point title	Concentrations of antibodies against pertussis toxoid (PT), filamentous haemagglutinin (FHA) and pertactin (PRN).

End point description:

Concentrations were expressed as geometric mean concentrations (GMCs) in ELISA units per millilitre (EU/mL). The cut-off of the assay was 5 EU/mL.

End point type	Secondary

End point timeframe:

Before booster vaccination at Month 0

End point values	Synflorix™ Commercial-Commercial + Infanrix™-IPV/Hib Group	Synflorix™ Clinical-Commercial + Infanrix™-IPV/Hib Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	47		
Units: EU/mL				
geometric mean (confidence interval 95%)				
Anti-PT [pre-booster] (N=41;45)	5.7 (4.5 to 7.2)	6.5 (4.7 to 8.9)		
Anti-FHA [pre-booster] (N=40;46)	19.5 (15.1 to 25.3)	29.2 (21.5 to 39.6)		
Anti-PRN [pre-booster] (N=42;47)	14.8 (10.7 to 20.6)	15.1 (11.1 to 20.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Concentrations of antibodies against polyribosyl-ribitol phosphate (PRP).

End point title	Concentrations of antibodies against polyribosyl-ribitol phosphate (PRP).

End point description:

Concentrations were expressed as geometric mean concentrations (GMCs) in microgram per millilitre (µg/mL). The cut-off of the assay was 0.15 µg/mL.

End point type	Secondary

End point timeframe:

Before booster vaccination at Month 0

End point values	Synflorix™ Commercial-Commercial + Infanrix™-IPV/Hib Group	Synflorix™ Clinical-Commercial + Infanrix™-IPV/Hib Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	57		
Units: µg/mL				
geometric mean (confidence interval 95%)				
Anti-PRP [pre-booster]	0.68 (0.5 to 0.92)	0.85 (0.65 to 1.11)		

Statistical analyses

No statistical analyses for this end point

Secondary: Titers of antibodies against poliovirus types 1, 2 and 3.

End point title	Titers of antibodies against poliovirus types 1, 2 and 3.

End point description:

Titers were expresses as geometric mean titers (GMTs). The cut-off of the assay was 8.

End point type	Secondary

End point timeframe:

Before booster vaccination at Month 0

End point values	Synflorix™ Commercial-Commercial + Infanrix™-IPV/Hib Group	Synflorix™ Clinical-Commercial + Infanrix™-IPV/Hib Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	25		
Units: Titers				
geometric mean (confidence interval 95%)				
Anti-polio 1 [pre-booster]	40.7 (23.2 to 71.3)	32.8 (19.1 to 56.3)		
Anti-polio 2 [pre-booster]	38.7 (26.5 to 56.7)	34.9 (18.8 to 64.7)		
Anti-polio 3 [pre-booster]	40.7 (24.4 to 67.8)	43.3 (24 to 78)		

Statistical analyses

No statistical analyses for this end point

Secondary: Concentrations of antibodies against vaccine pneumococcal serotypes.

End point title	Concentrations of antibodies against vaccine pneumococcal

	serotypes.

End point description:

Vaccine pneumococcal serotypes assessed were serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F. Concentrations were expressed as geometric mean concentrations (GMCs) in microgram per millilitre (µg/mL). Pneumococcal serotype specific total imunoglobuline G (IgG) antibodies were measured by 22F-inhibition Enzyme-linked immunosorbent assay (ELISA). The cut-off of the assay was 0.05 µg/mL.

End point type	Secondary

End point timeframe:

Before and one month after booster vaccination (at Month 0 and Month 1)

End point values	Synflorix™ Commercial-Commercial + Infanrix™-IPV/Hib Group	Synflorix™ Clinical-Commercial + Infanrix™-IPV/Hib Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	109	111		
Units: µg/mL				
geometric mean (confidence interval 95%)				
Anti-1 [pre-booster] (N=109;109)	0.48 (0.4 to 0.57)	0.35 (0.3 to 0.41)		
Anti-1 [post-booster] (N=107;111)	7.14 (6.12 to 8.32)	6.29 (5.38 to 7.35)		
Anti-4 [pre-booster] (N=105;103)	0.56 (0.47 to 0.67)	0.48 (0.4 to 0.58)		
Anti-4 [post-booster] (N=106;109)	7.53 (6.44 to 8.8)	7.43 (6.33 to 8.71)		
Anti-5 [pre-booster] (N=101;100)	0.77 (0.65 to 0.9)	0.54 (0.46 to 0.62)		
Anti-5 [post-booster] (N=106;108)	7.91 (6.91 to 9.06)	7.16 (6.25 to 8.2)		
Anti-6B [pre-booster] (N=101;99)	0.34 (0.29 to 0.4)	0.32 (0.25 to 0.41)		
Anti-6B [post-booster] (N=106;109)	3.3 (2.85 to 3.81)	3.12 (2.59 to 3.76)		
Anti-7F [pre-booster] (N=102;102)	0.88 (0.75 to 1.04)	0.93 (0.8 to 1.08)		
Anti-7F [post-booster] (N=106;109)	9.02 (7.77 to 10.47)	9.25 (8.04 to 10.64)		
Anti-9V [pre-booster] (N=103;99)	0.9 (0.77 to 1.06)	0.72 (0.62 to 0.84)		
Anti-9V [post-booster] (N=107;109)	9.36 (8.15 to 10.75)	10.42 (8.94 to 12.14)		
Anti-14 [pre-booster] (N=103;97)	1.05 (0.85 to 1.31)	0.93 (0.76 to 1.14)		
Anti-14 [post-booster] (N=106;106)	13.03 (10.95 to 15.5)	13.28 (11.06 to 15.95)		
Anti-18C [pre-booster] (N=107;105)	0.83 (0.69 to 1.01)	0.78 (0.66 to 0.94)		
Anti-18C [post-booster] (N=106;108)	19.8 (17.02 to 23.03)	24.19 (20.66 to 28.33)		
Anti-19F [pre-booster] (N=101;100)	1.11 (0.87 to 1.41)	0.97 (0.82 to 1.14)		
Anti-19F [post-booster] (N=106;108)	19.68 (17.22 to 22.51)	20.55 (17.62 to 23.98)		

Anti-23F [pre-booster] (N=106;103)	0.65 (0.5 to 0.83)	0.47 (0.38 to 0.59)		
Anti-23F [post-booster] (N=107;109)	7.19 (5.94 to 8.71)	6.83 (5.77 to 8.07)		

Statistical analyses

No statistical analyses for this end point

Secondary: Concentrations of antibodies against cross-reactive pneumococcal serotypes.

End point title	Concentrations of antibodies against cross-reactive pneumococcal serotypes.

End point description:

Cross-reactive pneumococcal serotypes assessed were serotypes 6A and 19A. Concentrations were expressed as geometric mean concentrations (GMCs) in microgram per millilitre (µg/mL). The antibody concentrations against the cross-reactive pneumococcal serotypes 6A and 19A were determined by 22F-inhibition Enzyme-linked immunosorbent assay (ELISA). The cut-off of the assay was 0.05 µg/mL.

End point type	Secondary

End point timeframe:

Before and one month after booster vaccination (at Month 0 and Month 1)

End point values	Synflorix™ Commercial-Commercial + Infanrix™-IPV/Hib Group	Synflorix™ Clinical-Commercial + Infanrix™-IPV/Hib Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	110	109		
Units: µg/mL				
geometric mean (confidence interval 95%)				
Anti-6A [pre-booster] (N=107;108)	0.23 (0.18 to 0.28)	0.21 (0.16 to 0.26)		
Anti-6A [post-booster] (N=106;108)	2.13 (1.7 to 2.66)	1.99 (1.6 to 2.49)		
Anti-19A [pre-booster] (N=110;106)	0.18 (0.14 to 0.22)	0.2 (0.15 to 0.25)		
Anti-19A [post-booster] (N=106;109)	2.13 (1.65 to 2.76)	2.96 (2.26 to 3.87)		

Statistical analyses

No statistical analyses for this end point

Secondary: Concentrations of antibodies against protein D (PD).

End point title	Concentrations of antibodies against protein D (PD).

End point description:

Anti-PD antibodies were determined using an ELISA assay. Concentration of specific PD antibodies was

determined, using a standard reference serum. The cut-off of the assay is 100 ELISA units per millilitre (EU/mL).

End point type	Secondary

End point timeframe:

Before and one month after booster vaccination (at Month 0 and Month 1)

End point values	Synflorix™ Commercial-Commercial + Infanrix™-IPV/Hib Group	Synflorix™ Clinical-Commercial + Infanrix™-IPV/Hib Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	113	115		
Units: EU/mL				
geometric mean (confidence interval 95%)				
Anti-PD [pre-booster] (N=113;115)	794.9 (686.3 to 920.7)	618.4 (527.8 to 724.6)		
Anti-PD [post-booster] (N=107;111)	3631.3 (3149.2 to 4187.2)	3115.9 (2634.7 to 3685.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Concentrations of antibodies against diphtheria and tetanus.

End point title	Concentrations of antibodies against diphtheria and tetanus.

End point description:

Concentrations were expressed as geometric mean concentrations (GMCs) in International units per millilitre (IU/mL). The cut-off of the assay was 0.1 IU/mL.

End point type	Secondary

End point timeframe:

Before and one month after booster vaccination (at Month 0 and Month 1)

End point values	Synflorix™ Commercial-Commercial + Infanrix™-IPV/Hib Group	Synflorix™ Clinical-Commercial + Infanrix™-IPV/Hib Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	55		
Units: IU/mL				
geometric mean (confidence interval 95%)				
Anti-diphtheria [pre-booster] (N=41;47)	0.31 (0.25 to 0.39)	0.29 (0.23 to 0.37)		
Anti-diphtheria [post-booster] (N=52;55)	8.17 (6.72 to 9.94)	10.89 (9.16 to 12.94)		

Anti-tetanus [pre-booster] (N=42;46)	0.52 (0.43 to 0.62)	0.46 (0.37 to 0.58)		
Anti-tetanus [post-booster] (N=52;55)	14.35 (12.41 to 16.6)	14.73 (12.75 to 17.01)		

Statistical analyses

No statistical analyses for this end point

Secondary: Concentrations of antibodies against pertussis toxoid (PT), filamentous haemagglutinin (FHA) and pertactin (PRN).

End point title	Concentrations of antibodies against pertussis toxoid (PT), filamentous haemagglutinin (FHA) and pertactin (PRN).

End point description:

Concentrations were expressed as geometric mean concentrations (GMCs) in ELISA units per millilitre (EU/mL). The cut-off of the assay was 5 EU/mL.

End point type	Secondary

End point timeframe:

Before and one month after booster vaccination (at Month 0 and Month 1)

End point values	Synflorix™ Commercial-Commercial + Infanrix™-IPV/Hib Group	Synflorix™ Clinical-Commercial + Infanrix™-IPV/Hib Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	55		
Units: EU/mL				
geometric mean (confidence interval 95%)				
Anti-PT [pre-booster] (N=40;43)	5.8 (4.5 to 7.3)	6.8 (4.9 to 9.3)		
Anti-PT [post-booster] (N=52;55)	80.8 (65.6 to 99.4)	86 (67.9 to 108.9)		
Anti-FHA [pre-booster] (N=39;44)	19.3 (14.8 to 25.2)	29.6 (21.5 to 40.7)		
Anti-FHA [post-booster] (N=52;54)	358.3 (290.5 to 442)	484.3 (418.9 to 559.9)		
Anti-PRN [pre-booster] (N=41;45)	15 (10.7 to 20.9)	15.4 (11.3 to 21)		
Anti-PRN [post-booster] (N=52;55)	314.3 (229.6 to 430.2)	509.5 (387 to 670.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Concentrations of antibodies against polyribosyl-ribitol phosphate (PRP).

End point title	Concentrations of antibodies against polyribosyl-ribitol

	phosphate (PRP).

End point description:

Concentrations were expressed as geometric mean concentrations (GMCs) in microgram per millilitre (µg/mL). The cut-off of the assay was 0.15 µg/mL.

End point type	Secondary

End point timeframe:

Before and one month after booster vaccination (at Month 0 and Month 1)

End point values	Synflorix™ Commercial-Commercial + Infanrix™-IPV/Hib Group	Synflorix™ Clinical-Commercial + Infanrix™-IPV/Hib Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	55		
Units: µg/mL				
geometric mean (confidence interval 95%)				
Anti-PRP [pre-booster] (N=51;55)	0.66 (0.48 to 0.9)	0.84 (0.64 to 1.12)		
Anti-PRP [post-booster] (N=53;55)	58.26 (43.71 to 77.66)	49.36 (37.4 to 65.15)		

Statistical analyses

No statistical analyses for this end point

Secondary: Titers of antibodies against poliovirus types 1, 2 and 3.

End point title	Titers of antibodies against poliovirus types 1, 2 and 3.

End point description:

Titers were expresses as geometric mean titers (GMTs). The cut-off of the assay was 8.

End point type	Secondary

End point timeframe:

Before and one month after booster vaccination (at Month 0 and Month 1)

End point values	Synflorix™ Commercial-Commercial + Infanrix™-IPV/Hib Group	Synflorix™ Clinical-Commercial + Infanrix™-IPV/Hib Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	27		
Units: Titers				
geometric mean (confidence interval 95%)				
Anti-polio 1 [pre-booster] (N=28;25)	44.2 (25.3 to 77.1)	32.8 (19.1 to 56.3)		

Anti-polio 1 [post-booster] (N=25;27)	982.2 (688 to 1402.3)	985.2 (627.9 to 1546)		
Anti-polio 2 [pre-booster] (N=28;25)	38 (25.7 to 56.4)	34.9 (18.8 to 64.7)		
Anti-polio 2 [post-booster] (N=25;27)	1144.1 (773.7 to 1691.7)	823.4 (553.5 to 1224.8)		
Anti-polio 3 [pre-booster] (N=28;25)	41 (24.2 to 69.7)	43.3 (24 to 78)		
Anti-polio 3 [post-booster] (N=25;26)	1350.8 (857.4 to 2128.2)	1527.4 (1016.6 to 2294.7)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Solicited AEs: Within 4 days (Days 0-3) after booster vaccination. SAEs: During the entire study period, from the booster vaccination, at Month 0, up to the study end, at Month 1. Unsolicited AEs:Within 31 days (Days 0-30) after booster vaccination.

Adverse event reporting additional description:

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

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	14.1

Reporting groups

Reporting group title	Synflorix™ Clinical-Commercial + Infanrix™-IPV/Hib Group

Reporting group description:

Children primed with 3 doses of clinical lot of Synflorix™ + Rotarix™ co-administered with Infanrix™-hexa in the primary phase of the study (NCT00808444) and boosted with commercial lot of Synflorix™ co-administered with Infanrix™-IPV/Hib. The Synflorix™ vaccine (clinical and commercial lots) was administered intramuscularly in the right deltoid or anterolateral thigh and the Infanrix™-IPV/Hib vaccine was administered intramuscularly in the left deltoid or anterolateral thigh.

Reporting group title	Synflorix™ Commercial-Commercial + Infanrix™-IPV/Hib Group

Reporting group description:

Children primed with 3 doses of commercial lot of Synflorix™ co-administered with Rotarix™ and Infanrix™-hexa in the primary phase of the study (NCT00808444) and boosted with commercial lot of Synflorix™ co-administered with Infanrix™-IPV/Hib. The Synflorix™ vaccine (clinical and commercial lots) was administered intramuscularly in the right deltoid or anterolateral thigh and the Infanrix™-IPV/Hib vaccine was administered intramuscularly in the left deltoid or anterolateral thigh.

Serious adverse events	Synflorix™ Clinical-Commercial + Infanrix™-IPV/Hib Group	Synflorix™ Commercial-Commercial + Infanrix™-IPV/Hib Group	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 118 (0.00%)	4 / 120 (3.33%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Laceration			
subjects affected / exposed	0 / 118 (0.00%)	1 / 120 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Leukopenia			

subjects affected / exposed	0 / 118 (0.00%)	1 / 120 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	0 / 118 (0.00%)	1 / 120 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	0 / 118 (0.00%)	2 / 120 (1.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchiolitis			
subjects affected / exposed	0 / 118 (0.00%)	1 / 120 (0.83%)	
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	Synflorix™ Clinical-Commercial + Infanrix™-IPV/Hib Group	Synflorix™ Commercial-Commercial + Infanrix™-IPV/Hib Group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	66 / 118 (55.93%)	75 / 120 (62.50%)	
General disorders and administration site conditions			
Pain			
alternative assessment type: Systematic			
subjects affected / exposed[1]	61 / 117 (52.14%)	70 / 117 (59.83%)	
occurrences (all)	61	70	
Redness			
alternative assessment type: Systematic			
subjects affected / exposed[2]	66 / 117 (56.41%)	61 / 117 (52.14%)	
occurrences (all)	66	61	
Swelling			
alternative assessment type:			

Systematic			
subjects affected / exposed[3]	45 / 117 (38.46%)	49 / 117 (41.88%)	
occurrences (all)	45	49	
Drowsiness			
alternative assessment type: Systematic			
subjects affected / exposed[4]	38 / 117 (32.48%)	49 / 117 (41.88%)	
occurrences (all)	38	49	
Fever			
alternative assessment type: Systematic			
subjects affected / exposed[5]	56 / 117 (47.86%)	75 / 117 (64.10%)	
occurrences (all)	56	75	
Irritability			
alternative assessment type: Systematic			
subjects affected / exposed[6]	51 / 117 (43.59%)	67 / 117 (57.26%)	
occurrences (all)	51	67	
Loss of appetite			
alternative assessment type: Systematic			
subjects affected / exposed[7]	42 / 117 (35.90%)	49 / 117 (41.88%)	
occurrences (all)	42	49	
Respiratory, thoracic and mediastinal disorders			
Rhinorrhoea			
subjects affected / exposed	7 / 118 (5.93%)	5 / 120 (4.17%)	
occurrences (all)	7	5	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	4 / 118 (3.39%)	6 / 120 (5.00%)	
occurrences (all)	4	6	

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 analysis was performed on the Total Vaccinated cohort, only on subjects with their symptom sheets completed.

[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 analysis was performed on the Total Vaccinated cohort, only on subjects with their symptom sheets completed.

[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 analysis was performed on the Total Vaccinated cohort, only on subjects with their symptom sheets completed.

[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 analysis was performed on the Total Vaccinated cohort, only on subjects with their symptom sheets completed.
[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 analysis was performed on the Total Vaccinated cohort, only on subjects with their symptom sheets completed.
[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 analysis was performed on the Total Vaccinated cohort, only on subjects with their symptom sheets completed.
[7] - 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 analysis was performed on the Total Vaccinated cohort, only on subjects with their symptom sheets completed.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported