



## Clinical trial results:

**A phase III, randomized, open, controlled study to assess the immunogenicity, safety and reactogenicity of GlaxoSmithKline (GSK) Biologicals' 10-valent pneumococcal conjugate vaccine as a 3-dose primary immunization course at 6, 10 and 14 weeks of age in Sub-Saharan Africa, co-administered with GSK Biologicals' DTPw-HBV/Hib and OPV vaccines.**

### Summary

EudraCT number	2011-004650-25
Trial protocol	Outside EU/EEA
Global end of trial date	10 December 2009

### Results information

Result version number	v3 (current)
This version publication date	22 July 2022
First version publication date	05 July 2015
Version creation reason	<ul style="list-style-type: none"><li>• Correction of full data set</li></ul> Correction of full data set and alignment between registries.

### Trial information

#### Trial identification

Sponsor protocol code	110521
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#### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00678301
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	13 October 2010
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	10 December 2009
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

To evaluate the immunogenicity of GSK Biologicals' 10-valent pneumococcal conjugate vaccine in infants in Sub-Saharan Africa, one month post dose 3.

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 consented to participate in the study through consent by his/her parents/guardians until she/he was discharged.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	18 June 2008
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	Nigeria: 127
Country: Number of subjects enrolled	Mali: 238
Worldwide total number of subjects	365
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)	365
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:

At screening, the following steps occurred: check for inclusion/exclusion criteria, contraindications/precautions, medical and vaccination history of the subjects and signing or thumb-printing informed consent forms.

### Pre-assignment

Screening details:

Among 365 enrolled subjects, 8 were not administered any study vaccine and hence were not considered as starting the study.

### Pre-assignment period milestones

Number of subjects started	365
Number of subjects completed	357

### Pre-assignment subject non-completion reasons

Reason: Number of subjects	Subject not vaccinated: 8
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### Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

### Arms

Are arms mutually exclusive?	Yes
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<b>Arm title</b>	Synflorix + Zilbrix Hib + Polio Sabin
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Arm description:

Subjects in this group received 3 doses of Synflorix vaccine according to a 3-dose schedule at 6-10-14 weeks of age co-administered with 3 doses of Expanded Program on Immunization (EPI) vaccines Zilbrix Hib and Polio Sabin according to the same schedule. The Synflorix and Zilbrix Hib vaccines were administered by intramuscular injection, in the right and left thigh respectively. The Polio Sabin vaccine was administered orally.

Arm type	Experimental
Investigational medicinal product name	Synflorix
Investigational medicinal product code	10Pn-PD-DiT
Other name	10Pn, 10Pn-PD-DiT, GSK1024850A
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

The Synflorix vaccine was administered by intramuscular injection, in the right thigh, according to a 3-dose schedule at 6-10-14 weeks of age.

Investigational medicinal product name	Polio Sabin
Investigational medicinal product code	
Other name	OPV (Oral polio vaccine)
Pharmaceutical forms	Oral suspension
Routes of administration	Oral use

Dosage and administration details:

The Polio Sabin vaccine was administered orally, according to a 3-dose schedule at 6-10-14 weeks of age.

Investigational medicinal product name	Zilbrix Hib
Investigational medicinal product code	
Other name	DTPw-HBV/Hib (Diphtheria-tetanus-whole cell pertussis-hepatitis B/ Haemophilus influenzae type b vaccine)
Pharmaceutical forms	Powder and solution for solution for injection
Routes of administration	Intramuscular use

**Dosage and administration details:**

The Zilbrix Hib vaccine was administered by intramuscular injection, in the left thigh, according to a 3-dose schedule at 6-10-14 weeks of age.

<b>Arm title</b>	Zilbrix Hib + Polio Sabin
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**Arm description:**

Subjects in this group received 3 doses of Expanded Program on Immunization (EPI) vaccines Zilbrix Hib and Polio Sabin according to a 3-dose schedule at 6-10-14 weeks of age. The Zilbrix Hib vaccine was administered by intramuscular injection, in the left thigh. The Polio Sabin vaccine was administered orally.

Arm type	Active comparator
Investigational medicinal product name	Polio Sabin
Investigational medicinal product code	
Other name	OPV
Pharmaceutical forms	Oral suspension
Routes of administration	Oral use

**Dosage and administration details:**

The Polio Sabin vaccine was administered orally, according to a 3-dose schedule at 6-10-14 weeks of age.

Investigational medicinal product name	Zilbrix Hib
Investigational medicinal product code	
Other name	DTPw-HBV/Hib
Pharmaceutical forms	Powder and solution for solution for injection
Routes of administration	Intramuscular use

**Dosage and administration details:**

The Zilbrix Hib vaccine was administered by intramuscular injection, in the left thigh, according to a 3-dose schedule at 6-10-14 weeks of age.

<b>Number of subjects in period 1<sup>[1]</sup></b>	<b>Synflorix + Zilbrix Hib + Polio Sabin</b>	<b>Zilbrix Hib + Polio Sabin</b>
Started	239	118
Completed	231	116
Not completed	8	2
Consent withdrawn by subject	4	-
Adverse event, non-fatal	1	-
Lost to follow-up	3	1
Non-compliance with study procedures	-	1

**Notes:**

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Among 365 enrolled participants, 8 were not administered any study vaccine and hence were not considered as starting the study.

## Baseline characteristics

### Reporting groups

Reporting group title	Synflorix + Zilbrix Hib + Polio Sabin
Reporting group description:	
Subjects in this group received 3 doses of Synflorix vaccine according to a 3-dose schedule at 6-10-14 weeks of age co-administered with 3 doses of Expanded Program on Immunization (EPI) vaccines Zilbrix Hib and Polio Sabin according to the same schedule. The Synflorix and Zilbrix Hib vaccines were administered by intramuscular injection, in the right and left thigh respectively. The Polio Sabin vaccine was administered orally.	
Reporting group title	Zilbrix Hib + Polio Sabin
Reporting group description:	
Subjects in this group received 3 doses of Expanded Program on Immunization (EPI) vaccines Zilbrix Hib and Polio Sabin according to a 3-dose schedule at 6-10-14 weeks of age. The Zilbrix Hib vaccine was administered by intramuscular injection, in the left thigh. The Polio Sabin vaccine was administered orally.	

Reporting group values	Synflorix + Zilbrix Hib + Polio Sabin	Zilbrix Hib + Polio Sabin	Total
Number of subjects	239	118	357
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	239	118	357
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Units: weeks			
arithmetic mean	7.1	7	
standard deviation	± 1.15	± 1.18	-
Gender categorical			
Units: Subjects			
Female	119	62	181
Male	120	56	176

## End points

### End points reporting groups

Reporting group title	Synflorix + Zilbrix Hib + Polio Sabin
Reporting group description:	
Subjects in this group received 3 doses of Synflorix vaccine according to a 3-dose schedule at 6-10-14 weeks of age co-administered with 3 doses of Expanded Program on Immunization (EPI) vaccines Zilbrix Hib and Polio Sabin according to the same schedule. The Synflorix and Zilbrix Hib vaccines were administered by intramuscular injection, in the right and left thigh respectively. The Polio Sabin vaccine was administered orally.	
Reporting group title	Zilbrix Hib + Polio Sabin
Reporting group description:	
Subjects in this group received 3 doses of Expanded Program on Immunization (EPI) vaccines Zilbrix Hib and Polio Sabin according to a 3-dose schedule at 6-10-14 weeks of age. The Zilbrix Hib vaccine was administered by intramuscular injection, in the left thigh. The Polio Sabin vaccine was administered orally.	

### Primary: Concentrations of antibodies against vaccine pneumococcal serotypes

End point title	Concentrations of antibodies against vaccine pneumococcal serotypes <sup>[1]</sup>
End point description:	
Pneumococcal serotypes assessed were vaccine pneumococcal serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F. Seropositivity cut-off for the assay was an anti-pneumococcal serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F antibody (Anti-1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F) concentrations greater than or equal to ( $\geq$ ) 0.05 microgram per milliliter ( $\mu\text{g/mL}$ ).	
End point type	Primary
End point timeframe:	
At Month 3, one month after the administration of the third dose of Synflorix vaccine	
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 + Zilbrix Hib + Polio Sabin	Zilbrix Hib + Polio Sabin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	217	112		
Units: $\mu\text{g/mL}$				
geometric mean (confidence interval 95%)				
Anti-1 [N=217;108]	2.69 (2.42 to 2.99)	0.03 (0.03 to 0.03)		
Anti-4 [N=217;112]	3.44 (3.06 to 3.87)	0.03 (0.03 to 0.03)		
Anti-5 [N=217;109]	4.17 (3.75 to 4.63)	0.03 (0.03 to 0.04)		
Anti-6B [N=217;112]	0.95 (0.76 to 1.2)	0.03 (0.03 to 0.03)		
Anti-7F [N=217;110]	3.33 (2.99 to 3.71)	0.03 (0.03 to 0.04)		
Anti-9V [N=217;112]	2.39 (2.06 to 2.76)	0.04 (0.03 to 0.05)		

Anti-14 [N=217;112]	3.8 (3.24 to 4.46)	0.14 (0.11 to 0.17)		
Anti-18C [N=217;112]	10.01 (8.49 to 11.8)	0.03 (0.03 to 0.04)		
Anti-19F [N=217;111]	7.65 (6.55 to 8.93)	0.08 (0.07 to 0.1)		
Anti-23F [N=217;112]	1.1 (0.91 to 1.33)	0.03 (0.03 to 0.04)		

## Statistical analyses

No statistical analyses for this end point

### Primary: Antibody concentrations against protein D (anti-PD antibodies)

End point title	Antibody concentrations against protein D (anti-PD)
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End point description:

Anti-PD antibody concentrations were expressed in enzyme-linked immunorbent assay (ELISA) units per millilitre (EL.U/mL). Seropositivity cut-off for the assay was an anti-PD antibody concentrations  $\geq 100$  EL.U/mL.

End point type	Primary
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End point timeframe:

At Month 3, one month after the administration of the third dose of Synflorix vaccine

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 + Zilbrix Hib + Polio Sabin	Zilbrix Hib + Polio Sabin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	217	112		
Units: EL.U/mL				
geometric mean (confidence interval 95%)				
Anti-PD	3791.8 (3448.4 to 4169.3)	85.4 (71.8 to 101.5)		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Concentrations of antibodies against cross-reactive pneumococcal serotypes 6A and 19A (Anti-6A and -19A)

End point title	Concentrations of antibodies against cross-reactive pneumococcal serotypes 6A and 19A (Anti-6A and -19A)
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End point description:

Seropositivity status was defined as anti-pneumococcal cross-reactive serotypes 6A/19A antibody concentrations (Anti-6A/19A)  $\geq 0.05$  microgram per millilitre ( $\mu\text{g/mL}$ ).



End point type	Secondary
End point timeframe:	
At Month 3, one month after the administration of the third dose of Synflorix vaccine	

End point values	Synflorix + Zilbrix Hib + Polio Sabin	Zilbrix Hib + Polio Sabin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	217	108		
Units: µg/mL				
geometric mean (confidence interval 95%)				
Anti-6A	0.09 (0.08 to 0.11)	0.04 (0.04 to 0.05)		
Anti-19A	0.15 (0.13 to 0.18)	0.06 (0.05 to 0.07)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Titers for opsonophagocytic activity (OPA) against vaccine pneumococcal serotypes

End point title	Titers for opsonophagocytic activity (OPA) against vaccine pneumococcal serotypes
End point description:	
Pneumococcal serotypes assessed were vaccine pneumococcal serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F. Seropositivity status was defined as an opsonophagocytic activity against vaccine pneumococcal serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F (OPA-1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F) $\geq 8$ .	
End point type	Secondary
End point timeframe:	
At Month 3, one month after the administration of the third dose of Synflorix vaccine	

End point values	Synflorix + Zilbrix Hib + Polio Sabin	Zilbrix Hib + Polio Sabin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	105	56		
Units: Titers				
geometric mean (confidence interval 95%)				
OPA-1 [N=105;56]	83 (61.7 to 111.7)	5 (3.8 to 6.4)		
OPA-4 [N=105;55]	892.5 (759.4 to 1049)	4.6 (3.9 to 5.5)		
OPA-5 [N=105;56]	82.7 (65.4 to 104.4)	4.5 (3.8 to 5.2)		

OPA-6B [N=103;54]	538.6 (346 to 838.3)	5.7 (4.1 to 7.9)		
OPA-7F [N=105;49]	2733 (2188.3 to 3413.3)	31.5 (15.5 to 64)		
OPA-9V [N=105;54]	1023.7 (784.8 to 1335.2)	8.4 (5.8 to 12.4)		
OPA-14 [N=104;53]	1079.2 (776 to 1500.9)	8.9 (5.7 to 14.1)		
OPA-18C [N=105;56]	617.6 (495.3 to 770)	4.4 (3.8 to 5.2)		
OPA-19F [N=105;56]	358.3 (269.9 to 475.5)	4.6 (3.8 to 5.7)		
OPA-23F [N=104;53]	881.8 (615 to 1264.4)	6.6 (4.2 to 10.3)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Titers for opsonophagocytic activity (OPA) against cross-reactive pneumococcal serotypes

End point title	Titers for opsonophagocytic activity (OPA) against cross-reactive pneumococcal serotypes
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End point description:

Pneumococcal serotypes assessed were cross-reactive pneumococcal serotypes 6A and 19A. Seropositivity status was defined as an opsonophagocytic activity against cross-reactive pneumococcal serotypes 6A and 19A (OPA-6A and 19A)  $\geq 8$ .

End point type	Secondary
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End point timeframe:

At Month 3, one month after the administration of the third dose of Synflorix vaccine

End point values	Synflorix + Zilbrix Hib + Polio Sabin	Zilbrix Hib + Polio Sabin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	105	56		
Units: Titres				
geometric mean (confidence interval 95%)				
OPA-6A [N=101;56]	14.1 (9.4 to 21.2)	6.1 (4.4 to 8.7)		
OPA-19A [N=105;56]	11 (8.3 to 14.6)	4.3 (4 to 4.6)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of subjects seropositive for antibodies against vaccine

## pneumococcal serotypes

End point title	Number of subjects seropositive for antibodies against vaccine pneumococcal serotypes
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End point description:

Pneumococcal serotypes assessed were vaccine pneumococcal serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F. Seropositivity cut-off for the assay was an anti-pneumococcal serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F antibody (Anti-1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F) concentrations  $\geq$  0.05 microgram per milliliter ( $\mu\text{g/mL}$ ).

End point type	Secondary
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End point timeframe:

At Month 3, one month after the administration of the third dose of Synflorix vaccine

End point values	Synflorix + Zilbrix Hib + Polio Sabin	Zilbrix Hib + Polio Sabin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	217	108		
Units: Subjects				
Anti-1 [N=217;108]	217	14		
Anti-4 [N=217;112]	217	12		
Anti-5 [N=217;109]	217	18		
Anti-6B [N=217;112]	196	15		
Anti-7F [N=217;110]	217	19		
Anti-9V [N=217;112]	213	31		
Anti-14 [N=217;112]	217	91		
Anti-18C [N=217;112]	216	23		
Anti-19F [N=217;111]	217	73		
Anti-23F [N=217;112]	207	23		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of subjects seroprotected against vaccine pneumococcal serotypes

End point title	Number of subjects seroprotected against vaccine pneumococcal serotypes
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End point description:

Pneumococcal serotypes assessed were vaccine pneumococcal serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F. Seroprotection cut-off for the assay was an anti-pneumococcal serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F antibody (Anti-1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F) concentrations  $\geq$  0.2 microgram per milliliter ( $\mu\text{g/mL}$ ).

End point type	Secondary
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End point timeframe:

At Month 3, one month after the administration of the third dose of Synflorix vaccine

End point values	Synflorix + Zilbrix Hib + Polio Sabin	Zilbrix Hib + Polio Sabin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	217	112		
Units: Subjects				
Anti-1 [N=217;108]	217	2		
Anti-4 [N=217;112]	217	3		
Anti-5 [N=217;109]	217	4		
Anti-6B [N=217;112]	178	2		
Anti-7F [N=217;110]	216	2		
Anti-9V [N=217;112]	211	11		
Anti-14 [N=217;112]	215	40		
Anti-18C [N=217;112]	216	4		
Anti-19F [N=217;111]	214	25		
Anti-23F [N=217;112]	190	3		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of subjects seropositive for antibodies against cross-reactive pneumococcal serotypes 6A and 19A (Anti-6A and -19A)

End point title	Number of subjects seropositive for antibodies against cross-reactive pneumococcal serotypes 6A and 19A (Anti-6A and -19A)
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End point description:

Serotypes assessed were cross-reactive pneumococcal serotypes 6A and 19A. Seropositivity status was defined as anti-pneumococcal cross-reactive serotypes 6A/19A antibody concentrations (Anti-6A/19A)  $\geq 0.05$  microgram per milliliter ( $\mu\text{g/mL}$ ).

End point type	Secondary
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End point timeframe:

At Month 3, one month after the administration of the third dose of Synflorix vaccine

End point values	Synflorix + Zilbrix Hib + Polio Sabin	Zilbrix Hib + Polio Sabin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	217	108		
Units: Subjects				
Anti-6A	152	36		
Anti-19A	176	49		

### Statistical analyses

No statistical analyses for this end point

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**Secondary: Number of subjects seroprotected against cross-reactive pneumococcal serotypes 6A and 19A (Anti-6A and -19A)**

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End point title	Number of subjects seroprotected against cross-reactive pneumococcal serotypes 6A and 19A (Anti-6A and -19A)
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End point description:

Serotypes assessed were cross-reactive pneumococcal serotypes 6A and 19A. Seroprotection cut-off for the assay was an anti-6A/19A antibody concentrations  $\geq 0.2$  microgram per milliliter ( $\mu\text{g/mL}$ ).

End point type	Secondary
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End point timeframe:

At Month 3, one month after the administration of the third dose of Synflorix vaccine

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End point values	Synflorix + Zilbrix Hib + Polio Sabin	Zilbrix Hib + Polio Sabin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	217	108		
Units: Subjects				
Anti-6A	56	8		
Anti-19A	95	15		

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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 seropositive for antibodies against protein D (Anti-PD antibodies)**

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End point title	Number of subjects seropositive for antibodies against protein D (Anti-PD antibodies)
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End point description:

Seropositivity cut-off for the assay was an anti-PD antibody concentrations  $\geq 100$  EL.U/mL.

End point type	Secondary
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End point timeframe:

At Month 3, one month after the administration of the third dose of Synflorix vaccine

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End point values	Synflorix + Zilbrix Hib + Polio Sabin	Zilbrix Hib + Polio Sabin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	217	112		
Units: Subjects				
Anti-PD	217	34		

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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 seropositive for opsonophagocytic activity against vaccine pneumococcal serotypes**

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End point title	Number of subjects seropositive for opsonophagocytic activity against vaccine pneumococcal serotypes
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End point description:

Pneumococcal serotypes assessed were vaccine pneumococcal serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F. Seropositivity status was defined as an opsonophagocytic activity against vaccine pneumococcal serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F (OPA-1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F)  $\geq 8$ .

End point type	Secondary
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End point timeframe:

At Month 3, one month after the administration of the third dose of Synflorix vaccine

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End point values	Synflorix + Zilbrix Hib + Polio Sabin	Zilbrix Hib + Polio Sabin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	105	56		
Units: Subjects				
OPA-1 [N=105;56]	92	3		
OPA-4 [N=105;55]	105	3		
OPA-5 [N=105;56]	100	2		
OPA-6B [N=103;54]	88	5		
OPA-7F [N=105;49]	105	21		
OPA-9V [N=105;54]	103	13		
OPA-14 [N=104;53]	100	13		
OPA-18C [N=105;56]	103	2		
OPA-19F [N=105;56]	101	2		
OPA-23F [N=104;53]	97	5		

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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 seropositive for opsonophagocytic activity against cross-reactive pneumococcal serotypes**

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End point title	Number of subjects seropositive for opsonophagocytic activity against cross-reactive pneumococcal serotypes
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End point description:

Pneumococcal serotypes assessed were cross-reactive pneumococcal serotypes 6A and 19A. Seropositivity status was defined as an opsonophagocytic activity against cross-reactive pneumococcal serotypes 6A and 19A (OPA-6A and 19A)  $\geq 8$ .

End point type	Secondary
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End point timeframe:

At Month 3, one month after the administration of the third dose of Synflorix vaccine

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End point values	Synflorix + Zilbrix Hib + Polio Sabin	Zilbrix Hib + Polio Sabin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	105	56		
Units: Subjects				
OPA-6A [N=101;56]	31	6		
OPA-19A [N=105;56]	39	3		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Anti-Bordetella pertussis (anti-BPT) antibody concentrations

End point title	Anti-Bordetella pertussis (anti-BPT) antibody concentrations
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End point description:

Anti-BPT antibody concentrations were expressed in enzyme-linked immunosorbent assay (ELISA) unit per millilitre (EL.U/mL). Seropositivity cut-off for the assay was defined as an anti-BPT antibody concentrations  $\geq 15$  EL.U/mL.

End point type	Secondary
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End point timeframe:

At Month 3, one month after the administration of the third dose of Tritanrix -HepB/ Hiberix vaccine

End point values	Synflorix + Zilbrix Hib + Polio Sabin	Zilbrix Hib + Polio Sabin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	110	111		
Units: EL.U/mL				
geometric mean (confidence interval 95%)				
Anti-BPT	111.9 (102 to 122.7)	124.9 (111.7 to 139.7)		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of subjects seropositive for antibodies against Bordetella pertussis (anti-BPT)

End point title	Number of subjects seropositive for antibodies against Bordetella pertussis (anti-BPT)
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End point description:

Seropositivity cut-off for the assay was defined as an anti-BPT antibody concentration  $\geq 15$  enzyme-linked immunosorbent assay (ELISA) unit per millilitre (EL.U/mL).

End point type	Secondary
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End point timeframe:

At Month 3, one month after the administration of the third dose of Tritanrix -HepB/ Hiberix vaccine

End point values	Synflorix + Zilbrix Hib + Polio Sabin	Zilbrix Hib + Polio Sabin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	110	111		
Units: Subjects				
Anti-BPT	110	111		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Anti-diphtheria (Anti-D) and anti-tetanus toxoids (Anti-TT) antibody concentrations

End point title	Anti-diphtheria (Anti-D) and anti-tetanus toxoids (Anti-TT) antibody concentrations
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End point description:

The seroprotection cut-off for the endpoint was an anti-diphtheria toxoid or anti-tetanus toxoid antibody concentrations  $\geq 0.1$  international unit per millilitre (IU/mL).

End point type	Secondary
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End point timeframe:

At Month 3, one month after the administration of the third dose of Tritanrix -HepB/ Hiberix vaccine

End point values	Synflorix + Zilbrix Hib + Polio Sabin	Zilbrix Hib + Polio Sabin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	110	112		
Units: IU/mL				
geometric mean (confidence interval 95%)				
Anti-D	4.103 (3.527 to 4.773)	3.13 (2.731 to 3.588)		
Anti-T	6.484 (5.511 to 7.628)	4.588 (3.88 to 5.426)		

### Statistical analyses



No statistical analyses for this end point

### Secondary: Number of subjects seroprotected against diphtheria (D) and tetanus toxoids (TT) antigens

End point title	Number of subjects seroprotected against diphtheria (D) and tetanus toxoids (TT) antigens
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End point description:

A subject seroprotected against D/TT antigens was defined as a subject with an Anti-D/-TT antibody concentration  $\geq 0.1$  international unit per milliliter (IU/mL).

End point type	Secondary
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End point timeframe:

At Month 3, one month after the administration of the third dose of Tritanrix -HepB/ Hiberix vaccine

End point values	Synflorix + Zilbrix Hib + Polio Sabin	Zilbrix Hib + Polio Sabin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	110	112		
Units: Subjects				
Anti-D	110	112		
Anti-T	110	112		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Anti-polyribosyl-ribitol-phosphate (Anti-PRP) antibody concentrations

End point title	Anti-polyribosyl-ribitol-phosphate (Anti-PRP) antibody concentrations
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End point description:

Anti-PRP antibody concentrations were measured and tabulated in microgram per millilitre ( $\mu\text{g/mL}$ ). Cut-off for the assay was  $\geq 0.15 \mu\text{g/mL}$ .

End point type	Secondary
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End point timeframe:

At Month 3, one month after the administration of the third dose of Tritanrix -HepB/ Hiberix vaccine

End point values	Synflorix + Zilbrix Hib + Polio Sabin	Zilbrix Hib + Polio Sabin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	110	112		
Units: $\mu\text{g/mL}$				
geometric mean (confidence interval 95%)				

Anti-PRP	18.461 (14.256 to 23.907)	10.137 (7.515 to 13.673)		
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### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of subjects seroprotected against polyribosyl-ribitol phosphate (PRP)

End point title	Number of subjects seroprotected against polyribosyl-ribitol phosphate (PRP)
End point description: Anti-PRP antibody concentrations were expressed in microgram per millilitre (µg/mL). The seroprotection cut-off applied for the assay was $\geq 0.15$ µg/mL.	
End point type	Secondary
End point timeframe: At Month 3, one month after the administration of the third dose of Tritanrix -HepB/ Hiberix vaccine	

End point values	Synflorix + Zilbrix Hib + Polio Sabin	Zilbrix Hib + Polio Sabin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	110	112		
Units: Subjects				
Anti-PRP	110	111		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of subjects seroprotected against polyribosyl-ribitol phosphate (PRP) antigens

End point title	Number of subjects seroprotected against polyribosyl-ribitol phosphate (PRP) antigens
End point description: Anti-PRP antibody concentrations were expressed in microgram per millilitre (µg/mL). The seroprotection cut-off applied for the assay was $\geq 1$ µg/mL.	
End point type	Secondary
End point timeframe: At Month 3, one month after the administration of the third dose of Tritanrix -HepB/ Hiberix vaccine	

End point values	Synflorix + Zilbrix Hib + Polio Sabin	Zilbrix Hib + Polio Sabin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	110	112		
Units: Subjects				
Anti-PRP	107	102		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Anti-hepatitis B surface antigen (HBs) antibody concentrations

End point title	Anti-hepatitis B surface antigen (HBs) antibody concentrations
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End point description:

The seroprotection cut-off for the endpoint was an anti-HBs antibody concentration  $\geq 10$  milli-international units per milliliter (mIU/mL).

End point type	Secondary
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End point timeframe:

At Month 3, one month after the administration of the third dose of Tritanrix -HepB/ Hiberix vaccine

End point values	Synflorix + Zilbrix Hib + Polio Sabin	Zilbrix Hib + Polio Sabin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	91	96		
Units: mIU/mL				
geometric mean (confidence interval 95%)				
Anti-HBs	1835.1 (1384 to 2433.2)	1485.5 (1198.7 to 1840.9)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of subjects seroprotected against anti-Hepatitis B surface antigens (HBs)

End point title	Number of subjects seroprotected against anti-Hepatitis B surface antigens (HBs)
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End point description:

The seroprotection cut-off values considered for this endpoint were an anti-HBs antibody concentration  $\geq 10$  and 100 milli-international units per milliliter (mIU/mL).

End point type	Secondary
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End point timeframe:

At Month 3, one month after the administration of the third dose of Tritanrix -HepB/ Hiberix vaccine

End point values	Synflorix + Zilbrix Hib + Polio Sabin	Zilbrix Hib + Polio Sabin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	91	96		
Units: Subjects				
Anti-HBs $\geq$ 10 mIU/mL	89	96		
Anti-HBs $\geq$ 100 mIU/mL	89	94		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of subjects with any and any Grade 3 solicited local symptoms

End point title	Number of subjects with any and any Grade 3 solicited local symptoms
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End point description:

Solicited local symptoms assessed include pain, redness and swelling. Grade 3 pain was defined as crying when limb was moved/spontaneously painful. Grade 3 swelling/redness was defined as swelling/redness greater than ( $>$ ) 30 millimeters (mm). "Any" was defined as incidence of the specified symptom regardless of intensity.

End point type	Secondary
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End point timeframe:

Within the 4-day (Days 0 to 3) follow-up periods after each vaccination, across doses and across vaccines

End point values	Synflorix + Zilbrix Hib + Polio Sabin	Zilbrix Hib + Polio Sabin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	239	118		
Units: Subjects				
Any Pain	234	112		
Grade 3 Pain	8	3		
Any Redness	57	30		
Grade 3 Redness	0	0		
Any Swelling	173	83		
Grade 3 Swelling	22	11		

## Statistical analyses

No statistical analyses for this end point

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**Secondary: Number of subjects with any and any Grade 3 and related solicited general symptoms**

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End point title	Number of subjects with any and any Grade 3 and related solicited general symptoms
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End point description:

Solicited general symptoms assessed include drowsiness, fever (defined as rectal temperature  $\geq 38.0^{\circ}\text{C}$ ), irritability, and loss of appetite. "Any" was defined as incidence of the specified symptom regardless of intensity or relationship to study vaccination. Grade 3 drowsiness was defined as drowsiness which prevented normal everyday activities. Grade 3 fever was defined as fever (rectal temperature) greater than ( $>$ )  $40.0^{\circ}\text{C}$ . Grade 3 irritability was defined as crying that could not be comforted/preventing normal activity. Grade 3 loss of appetite was defined as the subject not eating at all.

End point type	Secondary
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End point timeframe:

Within the 4-day (Days 0 to 3) follow-up periods after each vaccination, across doses and across vaccines

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End point values	Synflorix + Zilbrix Hib + Polio Sabin	Zilbrix Hib + Polio Sabin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	239	118		
Units: Subjects				
Any Drowsiness	24	12		
Grade 3 Drowsiness	0	0		
Any Fever (Rectally)	207	105		
Grade 3 Fever (Rectally)	1	0		
Any Irritability	192	88		
Grade 3 Irritability	6	2		
Any Loss of appetite	37	15		
Grade 3 Loss of appetite	1	0		

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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 with fever (temperature measured rectally) > the cut-off**

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End point title	Number of subjects with fever (temperature measured rectally) > the cut-off
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End point description:

The cut-off for the assay was  $> 39.0^{\circ}\text{C}$ .

End point type	Secondary
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End point timeframe:

Within the 4-day (Days 0 to 3) follow-up periods after each vaccination, across doses and across vaccines

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End point values	Synflorix + Zilbrix Hib + Polio Sabin	Zilbrix Hib + Polio Sabin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	239	118		
Units: Subjects				
Fever >39.0°C	40	13		

## Statistical analyses

No statistical analyses for this end point

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

End point title	Number of subjects with unsolicited adverse events (AEs)
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End point description:

An AE is any untoward medical occurrence in a clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. "Any" was defined as incidence of an unsolicited AE regardless of intensity or relationship to study vaccination.

End point type	Secondary
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End point timeframe:

Within the 31-day (Days 0-30) follow-up periods post vaccination, across doses and across vaccines

End point values	Synflorix + Zilbrix Hib + Polio Sabin	Zilbrix Hib + Polio Sabin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	239	118		
Units: Subjects				
Any AEs	176	92		

## Statistical analyses

No statistical analyses for this end point

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

End point title	Number of subjects with 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:

Throughout the entire study period, from Month 0 to Month 3

<b>End point values</b>	Synflorix + Zilbrix Hib + Polio Sabin	Zilbrix Hib + Polio Sabin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	239	118		
Units: Subjects				
Any SAEs	5	0		

### Statistical analyses

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Solicited symptoms and unsolicited AEs: During the 4-day (Days 0-3) and 31-day (Days 0-30) post vaccination follow-up periods, respectively, across doses and across vaccines. SAEs: throughout the entire study period, from Month 0 to Month 3.

Assessment type	Non-systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	12.0
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### Reporting groups

Reporting group title	Synflorix + Zilbrix Hib + Polio Sabin
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Reporting group description:

Subjects in this group received 3 doses of Synflorix vaccine, according to a 3-dose schedule at 6-10-14 weeks of age co-administered with 3 doses of Expanded Program on Immunization (EPI) vaccines Zilbrix Hib and Polio Sabin according to the same schedule. The Synflorix and Zilbrix Hib vaccines were administered by intramuscular injection, in the right and left thigh respectively. The Polio Sabin vaccine was administered orally.

Reporting group title	Zilbrix Hib + Polio Sabin
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Reporting group description:

Subjects in this group received 3 doses of Expanded Program on Immunization (EPI) vaccines Zilbrix Hib and Polio Sabin according to a 3-dose schedule at 6-10-14 weeks of age. The Zilbrix Hib vaccine was administered by intramuscular injection, in the left thigh. The Polio Sabin vaccine was administered orally.

Serious adverse events	Synflorix + Zilbrix Hib + Polio Sabin	Zilbrix Hib + Polio Sabin	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 239 (2.09%)	0 / 118 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Vascular disorders			
Bronchopneumonia			
subjects affected / exposed	4 / 239 (1.67%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma			
subjects affected / exposed	1 / 239 (0.42%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Febrile convulsion			



subjects affected / exposed	1 / 239 (0.42%)	0 / 118 (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>			
Malaria			
subjects affected / exposed	1 / 239 (0.42%)	0 / 118 (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>	Synflorix + Zilbrix Hib + Polio Sabin	Zilbrix Hib + Polio Sabin	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	238 / 239 (99.58%)	117 / 118 (99.15%)	
<b>General disorders and administration site conditions</b>			
Pain			
alternative assessment type: Systematic			
subjects affected / exposed	234 / 239 (97.91%)	112 / 118 (94.92%)	
occurrences (all)	571	257	
Redness			
alternative assessment type: Systematic			
subjects affected / exposed	57 / 239 (23.85%)	30 / 118 (25.42%)	
occurrences (all)	78	36	
Swelling			
alternative assessment type: Systematic			
subjects affected / exposed	173 / 239 (72.38%)	83 / 118 (70.34%)	
occurrences (all)	462	225	
Drowsiness			
alternative assessment type: Systematic			
subjects affected / exposed	24 / 239 (10.04%)	12 / 118 (10.17%)	
occurrences (all)	27	13	
Fever (rectal temperature $\geq 38.5^{\circ}$ C)			
alternative assessment type: Systematic			

subjects affected / exposed	207 / 239 (86.61%)	105 / 118 (88.98%)	
occurrences (all)	389	200	
Irritability			
alternative assessment type: Systematic			
subjects affected / exposed	192 / 239 (80.33%)	88 / 118 (74.58%)	
occurrences (all)	339	151	
Loss of appetite			
alternative assessment type: Systematic			
subjects affected / exposed	37 / 239 (15.48%)	15 / 118 (12.71%)	
occurrences (all)	39	17	
Injection site erosion			
subjects affected / exposed	1 / 239 (0.42%)	6 / 118 (5.08%)	
occurrences (all)	1	6	
Injection site induration			
subjects affected / exposed	22 / 239 (9.21%)	20 / 118 (16.95%)	
occurrences (all)	29	24	
Eye disorders			
Conjunctivitis			
subjects affected / exposed	35 / 239 (14.64%)	16 / 118 (13.56%)	
occurrences (all)	37	17	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	43 / 239 (17.99%)	22 / 118 (18.64%)	
occurrences (all)	55	26	
Gastrointestinal disorder			
subjects affected / exposed	25 / 239 (10.46%)	15 / 118 (12.71%)	
occurrences (all)	31	16	
Stomatitis			
subjects affected / exposed	13 / 239 (5.44%)	4 / 118 (3.39%)	
occurrences (all)	13	4	
Respiratory, thoracic and mediastinal disorders			
Allergic bronchitis			
subjects affected / exposed	83 / 239 (34.73%)	46 / 118 (38.98%)	
occurrences (all)	109	60	
Infections and infestations			

Bronchitis		
subjects affected / exposed	12 / 239 (5.02%)	6 / 118 (5.08%)
occurrences (all)	13	6
Ear infection		
subjects affected / exposed	42 / 239 (17.57%)	21 / 118 (17.80%)
occurrences (all)	46	24
Gastroenteritis		
subjects affected / exposed	61 / 239 (25.52%)	32 / 118 (27.12%)
occurrences (all)	71	38
Pharyngitis		
subjects affected / exposed	14 / 239 (5.86%)	5 / 118 (4.24%)
occurrences (all)	14	5
Respiratory tract infection		
subjects affected / exposed	17 / 239 (7.11%)	11 / 118 (9.32%)
occurrences (all)	19	15
Rhinitis		
subjects affected / exposed	85 / 239 (35.56%)	42 / 118 (35.59%)
occurrences (all)	119	54
Skin infection		
subjects affected / exposed	16 / 239 (6.69%)	16 / 118 (13.56%)
occurrences (all)	17	17
Urinary tract infection		
subjects affected / exposed	3 / 239 (1.26%)	8 / 118 (6.78%)
occurrences (all)	3	8

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 February 2008	Amendment 1 was made in response to comments of the Ethics Committee of Mali and included the following changes: 1) Data and related publications on invasive pneumococcal disease in Mali were included; 2) Update on the presentation and administration of the OPV vaccine (Polio Sabin); 3) Update in the statistical analysis of safety; 4) Clarification on recording in the clinical report form (CRF) of administered vaccines other than the study vaccines; 5) Correction in the reference to the standard operating procedure (SOP) on destruction of used/unused vaccine vials/syringes/containers.
17 March 2009	Amendment 2 was made to include the following changes: 1) Planning of an interim analysis on all cleaned demographic, reactogenicity and immunogenicity data pertaining to Malian subjects enrolled by 31 December 2008; 2) Change in coordinating author and contributing authors.

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported