Clinical trial results:
A Phase IIIb, open, randomized, controlled, multicenter study of the immunogenicity and safety of GlaxoSmithKline Biologicals' inactivated hepatitis A vaccine (Havrix) [720 El.U/ 0.5 mL dose] administered on a 0, 6-month schedule concomitantly with GlaxoSmithKline Biologicals' DTaP vaccine (Infanrix) and Aventis Pasteur's Haemophilus b conjugate (Tetanus Toxoid Conjugate) vaccine (ActHIB) in healthy children 15 months of age.

Summary

EudraCT number	2015-001530-25
Trial protocol	Outside EU/EEA
Global end of trial date	03 December 2007

Results information

Result version number	v1
This version publication date	27 April 2016
First version publication date	02 August 2015

Trial information

Trial identification

Sponsor protocol code	208109/232

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00197236
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 May 2008
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 December 2007
Global end of trial reached?	Yes
Global end of trial date	03 December 2007
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate non-inferiority of the anti-HAV immune response (with respect to both seropositivity rates and GMCs) 31 days following the second dose of Havrix when the first dose of Havrix is co-administered with Infanrix and ActHIB (HAV+DTaP+HIB Group) compared to Havrix given alone (HAV Group).
To demonstrate the non-inferiority of the anti-diphtheria (D) and anti-tetanus (T) seroprotection rates; anti-pertussis (PT), anti-filamentous hemagglutinin (FHA) and anti-pertactin (PRN) GMCs and vaccine response rates; and anti-polyribosylribitol phosphate (PRP) seroprotection rate 31 days following the co-administration of Infanrix and ActHIB with the first dose of Havrix (HAV+DTaP+HIB Group) compared to Infanrix and ActHIB given alone (DTaP+HIBHAV Group).

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	11 November 2003
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	United States: 468
Worldwide total number of subjects	468
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	468

months)	
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. Of the total of 468 subjects enrolled, only 394 were vaccinated and as such considered as 'started'.

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
Arm title	Havrix Group

Arm description:

Subjects received one dose of Havrix at Day 0 followed by a second dose of Havrix at Month 6-9.

Arm type	Active comparator
Investigational medicinal product name	Havrix™
Investigational medicinal product code	
Other name	HAV
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

2 intramuscular injections, 6 months apart

Arm title	Havrix + Infanrix + ActHIB Group

Arm description:

Subjects received one dose of Havrix co-administered with Infanrix and ActHIB vaccines at Day 0 followed by a second dose of Havrix at Month 6-9.

Arm type	Active comparator
Investigational medicinal product name	Havrix™
Investigational medicinal product code	
Other name	HAV
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

2 intramuscular injections, 6 months apart

Investigational medicinal product name	Infanrix™
Investigational medicinal product code	
Other name	DTPa
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

1 intramuscular injection

Investigational medicinal product name	ActHIB™
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:

1 intramuscular injection

Arm title	Infanrix + ActHIBHavrix Group

Arm description:

Subjects received Infanrix co-administered with ActHIB at Day 0, followed by one dose of Havix at Day 30 and a second dose of Havrix at Month 7-10.

Arm type	Experimental
Investigational medicinal product name	Havrix™
Investigational medicinal product code	
Other name	HAV
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

2 intramuscular injections, 6 months apart

Investigational medicinal product name	Infanrix™
Investigational medicinal product code	
Other name	DTPa
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

1 intramuscular injection

Investigational medicinal product name	ActHIB™
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:

1 intramuscular injection

Number of subjects in period 1[1]	Havrix Group	Havrix + Infanrix + ActHIB Group	Infanrix + ActHIBHavrix Group
Started	135	127	132
Completed	121	110	109
Not completed	14	17	23
Adverse event, serious fatal	1	-	1
Consent withdrawn by subject	7	3	11
Returned out of specified time window	-	-	1
Study drug/medication expiration	1	-	3
Lost to follow-up	5	14	6
Protocol deviation	-	-	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: Of the total of 468 subjects enrolled, only 394 were vaccinated and as such considered as 'started'.

Baseline characteristics

Reporting groups	
Reporting group title	Havrix Group
Reporting group description:	
Subjects received one dose of Havrix at Day 0 followed by a second dose of Havrix at Month 6-9.	
Reporting group title	Havrix + Infanrix + ActHIB Group
Reporting group description:	
Subjects received one dose of Havrix co-administered with Infanrix and ActHIB vaccines at Day 0 followed by a second dose of Havrix at Month 6-9.	
Reporting group title	Infanrix + ActHIBHavrix Group
Reporting group description:	
Subjects received Infanrix co-administered with ActHIB at Day 0, followed by one dose of Havix at Day 30 and a second dose of Havrix at Month 7-10.	

Reporting group values	Havrix Group	Havrix + Infanrix + ActHIB Group	Infanrix + ActHIBHavrix Group
Number of subjects	135	127	132
Age categorical Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous Units: months			
arithmetic mean	15.1	15.1	15
standard deviation	± 0.36	± 0.3	± 0.21
Gender categorical Units: Subjects			
Female	55	64	67
Male	80	63	65

Reporting group values	Total		
Number of subjects	394		
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			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	186		
Male	208		

End points

End points reporting groups

Reporting group title	Havrix Group
Reporting group description:	
Subjects received one dose of Havrix at Day 0 followed by a second dose of Havrix at Month 6-9.	
Reporting group title	Havrix + Infanrix + ActHIB Group
Reporting group description:	
Subjects received one dose of Havrix co-administered with Infanrix and ActHIB vaccines at Day 0 followed by a second dose of Havrix at Month 6-9.	
Reporting group title	Infanrix + ActHIBHavrix Group
Reporting group description:	
Subjects received Infanrix co-administered with ActHIB at Day 0, followed by one dose of Havix at Day 30 and a second dose of Havrix at Month 7-10.	

Primary: Number of seropositive subjects for anti-hepatitis A virus (HAV) antibodies following the second dose of Havrix

End point title	Number of seropositive subjects for anti-hepatitis A virus (HAV) antibodies following the second dose of Havrix
End point description:	
Subjects are defined as being anti-HAV seropositive if their anti-HAV antibody concentration is ≥ 15 milli-International Units per milliliter (mIU/mL).	
End point type	Primary
End point timeframe:	
31 days following the second dose of Havrix™	

End point values	Havrix Group	Havrix + Infanrix + ActHIB Group	Infanrix + ActHIBHavrix Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	88	84	77	
Units: Subjects				
Anti-hepatitis A virus (HAV) antibodies	88	84	77	

Statistical analyses

Statistical analysis title	Non-inferiority of HAV + DTaP + Hib vs. HAV
Statistical analysis description:	
Non-inferiority of the anti-HAV immune response (with respect to seropositivity rates) 31 days following the second dose of HAV when the first dose of HAV was co-administered with DTaP and Hib vaccines (Havrix + Infanrix + ActHIB Group) compared to HAV given alone (Havrix Group). Non-inferiority was to rule out more than a 5% decrease in the anti-HAV seropositivity rate between the Havrix + Infanrix + ActHIB Group and the Havrix Group 31 days following the second dose of HAV.	
Comparison groups	Havrix + Infanrix + ActHIB Group v Havrix Group

Number of subjects included in analysis	172
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Difference in seropositivity rate
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.4
upper limit	4.21

Primary: Number of anti-diphtheria, anti-tetanus and anti-polyribosylribitol phosphate (PRP) seroprotected subjects

End point title	Number of anti-diphtheria, anti-tetanus and anti-polyribosylribitol phosphate (PRP) seroprotected subjects[1]

End point description:

Subjects are defined as being anti-diphtheria, anti-tetanus and anti-PRP seroprotected if their anti-diphtheria and anti-tetanus antibody concentration is ≥ 0.1 International Units per milliliter (IU/mL) and if their anti-PRP antibody concentration is ≥ 1 microgram per milliliter (µg/mL), respectively. This outcome measure concerns subjects in the Havrix + Infanrix + ActHIB Group and Infanrix + ActHIBHavrix Group.

End point type	Primary

End point timeframe:

31 days following the administration of Infanrix™ and ActHIB

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This outcome measure concerns subjects in the Havrix + Infanrix + ActHIB Group and Infanrix + ActHIBHavrix Group.

End point values	Havrix + Infanrix + ActHIB Group	Infanrix + ActHIBHavrix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	90	80		
Units: Subjects				
Anti-diphtheria (n=89, 80)	89	80		
Anti-tetanus (n=88, 80)	88	80		
Anti-PRP (n=90, 79)	90	77		

Statistical analyses

Statistical analysis title	Non-inferiority of HAV+DTaP+Hib vs. DTaP+HibHAV

Statistical analysis description:

Non-inferiority of the anti-diphtheria (D) seroprotection rates, 31 days following the co-administration of DTaP and Hib vaccines with the first dose of HAV(Havrix + Infanrix + ActHIB Group) compared to DTaP and Hib vaccines given alone(Infanrix+ActHIBHavrix Group).Non-inferiority was to rule out more than a 10% decrease in the anti-D seroprotection rates between the Havrix + Infanrix + ActHIB Group and Infanrix + ActHIBHavrix Group 31 days following the administration of DTaP and Hib vaccines

Comparison groups	Havrix + Infanrix + ActHIB Group v Infanrix + ActHIBHavrix Group

Number of subjects included in analysis	170
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Difference in seroprotection rate
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.16
upper limit	4.61

Statistical analysis title	Non-inferiority of HAV+DTaP+Hib vs. DTaP+HibHAV

Statistical analysis description:

Non-inferiority of the anti-tetanus (T) seroprotection rates, 31 days following the co-administration of DTaP and Hib vaccines with the first dose of HAV(Havrix + Infanrix + ActHIB Group) compared to DTaP and Hib vaccines given alone(Infanrix+ActHIBHavrix Group).Non-inferiority was to rule out more than a 10% decrease in the anti-T seroprotection rates between the Havrix + Infanrix + ActHIB Group and Infanrix + ActHIBHavrix Group 31 days following the administration of DTaP and Hib vaccines.

Comparison groups	Havrix + Infanrix + ActHIB Group v Infanrix + ActHIBHavrix Group
Number of subjects included in analysis	170
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Difference in seroprotection rates
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.21
upper limit	4.61

Statistical analysis title	Non-inferiority of HAV+DTaP+Hib vs. DTaP+HibHAV

Statistical analysis description:

Non-inferiority of the anti-polyribosylribitol phosphate (PRP) seroprotection rate, 31 days following the co-administration of DTaP and Hib vaccines with the first dose of HAV(Havrix + Infanrix + ActHIB Group) compared to DTaP and Hib vaccines given alone(Infanrix+ActHIBHavrix Group).Non-inferiority was to rule out more than a 10% decrease in the anti-PRP seroprotection rate between the Havrix + Infanrix + ActHIB Group and Infanrix + ActHIBHavrix Group 31 days post DTaP and Hib administration.

Comparison groups	Infanrix + ActHIBHavrix Group v Havrix + Infanrix + ActHIB Group
Number of subjects included in analysis	170
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Difference in seroprotection rate
Point estimate	2.53

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.64
upper limit	8.8

Primary: Number of vaccine responders for anti-pertussis toxoid (PT), anti-filamentous hemagglutinin (FHA) and anti-pertactin (PRN)

End point title	Number of vaccine responders for anti-pertussis toxoid (PT), anti-filamentous hemagglutinin (FHA) and anti-pertactin (PRN)[2]

End point description:

Subjects are considered as being vaccine responders if they were initially seronegative and become seropositive (≥ 5 Enzyme Linked Immunosorbent Assay Units per Milliliter (EL.U/mL)), or were initially seropositive and have a 2-fold increase above pre-study concentrations. This outcome measure concerns subjects in the Havrix + Infanrix + ActHIB Group and Infanrix + ActHIBHavrix Group.

End point type	Primary

End point timeframe:

31 days following the administration of Infanrix™ and ActHIB

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This outcome measure concerns subjects in the Havrix + Infanrix + ActHIB Group and Infanrix + ActHIBHavrix Group.

End point values	Havrix + Infanrix + ActHIB Group	Infanrix + ActHIBHavrix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	88	76		
Units: Subjects				
Anti-PT (n=88,74)	87	71		
Anti-FHA (n=88,76)	85	75		
Anti-PRN (n=88,75)	86	74		

Statistical analyses

Statistical analysis title	Non-inferiority of HAV+DTaP+Hib vs. DTaP+HibHAV

Statistical analysis description:

Non-inferiority of the anti-pertussis toxin (PT) vaccine response rates 31 days following the co-administration of DTaP and Hib vaccines with the first dose of HAV (Havrix + Infanrix + ActHIB Group) compared to DTaP and Hib vaccines given alone. Non-inferiority was to rule out more than a 10% decrease in the anti-PT between the Havrix + Infanrix + ActHIB Group and the Infanrix + ActHIBHavrix Group 31 days following the administration of DTaP and Hib vaccines.

Comparison groups	Havrix + Infanrix + ActHIB Group v Infanrix + ActHIBHavrix Group

Number of subjects included in analysis	164
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Difference in vaccine response rate
Point estimate	2.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.6
upper limit	10.28

Statistical analysis title	Non-inferiority of HAV+DTaP+Hib vs. DTaP+HibHAV

Statistical analysis description:

Non-inferiority of the anti-filamentous hemagglutinin (FHA) vaccine response rates 31 days following the co-administration of DTaP and Hib vaccines with the first dose of HAV (Havrix + Infanrix + ActHIB Group) compared to DTaP and Hib vaccines given alone. Non-inferiority was to rule out more than a 10% decrease in the anti-FHA between the Havrix + Infanrix + ActHIB Group and the Infanrix + ActHIBHavrix Group 31 days following the administration of DTaP and Hib vaccines.

Comparison groups	Havrix + Infanrix + ActHIB Group v Infanrix + ActHIBHavrix Group
Number of subjects included in analysis	164
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Difference in vaccine response rate
Point estimate	-2.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.44
upper limit	4.02

Statistical analysis title	Non-inferiority of HAV+DTaP+Hib vs. DTaP+HibHAV

Statistical analysis description:

Non-inferiority of the anti-pertactin (PRN) vaccine response rates 31 days following the co-administration of DTaP and Hib vaccines with the first dose of HAV (Havrix + Infanrix + ActHIB Group) compared to DTaP and Hib vaccines given alone. Non-inferiority was to rule out more than a 10% decrease in the anti-PRN between the Havrix + Infanrix + ActHIB Group and the Infanrix + ActHIBHavrix Group 31 days following the administration of DTaP and Hib vaccines.

Comparison groups	Havrix + Infanrix + ActHIB Group v Infanrix + ActHIBHavrix Group
Number of subjects included in analysis	164
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Difference in vaccine response rate
Point estimate	-0.94

Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.77
upper limit	5.13

Primary: Anti-hepatitis virus A (HAV) antibody geometric mean concentrations (GMC) following the second dose of Havrix

End point title	Anti-hepatitis virus A (HAV) antibody geometric mean concentrations (GMC) following the second dose of Havrix[3]

End point description:

Anti-hepatitis A (HAV) antibody geometric mean concentrations (GMC) are expressed as milli-International Units per milliliter (mIU/mL). This outcome measure concerns subjects in the Havrix Group and Havrix + Infanrix + ActHIB Group.

End point type	Primary

End point timeframe:

31 days following the second dose of Havrix™

Notes:

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

End point values	Havrix Group	Havrix + Infanrix + ActHIB Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	88	84		
Units: mIU/mL				
geometric mean (confidence interval 95%)				
Anti-hepatitis virus A (HAV) antibodies	1700.4 (1306 to 2213.7)	1904.4 (1552.7 to 2335.7)		

Statistical analyses

Statistical analysis title	Non-inferiority of HAV + DTaP + Hib vs. HAV

Statistical analysis description:

Non-inferiority of the anti-HAV immune response (with respect to Geometric Mean Concentrations [GMCs]) 31 days following the second dose of HAV when the first dose of HAV was co-administered with DTaP and Hib vaccines (Havrix + Infanrix + ActHIB Group) compared to HAV given alone (Havrix Group). Non-inferiority was to rule out more than a 2-fold decrease in the anti-HAV antibody GMC between the Havrix + Infanrix + ActHIB Group and the Havrix Group 31 days following the second dose of HAV.

Comparison groups	Havrix + Infanrix + ActHIB Group v Havrix Group

Number of subjects included in analysis	172
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Adjusted GMC ratio
Point estimate	1.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.88
upper limit	1.59

Primary: Anti-pertussis toxoid (PT), anti-filamentous hemagglutinin (FHA), anti-pertactin (PRN) geometric mean concentrations following the administration of DTaP and Hib vaccines

End point title	Anti-pertussis toxoid (PT), anti-filamentous hemagglutinin (FHA), anti-pertactin (PRN) geometric mean concentrations following the administration of DTaP and Hib vaccines[4]

End point description:

Anti-PT, anti-FHA and anti-PRN antibody geometric mean concentrations (GMC) are expressed as EL.U/mL. This outcome measure concerns subjects in the Havrix + Infanrix + ActHIB Group and Infanrix + ActHIBHavrix Group.

End point type	Primary

End point timeframe:

31 days following the administration of Infanrix and ActHIB vaccines.

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This outcome measure concerns subjects in the Havrix + Infanrix + ActHIB Group and Infanrix + ActHIBHavrix Group.

End point values	Havrix + Infanrix + ActHIB Group	Infanrix + ActHIBHavrix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	89	80		
Units: EL.U/mL				
geometric mean (confidence interval 95%)				
Anti-PT	87.8 (76.8 to 100.4)	90.8 (78.9 to 104.5)		
Anti-FHA	558.4 (482.9 to 645.7)	519.8 (446 to 605.8)		
Anti-PRN	349 (288.8 to 421.9)	304.6 (241.2 to 384.6)		

Statistical analyses

Statistical analysis title	Non-inferiority of HAV+DTaP+Hib vs. DTaP+HibHAV

Statistical analysis description:

Non-inferiority of anti-PT antibody GMCs 31 days following the co-administration of DTaP and Hib vaccines with the first dose of HAV (Havrix + Infanrix + ActHIB Group) compared to DTaP and Hib vaccines given alone (Infanrix + ActHIBHavrix Group). Non-inferiority was to rule out more than a

1.5-fold decrease in the anti-PT GMCs between the Havrix + Infanrix+ ActHIB Group and the Infanrix + ActHIBHavrix Group 31 days following the administration of DTaP and Hib vaccines.

Comparison groups	Infanrix + ActHIBHavrix Group v Havrix + Infanrix + ActHIB Group
Number of subjects included in analysis	169
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Adjusted GMC ratio
Point estimate	0.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.78
upper limit	1.11

Statistical analysis title	Non-inferiority of HAV+DTaP+Hib vs. DTaP+HibHAV

Statistical analysis description:

Non-inferiority of anti-FHA antibody GMCs 31 days following the co-administration of DTaP and Hib vaccines with the first dose of HAV (Havrix + Infanrix + ActHIB Group) compared to DTaP and Hib vaccines given alone (Infanrix + ActHIBHavrix Group). Non-inferiority was to rule out more than a 1.5-fold decrease in the anti-FHA GMCs between the Havrix + Infanrix+ ActHIB Group and the Infanrix + ActHIBHavrix Group 31 days following the administration of DTaP and Hib vaccines.

Comparison groups	Infanrix + ActHIBHavrix Group v Havrix + Infanrix + ActHIB Group
Number of subjects included in analysis	169
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Adjusted GMC ratio
Point estimate	0.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.81
upper limit	1.2

Statistical analysis title	Non-inferiority of HAV+DTaP+Hib vs. DTaP+HibHAV

Statistical analysis description:

Non-inferiority of anti-PRN antibody GMCs 31 days following the co-administration of DTaP and Hib vaccines with the first dose of HAV (Havrix + Infanrix + ActHIB Group) compared to DTaP and Hib vaccines given alone (Infanrix + ActHIBHavrix Group). Non-inferiority was to rule out more than a 1.5-fold decrease in the anti-PRN GMCs between the Havrix + Infanrix+ ActHIB Group and the Infanrix + ActHIBHavrix Group 31 days following the administration of DTaP and Hib vaccines.

Comparison groups	Havrix + Infanrix + ActHIB Group v Infanrix + ActHIBHavrix Group

Number of subjects included in analysis	169
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Adjusted GMC ratio
Point estimate	1.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.83
upper limit	1.36

Secondary: Anti-diphtheria and anti-tetanus antibody geometric mean concentrations (GMC)

End point title	Anti-diphtheria and anti-tetanus antibody geometric mean concentrations (GMC)[5]

End point description:

GMCs are expressed as International Units per milliliter (IU/mL). This outcome measure concerns subjects in the Havrix + Infanrix + ActHIB Group and Infanrix + ActHIBHavrix Group.

End point type	Secondary

End point timeframe:

31 days following the administration of Infanrix™ and ActHIB

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This outcome measure concerns subjects in the Havrix + Infanrix + ActHIB Group and Infanrix + ActHIBHavrix Group.

End point values	Havrix + Infanrix + ActHIB Group	Infanrix + ActHIBHavrix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	89	80		
Units: IU/mL				
geometric mean (confidence interval 95%)				
Anti-diphtheria (n= 89, 80)	11.3 (9.8 to 13.1)	10.3 (8.7 to 12.3)		
Anti-tetanus (n= 88, 80)	7 (5.9 to 8.2)	7.3 (6 to 8.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Anti-polyribosylribitol phosphate (PRP) antibody geometric mean concentrations (GMC)

End point title	Anti-polyribosylribitol phosphate (PRP) antibody geometric mean concentrations (GMC)[6]

End point description:

GMCs are expressed as microgram/milliliter (µg/mL). This outcome measure concerns subjects in the Havrix + Infanrix + ActHIB Group and Infanrix + ActHIBHavrix Group.

End point type	Secondary

End point timeframe:

31 days following the administration of Infanrix™ and ActHIB

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This outcome measure concerns subjects in the Havrix + Infanrix + ActHIB Group and Infanrix + ActHIBHavrix Group.

End point values	Havrix + Infanrix + ActHIB Group	Infanrix + ActHIBHavrix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	90	79		
Units: µg/mL				
geometric mean (confidence interval 95%)				
Anti-polyribosylribitol phosphate (PRP) antibodies	60.8 (45.9 to 80.4)	41 (30 to 55.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects seropositive for anti-pertussis toxoid (PT), anti-filamentous hemagglutinin (FHA), anti-pertactin (PRN) and anti-polyribosylribitol phosphate (PRP)

End point title	Number of subjects seropositive for anti-pertussis toxoid (PT), anti-filamentous hemagglutinin (FHA), anti-pertactin (PRN) and anti-polyribosylribitol phosphate (PRP)[7]

End point description:

Seropositivity is defined as antibody concentrations ≥ 5 Enzyme Linked Immunosorbent Assay Units per Milliliter (EL.U/mL) for anti-PT, anti-FHA and anti-PRN antibodies and as antibody concentrations ≥ 0.15 microgram/milliliter (µg/mL) for anti-PRP antibodies. This outcome measure concerns subjects in the Havrix + Infanrix + ActHIB Group and Infanrix + ActHIBHavrix Group.

End point type	Secondary

End point timeframe:

31 days following the administration of Infanrix™ and ActHIB

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This outcome measure concerns subjects in the Havrix + Infanrix + ActHIB Group and Infanrix + ActHIBHavrix Group.

End point values	Havrix + Infanrix + ActHIB Group	Infanrix + ActHIBHavrix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	90	79		
Units: Subjects				
Anti-PT (n= 89, 80)	89	80		
Anti-FHA (n= 89, 80)	89	80		
Anti-PRN (n= 89, 80)	89	80		
Anti-PRP (n= 90, 79)	90	79		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of seropositive subjects for anti-hepatitis A virus (HAV) antibodies following the first dose of Havrix

End point title	Number of seropositive subjects for anti-hepatitis A virus (HAV) antibodies following the first dose of Havrix[8]

End point description:

Subjects are defined as being anti-HAV seropositive if their anti-HAV antibody concentration is ≥ 15 milli-International Units per milliliter (mIU/mL). This outcome measure concerns subjects in the Havrix Group and Havrix + Infanrix + ActHIB Group.

End point type	Secondary

End point timeframe:

31 days following the first dose of Havrix™

Notes:

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

End point values	Havrix Group	Havrix + Infanrix + ActHIB Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94	89		
Units: Subjects				
Anti-hepatitis A virus (HAV) antibodies	82	77		

Statistical analyses

No statistical analyses for this end point

Secondary: Anti-hepatitis A virus (HAV) antibody geometric mean concentrations (GMC) following the first dose of Havrix

End point title	Anti-hepatitis A virus (HAV) antibody geometric mean concentrations (GMC) following the first dose of Havrix[9]

End point description:

Anti-hepatitis A (HAV) antibody geometric mean concentrations (GMC) are expressed as milli-International Units per milliliter (mIU/mL). This outcome measure concerns subjects in the Havrix Group and Havrix + Infanrix + ActHIB Group.

End point type	Secondary

End point timeframe:

31 days following the first dose of Havrix™

Notes:

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

End point values	Havrix Group	Havrix + Infanrix + ActHIB Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94	89		
Units: mIU/mL				
geometric mean (confidence interval 95%)				
Anti-hepatitis A virus (HAV) antibodies	51.5 (41.7 to 63.7)	51.5 (41.8 to 63.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with vaccine response to Havrix™

End point title	Number of subjects with vaccine response to Havrix™

End point description:

Vaccine response to Havrix is defined as post-vaccination anti-HAV antibody concentrations ≥ 15 mIU/mL in initially seronegative subjects or a ≥ 2-fold increase above the pre-vaccination anti-HAV antibody concentration in initially seropositive subjects.

End point type	Secondary

End point timeframe:

31 days following the second dose

End point values	Havrix Group	Havrix + Infanrix + ActHIB Group	Infanrix + ActHIBHavrix Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	86	83	74	
Units: Subjects				
Vaccine response to Havrix™	86	83	74	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reporting solicited local adverse events (AEs)

End point title	Number of subjects reporting solicited local adverse events (AEs)

End point description:

Solicited local AEs assessed include pain, redness and swelling. Data across doses are presented in the table.

End point type	Secondary

End point timeframe:

4-day period following each dose of study vaccine(s)

End point values	Havrix Group	Havrix + Infanrix + ActHIB Group	Infanrix + ActHIBHavrix Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	130	118	122	
Units: Subjects				
Pain	44	60	70	
Redness	34	54	63	
Swelling	21	38	46	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reporting solicited general adverse events (AEs)

End point title	Number of subjects reporting solicited general adverse events (AEs)

End point description:

Solicited general AEs assessed include drowsiness, axillary fever ≥ 37.5°C, irritability and loss of appetite. Data across doses are presented in the table.

End point type	Secondary

End point timeframe:

4-day period following each dose of study vaccine(s)

End point values	Havrix Group	Havrix + Infanrix + ActHIB Group	Infanrix + ActHIBHavrix Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	130	118	123	
Units: Subjects				
Drowsiness	44	50	53	
Fever	16	26	31	
Irritability	56	62	70	
Loss of appetite	33	40	48	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reporting unsolicited adverse events (AEs)

End point title	Number of subjects reporting unsolicited adverse events (AEs)

End point description:

An Adverse Event is any untoward medical occurrence in a clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

End point type	Secondary

End point timeframe:

31-day period following each dose of study vaccine(s)

End point values	Havrix Group	Havrix + Infanrix + ActHIB Group	Infanrix + ActHIBHavrix Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	135	127	132	
Units: Subjects				
AEs	75	69	71	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reporting serious adverse events (SAEs), new chronic illnesses and medically significant events

End point title	Number of subjects reporting serious adverse events (SAEs), new chronic illnesses and medically significant events

End point description:

Since the related information about medically significant events was not specifically collected and new chronic illnesses were only collected in the extended safety follow-up phase, all unsolicited adverse events (AEs) throughout the study are reported in the table without identifying which event was a medically significant or new chronic illness.

End point type	Secondary

End point timeframe:

Active Phase and the 6-months Extended Safety Follow-up (ESFU) Phase.

End point values	Havrix Group	Havrix + Infanrix + ActHIB Group	Infanrix + ActHIBHavrix Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	135	127	132	
Units: Subjects				
SAEs (n= 135, 127, 132)	5	2	4	
AEs during Active Phase (n= 135, 127, 132)	80	74	72	

AEs during ESFU (n=119,111,109)	11	10	7	

Statistical analyses

No statistical analyses for this end point

Secondary: Anti-hepatitis virus A (HAV) antibody geometric mean concentrations

End point title	Anti-hepatitis virus A (HAV) antibody geometric mean concentrations[10]

End point description:

Anti-hepatitis A (HAV) antibody geometric mean concentrations (GMC) are expressed as milli-International Units per milliliter (mIU/mL). This outcome measure concerns subjects in the Infanrix + ActHIBHavrix Group only.

End point type	Secondary

End point timeframe:

31 days following the second dose of Havrix™

Notes:

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

End point values	Infanrix + ActHIBHavrix Group			
Subject group type	Reporting group			
Number of subjects analysed	77			
Units: mIU/mL				
geometric mean (confidence interval 95%)				
Anti-hepatitis virus A (HAV) antibodies	1625.1 (1378.2 to 1916.3)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

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	11.0

Reporting groups

Reporting group title	Havrix Group

Reporting group description:

Subjects received one dose of Havrix at Day 0 followed by a second dose of Havrix at Month 6-9.

Reporting group title	Havrix + Infanrix + ActHIB Group

Reporting group description:

Subjects received one dose of Havrix co-administered with Infanrix and ActHIB vaccines at Day 0 followed by a second dose of Havrix at Month 6-9.

Reporting group title	Infanrix + ActHIBHavrix Group

Reporting group description:

Subjects received Infanrix co-administered with ActHIB at Day 0, followed by one dose of Havix at Day 30 and a second dose of Havrix at Month 7-10.

Serious adverse events	Havrix Group	Havrix + Infanrix + ActHIB Group	Infanrix + ActHIBHavrix Group
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 135 (3.70%)	2 / 127 (1.57%)	4 / 132 (3.03%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Cardiac disorders			
Tachycardia			
subjects affected / exposed	0 / 135 (0.00%)	1 / 127 (0.79%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Developmental delay			
subjects affected / exposed	1 / 135 (0.74%)	0 / 127 (0.00%)	1 / 132 (0.76%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			

subjects affected / exposed	0 / 135 (0.00%)	1 / 127 (0.79%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 135 (0.74%)	0 / 127 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchial hyperreactivity			
subjects affected / exposed	0 / 135 (0.00%)	0 / 127 (0.00%)	1 / 132 (0.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory distress			
subjects affected / exposed	0 / 135 (0.00%)	0 / 127 (0.00%)	1 / 132 (0.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tonsillar hypertrophy			
subjects affected / exposed	0 / 135 (0.00%)	0 / 127 (0.00%)	1 / 132 (0.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Expressive language disorder			
subjects affected / exposed	1 / 135 (0.74%)	0 / 127 (0.00%)	1 / 132 (0.76%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	1 / 135 (0.74%)	1 / 127 (0.79%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthritis bacterial			
subjects affected / exposed	1 / 135 (0.74%)	0 / 127 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	2 / 135 (1.48%)	0 / 127 (0.00%)	1 / 132 (0.76%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Failure to thrive			
subjects affected / exposed	1 / 135 (0.74%)	0 / 127 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Havrix Group	Havrix + Infanrix + ActHIB Group	Infanrix + ActHIBHavrix Group
Total subjects affected by non-serious adverse events			
subjects affected / exposed	56 / 135 (41.48%)	62 / 127 (48.82%)	70 / 132 (53.03%)
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	9 / 135 (6.67%)	7 / 127 (5.51%)	9 / 132 (6.82%)
occurrences (all)	9	7	9
Pain at the injection site			
alternative assessment type: Systematic			
subjects affected / exposed[1]	44 / 130 (33.85%)	60 / 118 (50.85%)	70 / 122 (57.38%)
occurrences (all)	44	60	70
Redness at the injection site			
alternative assessment type: Systematic			
subjects affected / exposed[2]	34 / 130 (26.15%)	54 / 118 (45.76%)	63 / 122 (51.64%)
occurrences (all)	34	54	63
Swelling at the injection site			
alternative assessment type: Systematic			
subjects affected / exposed[3]	21 / 130 (16.15%)	38 / 118 (32.20%)	46 / 122 (37.70%)
occurrences (all)	21	38	46
Drowsiness			
alternative assessment type: Systematic			

subjects affected / exposed[4]	44 / 130 (33.85%)	50 / 118 (42.37%)	53 / 123 (43.09%)
occurrences (all)	44	50	53
Fever			
alternative assessment type: Systematic			
subjects affected / exposed[5]	16 / 130 (12.31%)	26 / 118 (22.03%)	31 / 123 (25.20%)
occurrences (all)	16	26	31
Irritability			
alternative assessment type: Systematic			
subjects affected / exposed[6]	56 / 130 (43.08%)	62 / 118 (52.54%)	70 / 123 (56.91%)
occurrences (all)	56	62	70
Loss of appetite			
alternative assessment type: Systematic			
subjects affected / exposed[7]	33 / 130 (25.38%)	40 / 118 (33.90%)	48 / 123 (39.02%)
occurrences (all)	33	40	48
Gastrointestinal disorders			
Diarrhea			
subjects affected / exposed	9 / 135 (6.67%)	4 / 127 (3.15%)	7 / 132 (5.30%)
occurrences (all)	9	4	7
Teething			
subjects affected / exposed	3 / 135 (2.22%)	8 / 127 (6.30%)	4 / 132 (3.03%)
occurrences (all)	3	8	4
Vomiting			
subjects affected / exposed	7 / 135 (5.19%)	4 / 127 (3.15%)	4 / 132 (3.03%)
occurrences (all)	7	4	4
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	8 / 135 (5.93%)	4 / 127 (3.15%)	14 / 132 (10.61%)
occurrences (all)	8	4	14
Rhinorrhea			
subjects affected / exposed	5 / 135 (3.70%)	4 / 127 (3.15%)	14 / 132 (10.61%)
occurrences (all)	5	4	14
Infections and infestations			
Otitis media			
subjects affected / exposed	13 / 135 (9.63%)	11 / 127 (8.66%)	22 / 132 (16.67%)
occurrences (all)	13	11	22
Upper respiratory tract infection			

subjects affected / exposed	18 / 135 (13.33%)	18 / 127 (14.17%)	16 / 132 (12.12%)
occurrences (all)	18	18	16
Viral infection			
subjects affected / exposed	3 / 135 (2.22%)	7 / 127 (5.51%)	3 / 132 (2.27%)
occurrences (all)	3	7	3

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: For a given subject cohort and the analysis of a given measurement, missing or non-evaluable measurements were not replaced. Therefore, an analysis excluded data points for subjects with missing or non-evaluable measurements i.e. analysis of solicited symptoms excluded vaccinated subjects without documented Diary Cards.

[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: For a given subject cohort and the analysis of a given measurement, missing or non-evaluable measurements were not replaced. Therefore, an analysis excluded data points for subjects with missing or non-evaluable measurements i.e. analysis of solicited symptoms excluded vaccinated subjects without documented Diary Cards.

[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: For a given subject cohort and the analysis of a given measurement, missing or non-evaluable measurements were not replaced. Therefore, an analysis excluded data points for subjects with missing or non-evaluable measurements i.e. analysis of solicited symptoms excluded vaccinated subjects without documented Diary Cards.

[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: For a given subject cohort and the analysis of a given measurement, missing or non-evaluable measurements were not replaced. Therefore, an analysis excluded data points for subjects with missing or non-evaluable measurements i.e. analysis of solicited symptoms excluded vaccinated subjects without documented Diary Cards.

[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: For a given subject cohort and the analysis of a given measurement, missing or non-evaluable measurements were not replaced. Therefore, an analysis excluded data points for subjects with missing or non-evaluable measurements i.e. analysis of solicited symptoms excluded vaccinated subjects without documented Diary Cards.

[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: For a given subject cohort and the analysis of a given measurement, missing or non-evaluable measurements were not replaced. Therefore, an analysis excluded data points for subjects with missing or non-evaluable measurements i.e. analysis of solicited symptoms excluded vaccinated subjects without documented Diary Cards.

[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: For a given subject cohort and the analysis of a given measurement, missing or non-evaluable measurements were not replaced. Therefore, an analysis excluded data points for subjects with missing or non-evaluable measurements i.e. analysis of solicited symptoms excluded vaccinated subjects without documented Diary Cards.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 March 2005	Rationale: Included the GMCs for anti-PT, anti-FHA and anti-PRN antibodies as a co-primary objective/endpoint rather than as a secondary one, Increase in the sample size from 750 to 840 in order to test the immune response with respect to GMCs for anti-PT, anti-FHA and anti-PRN antibodies as a co-primary objective/endpoint, Deletion of a history of non-response to any vaccine in the current routine immunization schedule as an exclusion criteria, Captured the brand of Hib vaccine used for pre-study priming, Provided instructions regarding the administration of concomitant influenza vaccine, Provided updated contact information for the Medical Monitor and the Study Manager, Included the additional descriptive analyses evaluating seroresponse at a level of 1.0 IU/mL for antibodies to diphtheria and tetanus antigens.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported