Clinical trial results:
A phase IIIb, open, randomized, controlled, multicenter study to assess the co-administration of Rotarix (GlaxoSmithKline Biologicals') with Hib-MenCY-TT (MenHibrix)(GlaxoSmithKline Biologicals' Meningococcal Groups C and Y and Haemophilus b Tetanus Toxoid Conjugate Vaccine) at 2 and 4 months of age, the co-administration of Prevnar 13 (Pfizer) with Hib-MenCY-TT (MenHibrix) at 2, 4 and 6 months of age and the co-administration of Prevnar 13 and Havrix (GlaxoSmithKline Biologicals') with Hib-MenCY-TT ((MenHibrix) at 12 to 15 months of age.

Summary

EudraCT number	2013-003459-39
Trial protocol	Outside EU/EEA
Global end of trial date	18 March 2016

Results information

Result version number	v2 (current)
This version publication date	13 June 2018
First version publication date	22 December 2016
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	112931

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01978093
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, 044 2089-904466, GSKClinicalSupportHD@gsk.com
Scientific contact	Clinical Trials Call Center, GlaxoSmithKline Biologicals, 044 2089-904466, 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	10 March 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 March 2016
Global end of trial reached?	Yes
Global end of trial date	18 March 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate non-inferiority of 4 doses of Hib-MenCY-TT compared to 3 doses of PedvaxHIB,when co-administered with Prevnar 13 and Havrix,in terms of anti-PRP concentration
Epoch 001:To demonstrate non-inferiority of 2 doses of Rotarix co-administered with Hib-MenCY-TT,Pediarix and Prevnar 13 compared to Rotarix co-administered with PedvaxHIB,Pediarix and Prevnar 13 in terms of Rotarix IgA GMCs
.3 doses of Prevnar 13 co-administered with Hib-MenCY-TT,Rotarix and Pediarix compared to Prevnar 13 co-administered with PedvaxHIB,Rotarix and Pediarix in terms of S. pneumoniae GMCs

Epoch 002:To demonstrate non-inferiority of 2 doses of Havrix when the 1st dose is co-administered with Hib-MenCY-TT and Prevnar 13 compared to Havrix when the 1st dose is co-administered with PedvaxHIB and Prevnar 13,at 12-15 months of age.4 doses of Prevnar 13 co-administered with Hib-MenCY-TT and Havrix compared to Prevnar 13 co-administered with PedvaxHIB and Havrix in terms of S. pneumoniae GMCs

Protection of trial subjects:

The subjects were observed closely for at least 30 minutes following the administration of the vaccines, with appropriate medical treatment readily available in case of anaphylaxis

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	19 February 2014
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: 600
Worldwide total number of subjects	600
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	600
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:

600 subjects were recruited from 27 centers in the United States. The study consists of 2 epochs: Epoch 001: starting at Day 0 and ending at the day preceding the 4th vaccination (Month 10-13) and Epoch 002: starting at Month 10-13 and ending at Month 17-20, 31 days after the 2nd Havrix vaccination

Pre-assignment

Screening details:

All enrolled subjects were included in the study.

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	HibCY Group

Arm description:

Subjects received 4 doses of Hib-MenCY-TT vaccine at Day 0, Month 2, Month 4 and Month 10-13, 3 doses of Pediarix vaccine at Day 0, Month 2 and Month 4, 2 doses of Rotarix vaccine at Day 0 and Month 2, 4 doses of Prevnar 13 vaccine at Day 0 and Month 2, Month 4 and Month 10-13 and 2 doses of Havrix vaccine at Month 10-13 and Month 16-19.

Arm type	Experimental
Investigational medicinal product name	Hib-MenCY-TT (MenHibrix)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solution for solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Four doses administered intramuscularly in the right upper anterolateral thigh at Day 0, Month 2, Month 4 and month 10-13

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

Dosage and administration details:

Two doses administered orally at Day 0 and month 2

Investigational medicinal product name	Havrix 720 Junior
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Two doses administered intramuscularly in the left upper anterolateral thigh at month 10-13 and month 16-19

Investigational medicinal product name	Prevnar 13
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection

Routes of administration	Intramuscular use

Dosage and administration details:

Four doses administered intramuscularly in the left lower anterolateral thigh at Day 0 and Month 2, Month 4 and Month 10-13.

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

Dosage and administration details:

Three doses administered intramuscularly in the left upper anterolateral thigh at day 0, month 2 and in the right upper anterolateral thigh at month 4.

Arm title	PedHIB Group

Arm description:

Subjects received 3 doses of PedvaxHIB vaccine at Day 0, Month 2 and Month 10-13, 3 doses of Pediarix vaccine at Day 0, Month 2 and Month 4, 2 doses of Rotarix vaccine at Day 0 and Month 2, 4 doses of Prevnar 13 vaccine at Day 0 and Month 2, Month 4 and Month 10-13 and 2 doses of Havrix vaccine at Month 10-13 and Month 16-19.

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

Dosage and administration details:

Two doses administered orally at Day 0 and month 2

Investigational medicinal product name	Havrix 720 Junior
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Two doses administered intramuscularly in the left upper anterolateral thigh at month 10-13 and month 16-19

Investigational medicinal product name	Prevnar 13
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Four doses administered intramuscularly in the left lower anterolateral thigh at Day 0 and Month 2, Month 4 and Month 10-13.

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

Dosage and administration details:

Three doses administered intramuscularly in the left upper anterolateral thigh at day 0, month 2 and in the right upper anterolateral thigh at month 4.

Investigational medicinal product name	Pedvax HIB
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection

Routes of administration	Intramuscular use

Dosage and administration details:

Three doses administered intramuscularly in the right upper anterolateral thigh at day 0, month 2 and month 10-13.

Number of subjects in period 1	HibCY Group	PedHIB Group
Started	297	303
Completed	232	230
Not completed	65	73
Adverse event, serious fatal	1	-
Loss of kaiser coverage	4	10
Consent withdrawn by subject	29	25
N/A for vaccine administration	-	1
Adverse event, non-fatal	-	5
Child was in care of grandmother	-	1
Mother lost custody of child	-	1
Migrated/moved from study area	11	13
Lost to follow-up	11	15
Lost kaiser health plan unable to contac	1	-
Protocol deviation	8	2

Baseline characteristics

Reporting groups	
Reporting group title	HibCY Group
Reporting group description:	
Subjects received 4 doses of Hib-MenCY-TT vaccine at Day 0, Month 2, Month 4 and Month 10-13, 3 doses of Pediarix vaccine at Day 0, Month 2 and Month 4, 2 doses of Rotarix vaccine at Day 0 and Month 2, 4 doses of Prevnar 13 vaccine at Day 0 and Month 2, Month 4 and Month 10-13 and 2 doses of Havrix vaccine at Month 10-13 and Month 16-19.	
Reporting group title	PedHIB Group
Reporting group description:	
Subjects received 3 doses of PedvaxHIB vaccine at Day 0, Month 2 and Month 10-13, 3 doses of Pediarix vaccine at Day 0, Month 2 and Month 4, 2 doses of Rotarix vaccine at Day 0 and Month 2, 4 doses of Prevnar 13 vaccine at Day 0 and Month 2, Month 4 and Month 10-13 and 2 doses of Havrix vaccine at Month 10-13 and Month 16-19.	

Reporting group values	HibCY Group	PedHIB Group	Total
Number of subjects	297	303	600
Age categorical Units: Subjects			
Infants and Toddlers	297	303	600
Age continuous Units: weeks			
arithmetic mean	8.6	8.6	
standard deviation	± 1.1	± 1.1	-
Gender categorical Units: Subjects			
Female	148	140	288
Male	149	163	312
Race/Ethnicity, Customized Units: Subjects			
African Heritage / African American	29	19	48
American Indian or Alaskan Native	11	12	23
Asian - Central/South Asian Heritage	5	4	9
Asian - East Asian Heritage	2	2	4
Asian - Japanese Heritage	1	0	1
Asian - South East Asian Heritage	9	8	17
Native Hawaiian or Other Pacific Islander	2	6	8
White - Arabic / North African Heritage	1	2	3
White - Caucasian / European Heritage	201	218	419
Unspecified	36	32	68

End points

End points reporting groups

Reporting group title	HibCY Group

Reporting group description:

Subjects received 4 doses of Hib-MenCY-TT vaccine at Day 0, Month 2, Month 4 and Month 10-13, 3 doses of Pediarix vaccine at Day 0, Month 2 and Month 4, 2 doses of Rotarix vaccine at Day 0 and Month 2, 4 doses of Prevnar 13 vaccine at Day 0 and Month 2, Month 4 and Month 10-13 and 2 doses of Havrix vaccine at Month 10-13 and Month 16-19.

Reporting group title	PedHIB Group

Reporting group description:

Subjects received 3 doses of PedvaxHIB vaccine at Day 0, Month 2 and Month 10-13, 3 doses of Pediarix vaccine at Day 0, Month 2 and Month 4, 2 doses of Rotarix vaccine at Day 0 and Month 2, 4 doses of Prevnar 13 vaccine at Day 0 and Month 2, Month 4 and Month 10-13 and 2 doses of Havrix vaccine at Month 10-13 and Month 16-19.

Primary: Percentage of subjects with Anti-Polyribosylribitol phosphate (Anti-PRP) antibody concentrations greater than or equal to (≥) 1.0 µg/mL

End point title	Percentage of subjects with Anti-Polyribosylribitol phosphate (Anti-PRP) antibody concentrations greater than or equal to (≥) 1.0 µg/mL

End point description:

Percentage of subjects with Anti-PRP antibody concentrations≥1.0 µg/mL were assessed. Analysis of Immunogenicity is performed on blood sample (BS) sub-cohorts. Assignment to a BS sub-cohort depends on the date of enrolment of the subject: BS sub-cohort for the first 200 , for the next 200 subjects or for the last 200 subjects. Within each BS sub-cohort subjects have been randomized 1:1 to either HibCY or PedHIB groups.As per an hierarchical procedure, the primary objective about Anti-PRP will first need to be met to be able to conclude on any other primary objective, and within each subsequent arm, the first primary objective will have to be reached to conclude on the second primary objective of that Epoch.

End point type	Primary

End point timeframe:

1 month after the fourth dose for HibCY Group and 1 month after third dose for PedHIB Group [Month (M) 11-14]

End point values	HibCY Group	PedHIB Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	223	218		
Units: Percentage of subjects				
number (confidence interval 95%)				
Anti-PRP≥1.0µg/mL (N=223,218)	98.2 (95.5 to 99.5)	97.2 (94.1 to 99.0)		

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Difference between HibCY and PedHIB groups in percentage of subjects with anti-PRP concentrations

equal to or above the cut-off value of 1.0 µg/mL one month after the fourth dose in HibCY Group and third dose in PedHIB Group.

Comparison groups	PedHIB Group v HibCY Group
Number of subjects included in analysis	441
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
Method	Group difference in proportions
Parameter estimate	Difference in percentage of subjects
Point estimate	0.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.12
upper limit	4.3

Notes:

[1] - Lower limit of the standardized asymptotic 95% CI for the difference (HibCY group minus the PedHIB group) in the percentage of subjects with anti-PRP concentrations ≥1.0 mg/mL is to be ≥-10% (clinical limit for non-inferiority).Before concluding on the primary objectives for Rotarix, Prevnar 13 and Havrix, this primary objective regarding anti-PRP needs to be reached.

Primary: Anti-rotavirus serum Immunoglobulin A (IgA) Geometric Mean concentrations (GMCs).

End point title	Anti-rotavirus serum Immunoglobulin A (IgA) Geometric Mean concentrations (GMCs).

End point description:

Anti-rotavirus serum IgA was assessed by ELISA, tabulated as GMCs and expressed in Units per mililiter (U/mL).Analysis of Immunogenicity is performed on blood sample (BS) sub-cohorts. Assignment to a BS sub-cohort depends on the date of enrolment of the subject: BS sub-cohort for the first 200 , for the next 200 subjects or for the last 200 subjects. Within each BS sub-cohort subjects have been randomized 1:1 to either HibCY or PedHIB groups.As per a hierarchical procedure, the primary objective about Anti-PRP will first need to be met to be able to conclude on any other primary objective, and within each subsequent arm, the first primary objective will have to be reached to conclude on the second primary objective of that Epoch

End point type	Primary

End point timeframe:

2 months post-dose 2 of Rotarix (Month 4)

End point values	HibCY Group	PedHIB Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	155	161		
Units: U/mL				
geometric mean (confidence interval 95%)				
Anti-rotavirus serum IgA GMCs (N=155,161)	138.9 (104.0 to 185.5)	115.0 (87.5 to 151.0)		

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

GMC ratios between HibCY and PedHIB groups for anti-Rota IgA concentrations 2 months after the

second dose of Rotarix vaccine. GMC adjusted for BS sub-cohorts;97.5% confidence interval calculated for adjusted GMC ratio(Ancova model:adjustment for BS subcohorts-pooled variance)

Comparison groups	HibCY Group v PedHIB Group
Number of subjects included in analysis	316
Analysis specification	Pre-specified
Analysis type	non-inferiority[2]
Method	ANCOVA
Parameter estimate	Adjusted GMC ratios
Point estimate	1.21
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	0.77
upper limit	1.9

Notes:

[2] - Non-inferiority is concluded if lower limit of the two-sided standardized asymptotic 97.5% CI on the ratio of anti-rotavirus IgA GMC (HibCY group over PedHIB group) is to be ≥0.5. To be able to conclude independently on primary objectives of Epoch 001(Rotarix & Prevnar13 Post dose 3)& Epoch 002 (Havrix & Prevnar13 post dose 4),a Bonferroni correction is used in order to test these objectives (1.25% 1sided for Epoch 001 & 002)

Primary: Anti-Streptococcus (S) pneumoniae GMCs

End point title	Anti-Streptococcus (S) pneumoniae GMCs

End point description:

Antibody concentrations against S. pneumoniae serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F were assessed by ELISA, tabulated as GMCs and expressed in µg/mL. Analysis of Immunogenicity is performed on blood sample (BS) sub-cohorts.Assignment to a BS sub-cohort depends on the date of enrolment of the subject: BS sub-cohort for the first 200 , for the next 200 subjects or for the last 200 subjects. Within each BS sub-cohort subjects have been randomized 1:1 to either HibCY or PedHIB groups.As per an hierarchical procedure, the primary objective about Anti-PRP will first need to be met to be able to conclude on any other primary objective, and within each subsequent arm, the first primary objective will have to be reached to conclude on the second primary objective of that Epoch.

End point type	Primary

End point timeframe:

1 month post-dose 3 of Prevnar 13 (Month 5)

End point values	HibCY Group	PedHIB Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	156	158		
Units: µg/mL				
geometric mean (confidence interval 95%)				
Anti-1 antibody (N-156,158)	1.49 (1.30 to 1.70)	1.26 (1.10 to 1.44)		
Anti-3 antibody (N=149,150)	0.55 (0.48 to 0.63)	0.48 (0.42 to 0.55)		
Anti-4 antibody (N=156,158)	0.81 (0.72 to 0.90)	0.74 (0.66 to 0.84)		
Anti-5 antibody (N=156,158)	0.80 (0.71 to 0.91)	0.68 (0.59 to 0.78)		
Anti-6A antibody(N=156,158)	1.76 (1.55 to 2.00)	1.37 (1.18 to 1.60)		
Anti-6B antibody(N=154,158)	1.00 (0.85 to 1.18)	0.87 (0.73 to 1.05)		

Anti-7F antibody (N=156,158)	2.59 (2.29 to 2.93)	2.36 (2.10 to 2.65)		
Anti-9V antibody(N=156,157)	0.78 (0.69 to 0.89)	0.63 (0.55 to 0.73)		
Anti-14 antibody (N=156,156)	4.77 (4.13 to 5.52)	4.16 (3.50 to 4.94)		
Anti-18C antibody (N=156,158)	0.91 (0.81 to 1.03)	0.74 (0.65 to 0.84)		
Anti-19A antibody (N=156,158)	1.31 (1.17 to 1.48)	1.13 (0.98 to 1.31)		
Anti-19F antibody(N=155,158)	2.25 (2.02 to 2.50)	2.10 (1.87 to 2.37)		
Anti-23F antibody(N=156,157)	0.94 (0.80 to 1.10)	0.80 (0.67 to 0.94)		

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

GMC ratio between HibCY and PedHIB groups for antibodies to S. pneumoniae serotype 1 concentrations one month after the third dose.
GMC adjusted for BS sub cohorts;97.5% CI for adjusted GMC ratio (Ancova Model: adjustment for BS sub cohorts-pooled variance)

Comparison groups	HibCY Group v PedHIB Group
Number of subjects included in analysis	314
Analysis specification	Pre-specified
Analysis type	non-inferiority[3]
Method	ANCOVA
Parameter estimate	Adjusted GMC ratio
Point estimate	1.18
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	0.95
upper limit	1.47

Notes:

[3] - Lower limit of the two-sided 97.5% CI on the GMC ratio (HibCY group over PedHIB group) for antibodies to S. pneumoniae serotype 1 is to be≥0.5 (clinical limit for non-inferiority).
To be able to conclude independently on primary objectives of Epoch 001(Rotarix & Prevnar13 post dose 3)& Epoch 002(Havrix & Prevnar13 post dose 4),Bonferroni correction is used to test these primary objectives(1.25% 1sided for Epoch 001 & Epoch 002)

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

GMC ratio between HibCY and PedHIB groups for antibodies to S. pneumoniae serotype 3 concentrations one month after the third dose.GMC adjusted for BS subcohorts;97.5% CI for the adjusted GMC ratio(Ancova model:adjustment for BS subcohorts-pooled variance)

Comparison groups	HibCY Group v PedHIB Group

Number of subjects included in analysis	314
Analysis specification	Pre-specified
Analysis type	non-inferiority[4]
Method	ANCOVA
Parameter estimate	Adjusted GMC ratio
Point estimate	1.15
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	0.93
upper limit	1.42

Notes:

[4] - Lower limit of the two-sided 97.5% CI on the GMC ratio (HibCY group over PedHIB group) for antibodies to S. pneumoniae serotype 3 is to be ≥0.5 (clinical limit for non-inferiority).To be able to conclude independently on primary objectives of Epoch 001(Rotarix & Prevnar13 post dose 3)& Epoch 002(Havrix&Prevnar13 post dose 4),a Bonferroni correction is used to test these primary objectives (1.25% 1sided for Epoch 001 & Epoch 002)

Statistical analysis title	Statistical analysis 3

Statistical analysis description:

GMC ratio between HibCY and PedHIB groups for antibodies to S. pneumoniae serotype 4 concentrations one month after the third dose.GMC adjusted for BS subcohorts;97.5% CI for the adjusted GMC ratio(Ancova model:adjustment for BS subcohorts-pooled variance)

Comparison groups	HibCY Group v PedHIB Group
Number of subjects included in analysis	314
Analysis specification	Pre-specified
Analysis type	non-inferiority[5]
Method	ANCOVA
Parameter estimate	Adjusted GMC ratio
Point estimate	1.08
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	0.9
upper limit	1.31

Notes:

[5] - Lower limit of the two-sided 97.5% CI on the GMC ratio (HibCY group over PedHIB group) for antibodies to S. pneumoniae serotype 4 is to be≥ 0.5 (clinical limit for non-inferiority).To be able to conclude independently on primary objectives of Epoch 001(Rotarix & Prevnar13 post dose 3)& Epoch 002(Havrix&Prevnar13 post dose 4),a Bonferroni correction is used to test these primary objectives (1.25% 1sided for Epoch 001 & Epoch 002)

Statistical analysis title	Statistical analysis 4

Statistical analysis description:

GMC ratio between HibCY and PedHIB groups for antibodies to S. pneumoniae serotype 5 concentrations one month after the third dose.GMC adjusted for BS subcohorts;97.5% CI for the adjusted GMC ratio(Ancova model:adjustment for BS subcohorts-pooled variance)

Comparison groups	HibCY Group v PedHIB Group

Number of subjects included in analysis	314
Analysis specification	Pre-specified
Analysis type	non-inferiority[6]
Method	ANCOVA
Parameter estimate	Adjusted GMC ratio
Point estimate	1.18
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	0.95
upper limit	1.47

Notes:

[6] - Lower limit of the two-sided 97.5% CI on the GMC ratio (HibCY group over PedHIB group) for antibodies to S. pneumoniae serotype 5 is to be ≥ 0.5 (clinical limit for non-inferiority).To be able to conclude independently on primary objectives of Epoch 001(Rotarix & Prevnar13 post dose 3)& Epoch 002(Havrix&Prevnar13 post dose 4),a Bonferroni correction is used to test these primary objectives (1.25% 1sided for Epoch 001 & Epoch 002)

Statistical analysis title	Statistical analysis 5

Statistical analysis description:

GMC ratio between HibCY and PedHIB groups for antibodies to S. pneumoniae serotype 6A concentrations one month after the third dose.GMC adjusted for BS subcohorts;97.5% CI for the adjusted GMC ratio(Ancova model:adjustment for BS subcohorts-pooled variance)

Comparison groups	HibCY Group v PedHIB Group
Number of subjects included in analysis	314
Analysis specification	Pre-specified
Analysis type	non-inferiority[7]
Method	ANCOVA
Parameter estimate	Adjusted GMC ratio
Point estimate	1.29
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	1.03
upper limit	1.63

Notes:

[7] - Lower limit of the two-sided 97.5% CI on the GMC ratio (HibCY group over PedHIB group) for antibodies to S. pneumoniae serotype 6A is to be≥0.5 (clinical limit for non-inferiority).To be able to conclude independently on primary objectives of Epoch 001(Rotarix & Prevnar13 post dose 3)& Epoch 002(Havrix&Prevnar13 post dose 4),a Bonferroni correction is used to test these primary objectives (1.25% 1sided for Epoch 001 & Epoch 002)

Statistical analysis title	Statistical analysis 6

Statistical analysis description:

GMC ratio between HibCY and PedHIB groups for antibodies to S. pneumoniae serotype 6B concentrations one month after the third dose.GMC adjusted for BS subcohorts;97.5% CI for the adjusted GMC ratio(Ancova model:adjustment for BS subcohorts-pooled variance)

Comparison groups	HibCY Group v PedHIB Group

Number of subjects included in analysis	314
Analysis specification	Pre-specified
Analysis type	non-inferiority[8]
Method	ANCOVA
Parameter estimate	Adjusted GMC ratio
Point estimate	1.17
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	0.88
upper limit	1.55

Notes:

[8] - Lower limit of the two-sided 97.5% CI on the GMC ratio (HibCY group over PedHIB group) for antibodies to S. pneumoniae serotype 6B is to be ≥0.5 (clinical limit for non-inferiority).To be able to conclude independently on primary objectives of Epoch 001(Rotarix & Prevnar13 post dose 3)& Epoch 002(Havrix&Prevnar13 post dose 4),a Bonferroni correction is used to test these primary objectives (1.25% 1sided for Epoch 001 & Epoch 002)

Statistical analysis title	Statistical analysis 7

Statistical analysis description:

GMC ratio between HibCY and PedHIB groups for antibodies to S. pneumoniae serotype 7F concentrations one month after the third dose.GMC adjusted for BS subcohorts;97.5% CI for the adjusted GMC ratio(Ancova model:adjustment for BS subcohorts-pooled variance)

Comparison groups	HibCY Group v PedHIB Group
Number of subjects included in analysis	314
Analysis specification	Pre-specified
Analysis type	non-inferiority[9]
Method	ANCOVA
Parameter estimate	Adjusted GMC ratio
Point estimate	1.11
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	0.91
upper limit	1.34

Notes:

[9] - Lower limit of the two-sided 97.5% CI on the GMC ratio (HibCY group over PedHIB group) for antibodies to S. pneumoniae serotype 7F is to be≥0.5 (clinical limit for non-inferiority).To be able to conclude independently on primary objectives of Epoch 001(Rotarix & Prevnar13 post dose 3)& Epoch 002(Havrix&Prevnar13 post dose 4),a Bonferroni correction is used to test these primary objectives (1.25% 1sided for Epoch 001 & Epoch 002)

Statistical analysis title	Statistical analysis 8

Statistical analysis description:

GMC ratio between HibCY and PedHIB groups for antibodies to S. pneumoniae serotype 9V concentrations one month after the third dose.GMC adjusted for BS subcohorts;97.5% CI for the adjusted GMC ratio(Ancova model:adjustment for BS subcohorts-pooled variance)

Comparison groups	HibCY Group v PedHIB Group

Number of subjects included in analysis	314
Analysis specification	Pre-specified
Analysis type	non-inferiority[10]
Method	ANCOVA
Parameter estimate	Adjusted GMC ratio
Point estimate	1.25
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	1
upper limit	1.55

Notes:

[10] - Lower limit of the two-sided 97.5% CI on the GMC ratio (HibCY group over PedHIB group) for antibodies to S. pneumoniae serotype 9V is to be≥0.5 (clinical limit for non-inferiority).To be able to conclude independently on primary objectives of Epoch 001(Rotarix & Prevnar13 post dose 3)& Epoch 002(Havrix&Prevnar13 post dose 4),a Bonferroni correction is used to test these primary objectives (1.25% 1sided for Epoch 001 & Epoch 002)

Statistical analysis title	Statistical analysis 9

Statistical analysis description:

GMC ratio between HibCY and PedHIB groups for antibodies to S. pneumoniae serotype 14 concentrations one month after the third dose.GMC adjusted for BS subcohorts;97.5% CI for the adjusted GMC ratio(Ancova model:adjustment for BS subcohorts-pooled variance)

Comparison groups	HibCY Group v PedHIB Group
Number of subjects included in analysis	314
Analysis specification	Pre-specified
Analysis type	non-inferiority[11]
Method	ANCOVA
Parameter estimate	Adjusted GMC ratio
Point estimate	1.16
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	0.9
upper limit	1.5

Notes:

[11] - Lower limit of the two-sided 97.5% CI on the GMC ratio (HibCY group over PedHIB group) for antibodies to S. pneumoniae serotype 14 is to be≥0.5 (clinical limit for non-inferiority).To be able to conclude independently on primary objectives of Epoch 001(Rotarix & Prevnar13 post dose 3)& Epoch 002(Havrix&Prevnar13 post dose 4),a Bonferroni correction is used to test these primary objectives (1.25% 1sided for Epoch 001 & Epoch 002)

Statistical analysis title	Statistical analysis 10

Statistical analysis description:

GMC ratio between HibCY and PedHIB groups for antibodies to S. pneumoniae serotype 18C concentrations one month after the third dose.GMC adjusted for BS subcohorts;97.5% CI for the adjusted GMC ratio(Ancova model:adjustment for BS subcohorts-pooled variance)

Comparison groups	HibCY Group v PedHIB Group

Number of subjects included in analysis	314
Analysis specification	Pre-specified
Analysis type	non-inferiority[12]
Method	ANCOVA
Parameter estimate	Adjusted GMC ratio
Point estimate	1.24
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	1.01
upper limit	1.52

Notes:

[12] - Lower limit of the two-sided 97.5% CI on the GMC ratio (HibCY group over PedHIB group) for antibodies to S. pneumoniae serotype 18C is to be ≥0.5 (clinical limit for non-inferiority).To be able to conclude independently on primary objectives of Epoch 001(Rotarix & Prevnar13 post dose 3)& Epoch 002(Havrix&Prevnar13 post dose 4),a Bonferroni correction is used to test these primary objectives (1.25% 1sided for Epoch 001 & Epoch 002)

Statistical analysis title	Statistical analysis 11

Statistical analysis description:

GMC ratio between HibCY and PedHIB groups for antibodies to S. pneumoniae serotype 19A concentrations one month after the third dose.GMC adjusted for BS subcohorts;97.5% CI for the adjusted GMC ratio(Ancova model:adjustment for BS subcohorts-pooled variance)

Comparison groups	HibCY Group v PedHIB Group
Number of subjects included in analysis	314
Analysis specification	Pre-specified
Analysis type	non-inferiority[13]
Method	ANCOVA
Parameter estimate	Adjusted GMC ratio
Point estimate	1.16
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	0.94
upper limit	1.43

Notes:

[13] - Lower limit of the two-sided 97.5% CI on the GMC ratio (HibCY group over PedHIB group) for antibodies to S. pneumoniae serotype 19A is to be≥0.5 (clinical limit for non-inferiority).To be able to conclude independently on primary objectives of Epoch 001(Rotarix & Prevnar13 post dose 3)& Epoch 002(Havrix&Prevnar13 post dose 4),a Bonferroni correction is used to test these primary objectives (1.25% 1sided for Epoch 001 & Epoch 002)

Statistical analysis title	Statistical analysis 12

Statistical analysis description:

GMC ratio between HibCY and PedHIB groups for antibodies to S. pneumoniae serotype 19F concentrations one month after the third dose.GMC adjusted for BS subcohorts;97.5% CI for the adjusted GMC ratio(Ancova model:adjustment for BS subcohorts-pooled variance)

Comparison groups	HibCY Group v PedHIB Group

Number of subjects included in analysis	314
Analysis specification	Pre-specified
Analysis type	non-inferiority[14]
Method	ANCOVA
Parameter estimate	Adjusted GMC ratio
Point estimate	1.07
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	0.89
upper limit	1.29

Notes:

[14] - Lower limit of the two-sided 97.5% CI on the GMC ratio (HibCY group over PedHIB group) for antibodies to S. pneumoniae serotype 19F is to be≥0.5 (clinical limit for non-inferiority).To be able to conclude independently on primary objectives of Epoch 001(Rotarix & Prevnar13 post dose 3)& Epoch 002(Havrix&Prevnar13 post dose 4),a Bonferroni correction is used to test these primary objectives (1.25% 1sided for Epoch 001 & Epoch 002)

Statistical analysis title	Statistical analysis 13

Statistical analysis description:

GMC ratio between HibCY and PedHIB groups for antibodies to S. pneumoniae serotype 23F concentrations one month after the third dose. GMC adjusted for BS subcohorts;97.5% CI for the adjusted GMC ratio(Ancova model:adjustment for BS subcohorts-pooled variance

Comparison groups	HibCY Group v PedHIB Group
Number of subjects included in analysis	314
Analysis specification	Pre-specified
Analysis type	non-inferiority[15]
Method	ANCOVA
Parameter estimate	Adjusted GMC ratio
Point estimate	1.18
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	0.91
upper limit	1.53

Notes:

[15] - Lower limit of the two-sided 97.5% CI on the GMC ratio (HibCY group over PedHIB group) for antibodies to S. pneumoniae serotype 23F is to be ≥0.5 (clinical limit for non-inferiority).To be able to conclude independently on primary objectives of Epoch 001(Rotarix & Prevnar13 post dose 3)& Epoch 002(Havrix&Prevnar13 post dose 4),a Bonferroni correction is used to test these primary objectives (1.25% 1sided for Epoch 001 & Epoch 002)

Primary: Percentage of subjects with Anti-Hepatitis A Vaccine (Anti-Havrix) antibody concentrations ≥ 15mIU/mL

End point title	Percentage of subjects with Anti-Hepatitis A Vaccine (Anti-Havrix) antibody concentrations ≥ 15mIU/mL

End point description:

Percentage of subjects with Anti-Havrix (Anti-HAV) antibody concentrations was assessed. The cut-off value is ≥15 mIU/mL. Analysis of Immunogenicity is performed on blood sample (BS) sub-cohorts.Assignment to a BS sub-cohort depends on the date of enrolment of the subject: BS sub-cohort for the first 200 , for the next 200 subjects or for the last 200 subjects. Within each BS sub-cohort subjects have been randomized 1:1 to either HibCY or PedHIB groups.As per an hierarchical procedure, the primary objective about Anti-PRP will first need to be met to be able to conclude on any other primary objective, and within each subsequent arm, the first primary objective will have to be reached to conclude on the second primary objective of that Epoch

End point type	Primary

End point timeframe:

1 month post-dose 2 of Havrix (Month 17-20)

End point values	HibCY Group	PedHIB Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	129	124		
Units: Percentage of subjects				
number (confidence interval 95%)				
Anti-Havrix antibody≥15 mIU/mL (N=129,124)	100 (97.2 to 100)	100 (97.1 to 100)		

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Difference between HibCY and PedHIB groups in percentage of subjects with anti-HAV concentrations equal to or above the cut-off value of 15 mIU/mL one month after the second Havrix dose.

Comparison groups	HibCY Group v PedHIB Group
Number of subjects included in analysis	253
Analysis specification	Pre-specified
Analysis type	non-inferiority[16]
Method	Group difference in proportions
Parameter estimate	Difference in percentage of subjects
Point estimate	0
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-3.76
upper limit	3.91

Notes:

[16] - Lower limit of the two-sided standardized asymptotic 97.5% CI on the difference (HibCY group minus the PedHIB group) in the percentage of subjects with anti-HAV concentrations ≥15 mIU/mL is to be≥-10% (clinical limit for non-inferiority).To be able to conclude independently on primary objectives of Epoch 001(Rotarix & Prevnar13 post dose 3)& Epoch 002(Havrix & Prevnar13 post dose 4),Bonferroni correction is used to test these primary objectives(1.25% 1sided for Epoch 001 & Epoch 002)

Primary: Anti-S. pneumoniae GMCs

End point title	Anti-S. pneumoniae GMCs

End point description:

Antibody concentrations against S. pneumoniae serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F were assessed by ELISA, tabulated as GMCs and expressed in µg/mL. Analysis of Immunogenicity is performed on blood sample (BS) sub-cohorts.Assignment to a BS sub-cohort depends on the date of enrolment of the subject: BS sub-cohort for the first 200 , for the next 200 subjects or for the last 200 subjects. Within each BS sub-cohort subjects have been randomized 1:1 to either HibCY or PedHIB groups.As per an hierarchical procedure, the primary objective about Anti-PRP will first need to be met to be able to conclude on any other primary objective, and within each subsequent arm, the first primary objective will have to be reached to conclude on the second primary objective of that Epoch

End point type	Primary

End point timeframe:

1 month post-dose 4 of Prevnar 13 (Month 11-14)

End point values	HibCY Group	PedHIB Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	216	205		
Units: µg/mL				
geometric mean (confidence interval 95%)				
Anti-1 antibody (N=216,205)	2.00 (1.78 to 2.25)	1.60 (1.43 to 1.79)		
Anti-3 antibody (N=169,167)	0.52 (0.46 to 0.58)	0.51 (0.44 to 0.59)		
Anti-4 antibody (N=216,205)	1.36 (1.23 to 1.50)	1.24 (1.10 to 1.39)		
Anti-5 antibody (N=215,205)	2.36 (2.10 to 2.64)	2.23 (1.97 to 2.52)		
Anti-6A antibody (N=216,205)	6.80 (6.10 to 7.57)	5.63 (5.05 to 6.26)		
Anti-6B antibody (N=215,205)	5.57 (4.97 to 6.24)	4.94 (4.40 to 5.55)		
Anti-7F antibody (N=216,205)	4.16 (3.76 to 4.61)	3.81 (3.45 to 4.21)		
Anti-9V antibody (N=215,205)	1.38 (1.25 to 1.53)	1.24 (1.11 to 1.39)		
Anti-14 antibody (N=216,205)	7.14 (6.32 to 8.07)	6.13 (5.48 to 6.86)		
Anti-18C antibody(N=216,204)	1.62 (1.46 to 1.80)	1.42 (1.28 to 1.57)		
Anti-19A antibody (N=216,204)	5.47 (4.87 to 6.14)	5.03 (4.47 to 5.64)		
Anti-19F antibody (N=215,205)	6.23 (5.61 to 6.92)	5.54 (4.97 to 6.18)		
Anti-23F antibody (N=216,205)	3.28 (2.90 to 3.71)	2.68 (2.37 to 3.05)		

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

GMC ratios between HibCY and PedHIB groups for antibodies to S. pneumoniae serotype 1 concentrations one month after the fourth dose. GMC adjusted for BS sub cohorts;97.5% CI for adjusted GMC ratio(Ancova model:adjustment for BS sub cohorts-pooled variance)

Comparison groups	HibCY Group v PedHIB Group
Number of subjects included in analysis	421
Analysis specification	Pre-specified
Analysis type	non-inferiority[17]
Method	ANCOVA
Parameter estimate	Adjusted GMC ratio
Point estimate	1.25

Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	1.04
upper limit	1.51

Notes:

[17] - Lower limit of the two-sided 97.5% CI on the GMC ratio (HibCY group over PedHIB group) for antibodies to S. pneumoniae serotype 1 is to be ≥0.5 (clinical limit for non-inferiority).To be able to conclude independently on primary objectives of Epoch 001 & Epoch 002, a Bonferroni correction is used to test these primary objectives(1.25% one-sided for Epoch 001 and Epoch 002)

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

GMC ratios between HibCY and PedHIB groups for antibodies to S. pneumoniae serotype 3 concentrations one month after the fourth dose. GMC adjusted for BS sub cohorts;97.5% CI for adjusted GMC ratio(Ancova model:adjustment for BS sub cohorts-pooled variance)

Comparison groups	HibCY Group v PedHIB Group
Number of subjects included in analysis	421
Analysis specification	Pre-specified
Analysis type	non-inferiority[18]
Method	ANCOVA
Parameter estimate	Adjusted GMC ratio
Point estimate	1.01
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	0.83
upper limit	1.24

Notes:

[18] - Lower limit of the two-sided 97.5% CI on the GMC ratio (HibCY group over PedHIB group) for antibodies to S. pneumoniae serotype 3 is to be≥0.5 (clinical limit for non-inferiority).To be able to conclude independently on primary objectives of Epoch 001 & Epoch 002, a Bonferroni correction is used to test these primary objectives(1.25% one-sided for Epoch 001 and Epoch 002)

Statistical analysis title	Statistical analysis 3

Statistical analysis description:

GMC ratios between HibCY and PedHIB groups for antibodies to S. pneumoniae serotype 4 concentrations one month after the fourth dose.GMC adjusted for BS sub cohorts;97.5% CI for adjusted GMC ratio(Ancova model:adjustment for BS sub cohorts-pooled variance)

Comparison groups	HibCY Group v PedHIB Group
Number of subjects included in analysis	421
Analysis specification	Pre-specified
Analysis type	non-inferiority[19]
Method	ANCOVA
Parameter estimate	Adjusted GMC ratio
Point estimate	1.1
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	0.92
upper limit	1.31

Notes:

[19] - Lower limit of the two-sided 97.5% CI on the GMC ratio (HibCY group over PedHIB group) for antibodies to S. pneumoniae serotype 4 is to be≥0.5 (clinical limit for non-inferiority).To be able to conclude independently on primary objectives of Epoch 001 & Epoch 002, a Bonferroni correction is used to test these primary objectives(1.25% one-sided for Epoch 001 and Epoch 002)

Statistical analysis title	Statistical analysis 4

Statistical analysis description:

GMC ratios between HibCY and PedHIB groups for antibodies to S. pneumoniae serotype 5 concentrations one month after the fourth dose. GMC adjusted for BS sub cohorts;97.5% CI for adjusted GMC ratio(Ancova model:adjustment for BS sub cohorts-pooled variance)

Comparison groups	HibCY Group v PedHIB Group
Number of subjects included in analysis	421
Analysis specification	Pre-specified
Analysis type	non-inferiority[20]
Method	ANCOVA
Parameter estimate	Adjusted GMC ratio
Point estimate	1.06
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	0.87
upper limit	1.28

Notes:

[20] - Lower limit of the two-sided 97.5% CI on the GMC ratio (HibCY group over PedHIB group) for antibodies to S. pneumoniae serotype 5 is to be ≥0.5 (clinical limit for non-inferiority).To be able to conclude independently on primary objectives of Epoch 001 & Epoch 002, a Bonferroni correction is used to test these primary objectives(1.25% one-sided for Epoch 001 and Epoch 002)

Statistical analysis title	Statistical analysis 5

Statistical analysis description:

GMC ratios between HibCY and PedHIB groups for antibodies to S. pneumoniae serotype 6A concentrations one month after the fourth dose. GMC adjusted for BS sub cohorts;97.5% CI for adjusted GMC ratio(Ancova model:adjustment for BS sub cohorts-pooled variance)

Comparison groups	HibCY Group v PedHIB Group
Number of subjects included in analysis	421
Analysis specification	Pre-specified
Analysis type	non-inferiority[21]
Method	ANCOVA
Parameter estimate	Adjusted GMC ratio
Point estimate	1.21
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	1.01
upper limit	1.44

Notes:

[21] - Lower limit of the two-sided 97.5% CI on the GMC ratio (HibCY group over PedHIB group) for antibodies to S. pneumoniae serotype 6A is to be≥0.5 (clinical limit for non-inferiority).To be able to conclude independently on primary objectives of Epoch 001 & Epoch 002, a Bonferroni correction is used to test these primary objectives(1.25% one-sided for Epoch 001 and Epoch 002)

Statistical analysis title	Statistical analysis 6

Statistical analysis description:

GMC ratios between HibCY and PedHIB groups for antibodies to S. pneumoniae serotype 6B concentrations one month after the fourth dose. GMC adjusted for BS sub cohorts;97.5% CI for adjusted GMC ratio(Ancova model:adjustment for BS sub cohorts-pooled variance)

Comparison groups	HibCY Group v PedHIB Group
Number of subjects included in analysis	421
Analysis specification	Pre-specified
Analysis type	non-inferiority[22]
Method	ANCOVA
Parameter estimate	Adjusted GMC ratio
Point estimate	1.13
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	0.94
upper limit	1.36

Notes:

[22] - Lower limit of the two-sided 97.5% CI on the GMC ratio (HibCY group over PedHIB group) for antibodies to S. pneumoniae serotype 6B is to be≥0.5 (clinical limit for non-inferiority).To be able to conclude independently on primary objectives of Epoch 001 & Epoch 002, a Bonferroni correction is used to test these primary objectives(1.25% one-sided for Epoch 001 and Epoch 002)

Statistical analysis title	Statistical analysis 7

Statistical analysis description:

GMC ratios between HibCY and PedHIB groups for antibodies to S. pneumoniae serotype 7F concentrations one month after the fourth dose. GMC adjusted for BS sub cohorts;97.5% CI for adjusted GMC ratio(Ancova model:adjustment for BS sub cohorts-pooled variance)

Comparison groups	HibCY Group v PedHIB Group
Number of subjects included in analysis	421
Analysis specification	Pre-specified
Analysis type	non-inferiority[23]
Method	ANCOVA
Parameter estimate	Adjusted GMC ratio
Point estimate	1.09
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	0.93
upper limit	1.29

Notes:

[23] - Lower limit of the two-sided 97.5% CI on the GMC ratio (HibCY group over PedHIB group) for antibodies to S. pneumoniae serotype 7F is to be≥0.5 (clinical limit for non-inferiority).To be able to conclude independently on primary objectives of Epoch 001 & Epoch 002, a Bonferroni correction is used to test these primary objectives(1.25% one-sided for Epoch 001 and Epoch 002)

Statistical analysis title	Statistical analysis 8

Statistical analysis description:

GMC ratios between HibCY and PedHIB groups for antibodies to S. pneumoniae serotype 9V concentrations one month after the fourth dose. GMC adjusted for BS sub cohorts;97.5% CI for adjusted GMC ratio(Ancova model:adjustment for BS sub cohorts-pooled variance)

Comparison groups	HibCY Group v PedHIB Group

Number of subjects included in analysis	421
Analysis specification	Pre-specified
Analysis type	non-inferiority[24]
Method	ANCOVA
Parameter estimate	Adjusted GMC ratio
Point estimate	1.12
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	0.94
upper limit	1.33

Notes:

[24] - Lower limit of the two-sided 97.5% CI on the GMC ratio (HibCY group over PedHIB group) for antibodies to S. pneumoniae serotype 9V is to be≥0.5 (clinical limit for non-inferiority).To be able to conclude independently on primary objectives of Epoch 001 & Epoch 002, a Bonferroni correction is used to test these primary objectives(1.25% one-sided for Epoch 001 and Epoch 002)

Statistical analysis title	Statistical analysis 9

Statistical analysis description:

GMC ratios between HibCY and PedHIB groups for antibodies to S. pneumoniae serotype 14 concentrations one month after the fourth dose. GMC adjusted for BS sub cohorts;97.5% CI for adjusted GMC ratio(Ancova model:adjustment for BS sub cohorts-pooled variance)

Comparison groups	HibCY Group v PedHIB Group
Number of subjects included in analysis	421
Analysis specification	Pre-specified
Analysis type	non-inferiority[25]
Method	ANCOVA
Parameter estimate	Adjusted GMC ratio
Point estimate	1.16
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	0.96
upper limit	1.41

Notes:

[25] - Lower limit of the two-sided 97.5% CI on the GMC ratio (HibCY group over PedHIB group) for antibodies to S. pneumoniae serotype 14 is to be≥0.5 (clinical limit for non-inferiority).To be able to conclude independently on primary objectives of Epoch 001 & Epoch 002, a Bonferroni correction is used to test these primary objectives(1.25% one-sided for Epoch 001 and Epoch 002)

Statistical analysis title	Statistical analysis 10

Statistical analysis description:

GMC ratios between HibCY and PedHIB groups for antibodies to S. pneumoniae serotype 18C concentrations one month after the fourth dose. GMC adjusted for BS sub cohorts;97.5% CI for adjusted GMC ratio(Ancova model:adjustment for BS sub cohorts-pooled variance)

Comparison groups	HibCY Group v PedHIB Group

Number of subjects included in analysis	421
Analysis specification	Pre-specified
Analysis type	non-inferiority[26]
Method	ANCOVA
Parameter estimate	Adjusted GMC ratio
Point estimate	1.14
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	0.97
upper limit	1.35

Notes:

[26] - Lower limit of the two-sided 97.5% CI on the GMC ratio (HibCY group over PedHIB group) for antibodies to S. pneumoniae serotype 18C is to be≥0.5 (clinical limit for non-inferiority).To be able to conclude independently on primary objectives of Epoch 001 & Epoch 002, a Bonferroni correction is used to test these primary objectives(1.25% one-sided for Epoch 001 and Epoch 002)

Statistical analysis title	Statistical analysis 11

Statistical analysis description:

GMC ratios between HibCY and PedHIB groups for antibodies to S. pneumoniae serotype 19A concentrations one month after the fourth dose.GMC adjusted for BS sub cohorts;97.5% CI for adjusted GMC ratio(Ancova model:adjustment for BS sub cohorts-pooled variance)

Comparison groups	HibCY Group v PedHIB Group
Number of subjects included in analysis	421
Analysis specification	Pre-specified
Analysis type	non-inferiority[27]
Method	ANCOVA
Parameter estimate	Adjusted GMC ratio
Point estimate	1.09
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	0.9
upper limit	1.31

Notes:

[27] - Lower limit of the two-sided 97.5% CI on the GMC ratio (HibCY group over PedHIB group) for antibodies to S. pneumoniae serotype 19A is to be≥0.5 (clinical limit for non-inferiority).To be able to conclude independently on primary objectives of Epoch 001 & Epoch 002, a Bonferroni correction is used to test these primary objectives(1.25% one-sided for Epoch 001 and Epoch 002)

Statistical analysis title	Statistical analysis 12

Statistical analysis description:

GMC ratios between HibCY and PedHIB groups for antibodies to S. pneumoniae serotype 19F concentrations one month after the fourth dose.GMC adjusted for BS sub cohorts;97.5% CI for adjusted GMC ratio(Ancova model:adjustment for BS sub cohorts-pooled variance)

Comparison groups	HibCY Group v PedHIB Group

Number of subjects included in analysis	421
Analysis specification	Pre-specified
Analysis type	non-inferiority[28]
Method	ANCOVA
Parameter estimate	Adjusted GMC ratio
Point estimate	1.12
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	0.95
upper limit	1.34

Notes:

[28] - Lower limit of the two-sided 97.5% CI on the GMC ratio (HibCY group over PedHIB Group) for antibodies to S. pneumoniae serotype 19F is to be≥0.5 (clinical limit for non-inferiority).To be able to conclude independently on primary objectives of Epoch 001 & Epoch 002, a Bonferroni correction is used to test these primary objectives(1.25% one-sided for Epoch 001 and Epoch 002)

Statistical analysis title	Statistical analysis 13

Statistical analysis description:

GMC ratios between HibCY and PedHIB groups for antibodies to S. pneumoniae serotype 23F concentrations one month after the fourth dose. GMC adjusted for BS sub cohorts;97.5% CI for adjusted GMC ratio(Ancova model:adjustment for BS sub cohorts-pooled variance)

Comparison groups	HibCY Group v PedHIB Group
Number of subjects included in analysis	421
Analysis specification	Pre-specified
Analysis type	non-inferiority[29]
Method	ANCOVA
Parameter estimate	Adjusted GMC ratio
Point estimate	1.22
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	1
upper limit	1.5

Notes:

[29] - Lower limit of the two-sided 97.5% CI on the GMC ratio (HibCY group over PedHIB group) for antibodies to S. pneumoniae serotype 23F is to be≥0.5 (clinical limit for non-inferiority).To be able to conclude independently on primary objectives of Epoch 001 & Epoch 002, a Bonferroni correction is used to test these primary objectives(1.25% one-sided for Epoch 001 and Epoch 002)

Secondary: Percentage of subjects with anti-PRP antibody concentrations ≥0.15 µg/mL.

End point title	Percentage of subjects with anti-PRP antibody concentrations ≥0.15 µg/mL.

End point description:

The cut-off value for this assay was 0.15 µg/mL. Analysis of Immunogenicity is performed on blood sample (BS) sub-cohorts.Assignment to a BS sub-cohort depends on the date of enrolment of the subject: BS sub-cohort for the first 200 , for the next 200 subjects or for the last 200 subjects. Within each BS sub-cohort subjects have been randomized 1:1 to either HibCY or PedHIB groups.

End point type	Secondary

End point timeframe:

2 months post-dose 2 [PedHib Group only (Month 4)], 1 month post-dose 3 (Month 5 for HibCY group and Months 11-14 for PedHib Group) and 1 month post-dose 4 [HibCY Group only (Month 11-14)]

End point values	HibCY Group	PedHIB Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	223	218		
Units: Percentage of subjects				
number (confidence interval 95%)				
Month 4 (N=0,165)	0 (0 to 0)	98.8 (95.7 to 99.9)		
Month 5 (N=167,0)	99.4 (96.7 to 100)	0 (0 to 0)		
Month 11-14 (N=223, 218)	99.6 (97.5 to 100)	100 (98.3 to 100)		

Statistical analyses

No statistical analyses for this end point

Secondary: Anti-PRP GMCs ≥ 0.15 µg/mL.

End point title	Anti-PRP GMCs ≥ 0.15 µg/mL.

End point description:

Anti-PRP antibody concentrations were assessed by Enzyme-Linked-Immunosorbent-Assay (ELISA), tabulated as Geometric Mean Concentrations (GMCs) and expressed in micrograms per mililiter (µg/mL).The cut-off value for this assay was 0.15 µg/mL. Analysis of Immunogenicity is performed on blood sample (BS) sub-cohorts.Assignment to a BS sub-cohort depends on the date of enrolment of the subject: BS sub-cohort for the first 200 , for the next 200 subjects or for the last 200 subjects. Within each BS sub-cohort subjects have been randomized 1:1 to either HibCY or PedHIB groups.

End point type	Secondary

End point timeframe:

2 months post-dose 2 [PedHib Group only (Month 4)], 1 month post-dose 3 (Month 5 for HibCY group and Month 11-14 for PedHib Group) and 1 month post-dose 4 [HibCY Group only (Month 11-14)]

End point values	HibCY Group	PedHIB Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	223	218		
Units: µg/mL				
geometric mean (confidence interval 95%)				
Month 4 (N=0, 165)	0 (0 to 0)	11.053 (8.740 to 13.979)		
Month 5 (N=167,0)	8.414 (7.070 to 10.014)	0 (0 to 0)		
Month 11-14 (N=223, 218)	28.090 (24.012 to 32.862)	20.869 (17.799 to 24.468)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects with anti-PRP antibody concentrations ≥1.0 µg/mL

End point title	Percentage of subjects with anti-PRP antibody concentrations ≥1.0 µg/mL

End point description:

The cut-off value for this assay was 1.0 µg/mL. Analysis of Immunogenicity is performed on blood sample (BS) sub-cohorts.Assignment to a BS sub-cohort depends on the date of enrolment of the subject: BS sub-cohort for the first 200 , for the next 200 subjects or for the last 200 subjects. Within each BS sub-cohort subjects have been randomized 1:1 to either HibCY or PedHIB groups.

End point type	Secondary

End point timeframe:

2 months post-dose 2 [PedHib group only (Month 4)] and 1 month postdose 3 [HibCY group only (Month 5)].

End point values	HibCY Group	PedHIB Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	167	165		
Units: Percentage of subjects				
number (confidence interval 95%)				
Month 4 (N=167,0)	0 (0 to 0)	91.5 (86.2 to 95.3)		
Month 5 (N=0,165)	94.0 (89.3 to 97.1)	0 (0 to 0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects with Serum bactericidal assay to N. meningitidis serogroup C (hSBA-MenC) and N. meningitidis serogroup Y (hSBA-MenY) antibody titers ≥1:8, ≥1:16, ≥1:32.

End point title	Percentage of subjects with Serum bactericidal assay to N. meningitidis serogroup C (hSBA-MenC) and N. meningitidis serogroup Y (hSBA-MenY) antibody titers ≥1:8, ≥1:16, ≥1:32.

End point description:

The cut off values are dilutions of 1:8, 1:16 and 1:32. Analysis of Immunogenicity is performed on blood sample (BS) sub-cohorts.Assignment to a BS sub-cohort depends on the date of enrolment of the subject: BS sub-cohort for the first 200 , for the next 200 subjects or for the last 200 subjects. Within each BS sub-cohort subjects have been randomized 1:1 to either HibCY or PedHIB groups.

End point type	Secondary

End point timeframe:

1 month post-dose 3 (Month 5) and 1 month post-dose 4 (Month 11-14).

End point values	HibCY Group	PedHIB Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	215	187		
Units: Percentage of subjects				
number (confidence interval 95%)				
hSBA-MenC, Month 5, ≥ 8 (N=144,141)	100 (97.5 to 100)	1.4 (0.2 to 5.0)		
hSBA-MenC, Month 5, ≥ 16 (N=144,141)	100 (97.5 to 100)	1.4 (0.2 to 5.0)		
hSBA-MenC, Month 5, ≥ 32 (N=144,141)	99.3 (96.2 to 100)	0.7 (0.0 to 3.9)		
hSBA-MenY, Month 5, ≥ 8 (N=130, 150)	97.7 (93.4 to 99.5)	100 (97.6 to 100)		
hSBA-MenY, Month 5, ≥ 16 (N=130, 150)	97.7 (93.4 to 99.5)	100 (97.6 to 100)		
hSBA-MenY, Month 5, ≥ 32 (N=130,150)	97.7 (93.4 to 99.5)	100 (97.6 to 100)		
hSBA-MenC, Month 11-14, ≥ 8 (N=215,168)	99.1 (96.7 to 99.9)	0.6 (0.0 to 3.3)		
hSBA-MenC, Month 11-14, ≥ 16 (N=215, 168)	98.6 (96.0 to 99.7)	0.6 (0.0 to 3.3)		
hSBA-MenC, Month 11-14, ≥ 32 (N=215, 168)	98.1 (95.3 to 99.5)	0.0 (0.0 to 2.2)		
hSBA-MenY, Month 11-14, ≥ 8 (N=198, 187)	98.5 (95.6 to 99.7)	100 (98.0 to 100)		
hSBA-MenY, Month 11-14, ≥ 16 (N=198, 187)	98.5 (95.6 to 99.7)	100 (98.0 to 100)		
hSBA-MenY, Month 11-14, ≥ 32 (N=198, 187)	98.5 (95.6 to 99.7)	100 (98.0 to 100)		

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric Mean Titres (GMTs) of human complement serum bactericidal assay to N. meningitidis serogroup C (hSBA-MenC) and to hSBA-MenY

End point title	Geometric Mean Titres (GMTs) of human complement serum bactericidal assay to N. meningitidis serogroup C (hSBA-MenC) and to hSBA-MenY

End point description:

The cut-off values are dilutions of 1:8, 1:16 and 1:32. Analysis of Immunogenicity is performed on blood sample (BS) sub-cohorts.Assignment to a BS sub-cohort depends on the date of enrolment of the subject: BS sub-cohort for the first 200 , for the next 200 subjects or for the last 200 subjects. Within each BS sub-cohort subjects have been randomized 1:1 to either HibCY or PedHIB groups.

End point type	Secondary

End point timeframe:

1 month post-dose 3 (Month 5) and 1 month post-dose 4 (Month 11-14).

End point values	HibCY Group	PedHIB Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	215	187		
Units: Titres				
geometric mean (confidence interval 95%)				
hSBA-MenC, Month 5 (N=144, 141)	807.3 (659.2 to 988.6)	2.1 (2.0 to 2.3)		
hSBA-MenY, Month 5 (N=130, 150)	510.9 (405.7 to 643.3)	550.2 (474.4 to 638.1)		
hSBA-MenC, Month 11-14 (N=215, 168)	2566.2 (2046.3 to 3218.1)	2.0 (2.0 to 2.1)		
hSBA-MenY, Month 11-14 (N=198,187)	2761.4 (2274.2 to 3353.1)	2728.2 (2412.7 to 3085.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects with Anti-rotavirus IgA antibody concentrations ≥ 20 Units (U)/mL

End point title	Percentage of subjects with Anti-rotavirus IgA antibody concentrations ≥ 20 Units (U)/mL

End point description:

The cut-off value is 20 Units (U)/mL Analysis of Immunogenicity is performed on blood sample (BS) sub-cohorts.Assignment to a BS sub-cohort depends on the date of enrolment of the subject: BS sub-cohort for the first 200 , for the next 200 subjects or for the last 200 subjects. Within each BS sub-cohort subjects have been randomized 1:1 to either HibCY or PedHIB groups.

End point type	Secondary

End point timeframe:

2 month post-dose 2 of Rotarix (Month 4)

End point values	HibCY Group	PedHIB Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	155	161		
Units: Percentage of subjects				
number (confidence interval 95%)				
Anti-rota virus IgA ≥20 U/mL (N=155, 161)	81.3 (74.2 to 87.1)	80.1 (73.1 to 86.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects with Anti-HAV antibodies ≥ 15 mIU/mL

End point title	Percentage of subjects with Anti-HAV antibodies ≥ 15 mIU/mL

End point description:

The cut-off value is 15 mIU/mL. Analysis of Immunogenicity is performed on blood sample (BS) sub-cohorts.Assignment to a BS sub-cohort depends on the date of enrolment of the subject: BS sub-cohort for the first 200 , for the next 200 subjects or for the last 200 subjects. Within each BS sub-cohort subjects have been randomized 1:1 to either HibCY or PedHIB groups.

End point type	Secondary

End point timeframe:

1 month post-dose 1 of Havrix (Month 11-14)

End point values	HibCY Group	PedHIB Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	182	168		
Units: percentage of subjects				
number (confidence interval 95%)				
Anti-HAV antibodies ≥15mIU/mL (N=182, 168)	85.2 (79.2 to 90.0)	89.3 (83.6 to 93.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Anti-HAV GMCs ≥ 15 mIU/mL

End point title	Anti-HAV GMCs ≥ 15 mIU/mL

End point description:

The cut-off value is 15 mIU/mL. Analysis of Immunogenicity is performed on blood sample (BS) sub-cohorts.Assignment to a BS sub-cohort depends on the date of enrolment of the subject: BS sub-cohort for the first 200 , for the next 200 subjects or for the last 200 subjects. Within each BS sub-cohort subjects have been randomized 1:1 to either HibCY or PedHIB groups

End point type	Secondary

End point timeframe:

1 month post-dose 1 of HAV (M11-14).

End point values	HibCY Group	PedHIB Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	182	168		
Units: mIU/mL				
geometric mean (confidence interval 95%)				
Anti-HAV antibodies≥15mIU/mL (N=182, 168)	44.8 (38.3 to 52.5)	47.3 (40.9 to 54.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: GMCs for anti-HAV antibodies ≥15mIU/mL.

End point title	GMCs for anti-HAV antibodies ≥15mIU/mL.

End point description:

The cut-off value is 15 mIU/mL. Analysis of Immunogenicity is performed on blood sample (BS) sub-cohorts.Assignment to a BS sub-cohort depends on the date of enrolment of the subject: BS sub-cohort for the first 200 , for the next 200 subjects or for the last 200 subjects. Within each BS sub-cohort subjects have been randomized 1:1 to either HibCY or PedHIB groups

End point type	Secondary

End point timeframe:

1 month post-dose 2 of HAV (Month 17-20).

End point values	HibCY Group	PedHIB Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	129	124		
Units: mIU/mL				
geometric mean (confidence interval 95%)				
Anti-HAV antibodies ≥15mIU/mL (N=129, 124)	1590.7 (1312.7 to 1927.5)	1390.6 (1147.8 to 1684.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects with S. pneumoniae antibody concentrations ≥ 0.15 µg/mL, ≥ 0.26 µg/mL and ≥ 0.35 µg/mL for serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F

End point title	Percentage of subjects with S. pneumoniae antibody concentrations ≥ 0.15 µg/mL, ≥ 0.26 µg/mL and ≥ 0.35 µg/mL for serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F

End point description:

The cut-off values are 0.15, 0.26, 0.35 µg/mL. Analysis of Immunogenicity is performed on blood sample (BS) sub-cohorts.Assignment to a BS sub-cohort depends on the date of enrolment of the subject: BS sub-cohort for the first 200 , for the next 200 subjects or for the last 200 subjects. Within each BS sub-cohort subjects have been randomized 1:1 to either HibCY or PedHIB groups

End point type	Secondary

End point timeframe:

1 month post-dose 3 (Month 5) and 1 month post-dose 4 (Month 11-14)

End point values	HibCY Group	PedHIB Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	216	205		
Units: Percentage of subjects				
number (confidence interval 95%)				
Anti-1 antibody,Month 5, ≥ 0.15(N=156, 158)	100 (97.7 to 100)	100 (97.7 to 100)		
Anti-1 antibody,Month 5, ≥ 0.26(N=156, 158)	98.1 (94.5 to 99.6)	98.7 (95.5 to 99.8)		
Anti-1 antibody,Month 5, ≥ 0.35(N=156, 158)	96.8 (92.7 to 99.0)	93.7 (88.7 to 96.9)		
Anti-3 antibody,Month 5, ≥ 0.15(N=149, 150)	96.6 (92.3 to 98.9)	94.0 (88.9 to 97.2)		
Anti-3 antibody,Month 5, ≥ 0.26(N=149, 150)	84.6 (77.7 to 90.0)	78.7 (71.2 to 84.9)		
Anti-3 antibody,Month 5, ≥ 0.35(N=149, 150)	69.8 (61.7 to 77.0)	69.3 (61.3 to 76.6)		
Anti-4 antibody,Month 5, ≥ 0.15(N=156, 158)	98.7 (95.4 to 99.8)	98.1 (94.6 to 99.6)		
Anti-4 antibody,Month 5, ≥ 0.26(N=156, 158)	96.8 (92.7 to 99.0)	91.8 (86.3 to 95.5)		
Anti-4 antibody,Month 5, ≥ 0.35(N=156, 158)	91.0 (85.4 to 95.0)	84.8 (78.2 to 90.0)		
Anti-5 antibody,Month 5, ≥ 0.15(N=156, 158)	97.4 (93.6 to 99.3)	96.8 (92.8 to 99.0)		
Anti-5 antibody, Month 5, ≥ 0.26(N=156, 158)	93.6 (88.5 to 96.9)	86.7 (80.4 to 91.6)		
Anti-5 antibody, Month 5, ≥ 0.35(N=156, 158)	91.0 (85.4 to 95.0)	80.4 (73.3 to 86.3)		
Anti-6A antibody, Month 5, ≥ 0.15(N=156, 158)	100 (97.7 to 100)	98.7 (95.5 to 99.8)		
Anti-6A antibody, Month 5, ≥ 0.26(N=156, 158)	98.7 (95.4 to 99.8)	94.3 (89.5 to 97.4)		
Anti-6A antibody, Month 5, ≥ 0.35(N=156, 158)	98.1 (94.5 to 99.6)	91.8 (86.3 to 95.5)		
Anti-6B antibody, Month 5, ≥ 0.15(N=154, 158)	95.5 (90.9 to 98.2)	93.7 (88.7 to 96.9)		
Anti-6B antibody, Month 5, ≥ 0.26(N=154, 158)	90.9 (85.2 to 94.9)	86.1 (79.7 to 91.1)		
Anti-6B antibody, Month 5, ≥ 0.35(N=154, 158)	83.8 (77.0 to 89.2)	80.4 (73.3 to 86.3)		
Anti-7F antibody, Month 5, ≥ 0.15(N=156, 158)	100 (97.7 to 100)	100 (97.7 to 100)		
Anti-7F antibody, Month 5, ≥ 0.26(N=156, 158)	100 (97.7 to 100)	100 (97.7 to 100)		
Anti-7F antibody, Month 5, ≥ 0.35(N=156, 158)	100 (97.7 to 100)	100 (97.7 to 100)		
Anti-9V antibody, Month 5, ≥ 0.15(N=156, 157)	99.4 (96.5 to 100)	94.9 (90.2 to 97.8)		
Anti-9V antibody, Month 5, ≥ 0.26(N=156, 157)	92.9 (87.7 to 96.4)	86.6 (80.3 to 91.5)		
Anti-9V antibody, Month 5, ≥ 0.35(N=156, 157)	83.3 (76.5 to 88.8)	76.4 (69.0 to 82.8)		
Anti-14 antibody, Month 5, ≥ 0.15(N=156, 156)	100 (97.7 to 100)	99.4 (96.5 to 100)		
Anti-14 antibody, Month 5, ≥ 0.26(N=156, 156)	100 (97.7 to 100)	98.1 (94.5 to 99.6)		
Anti-14 antibody, Month 5, ≥ 0.35(N=156, 156)	99.4 (96.5 to 100)	97.4 (93.6 to 99.3)		
Anti-18C antibody, Month 5, ≥ 0.15(N=156, 158)	100 (97.7 to 100)	98.1 (94.6 to 99.6)		

Anti-18C antibody, Month 5, ≥ 0.26(N=156, 158)	96.8 (92.7 to 99.0)	91.1 (85.6 to 95.1)		
Anti-18C antibody, Month 5, ≥ 0.35(N=156, 158)	87.2 (80.9 to 92.0)	82.3 (75.4 to 87.9)		
Anti-19A antibody, Month 5, ≥ 0.15(N=156, 158)	100 (97.7 to 100)	98.1 (94.6 to 99.6)		
Anti-19A antibody, Month 5, ≥ 0.26(N=156, 158)	99.4 (96.5 to 100)	93.0 (87.9 to 96.5)		
Anti-19A antibody, Month 5, ≥ 0.35(N=156, 158)	97.4 (93.6 to 99.3)	90.5 (84.8 to 94.6)		
Anti-19F antibody, Month 5, ≥ 0.15(N=155, 158)	100 (97.6 to 100)	100 (97.7 to 100)		
Anti-19F antibody, Month 5, ≥ 0.26(N=155, 158)	100 (97.6 to 100)	100 (97.7 to 100)		
Anti-19F antibody, Month 5, ≥ 0.35(N=155, 158)	98.7 (95.4 to 99.8)	100 (97.7 to 100)		
Anti-23F antibody, Month 5, ≥ 0.15(N=156, 157)	96.8 (92.7 to 99.0)	96.2 (91.9 to 98.6)		
Anti-23F antibody, Month 5, ≥ 0.26(N=156, 157)	91.7 (86.2 to 95.5)	84.1 (77.4 to 89.4)		
Anti-23F antibody, Month 5, ≥ 0.35(N=156, 157)	83.3 (76.5 to 88.8)	77.1 (69.7 to 83.4)		
Anti-1 antibody, Month 11-14, ≥ 0.15(N=216, 205)	100 (98.3 to 100)	100 (98.2 to 100)		
Anti-1 antibody,Month 11-14, ≥ 0.26(N=216, 205)	99.5 (97.4 to 100)	99.5 (97.3 to 100)		
Anti-1 antibody,Month 11-14, ≥0.35(N=216, 205)	97.7 (94.7 to 99.2)	97.1 (93.7 to 98.9)		
Anti-3 antibody,Month 11-14, ≥ 0.15(N=169,167)	97.0 (93.2 to 99.0)	94.0 (89.3 to 97.1)		
Anti-3 antibody,Month 11-14, ≥ 0.26(N=169,167)	85.2 (78.9 to 90.2)	81.4 (74.7 to 87.0)		
Anti-3 antibody,Month 11-14, ≥0.35(N=169,167)	71.6 (64.2 to 78.3)	69.5 (61.9 to 76.3)		
Anti-4 antibody,Month 11-14, ≥ 0.15(N=216,205)	100 (98.3 to 100)	98.5 (95.8 to 99.7)		
Anti-4 antibody,Month 11-14, ≥ 0.26(N=216,205)	98.6 (96.0 to 99.7)	97.1 (93.7 to 98.9)		
Anti-4 antibody,Month 11-14, ≥0.35(N=216,205)	97.7 (94.7 to 99.2)	94.1 (90.0 to 96.9)		
Anti-5 antibody,Month 11-14, ≥ 0.15(N=215,205)	100 (98.3 to 100)	100 (98.2 to 100)		
Anti-5 antibody,Month 11-14, ≥ 0.26(N=215,205)	99.5 (97.4 to 100)	99.5 (97.3 to 100)		
Anti-5 antibody,Month 11-14, ≥0.35(N=215,205)	99.1 (96.7 to 99.9)	98.0 (95.1 to 99.5)		
Anti-6A antibody,Month 11-14, ≥ 0.15(N=216,205)	100 (98.3 to 100)	100 (98.2 to 100)		
Anti-6A antibody,Month 11-14, ≥ 0.26(N=216,205)	100 (98.3 to 100)	100 (98.2 to 100)		
Anti-6A antibody,Month 11-14, ≥0.35(N=216,205)	100 (98.3 to 100)	100 (98.2 to 100)		
Anti-6B antibody,Month 11-14, ≥ 0.15(N=215,205)	100 (98.3 to 100)	100 (98.2 to 100)		
Anti-6B antibody,Month 11-14, ≥ 0.26(N=215,205)	100 (98.3 to 100)	100 (98.2 to 100)		
Anti-6B antibody,Month 11-14, ≥0.35(N=215,205)	100 (98.3 to 100)	100 (98.2 to 100)		
Anti-7F antibody,Month 11-14, ≥ 0.15(N=216,205)	100 (98.3 to 100)	100 (98.2 to 100)		
Anti-7F antibody, Month 11-14, ≥ 0.26(N=216,205)	100 (98.3 to 100)	99.5 (97.3 to 100)		

Anti-7F antibody, Month 11-14, ≥0.35(N=216,205)	100 (98.3 to 100)	99.5 (97.3 to 100)		
Anti-9V antibody, Month 11-14, ≥ 0.15(N=215,205)	100 (98.3 to 100)	99.0 (96.5 to 99.9)		
Anti-9V antibody, Month 11-14, ≥ 0.26(N=215,205)	99.1 (96.7 to 99.9)	98.5 (95.8 to 99.7)		
Anti-9V antibody, Month 11-14, ≥0.35(N=215,205)	97.7 (94.7 to 99.2)	96.6 (93.1 to 98.6)		
Anti-14 antibody, Month 11-14, ≥ 0.15(N=216,205)	99.5 (97.4 to 100)	100 (98.2 to 100)		
Anti-14 antibody, Month 11-14, ≥ 0.26(N=216,205)	99.5 (97.4 to 100)	100 (98.2 to 100)		
Anti-14 antibody, Month 11-14, ≥0.35(N=216,205)	99.5 (97.4 to 100)	100 (98.2 to 100)		
Anti-18C antibody, Month 11-14, ≥ 0.15(N=216,204)	100 (98.3 to 100)	100 (98.2 to 100)		
Anti-18C antibody, Month 11-14, ≥ 0.26(N=216,204)	99.5 (97.4 to 100)	99.0 (96.5 to 99.9)		
Anti-18C antibody, Month 11-14, ≥0.35(N=216,204)	98.6 (96.0 to 99.7)	97.5 (94.4 to 99.2)		
Anti-19A antibody, Month 11-14, ≥ 0.15(N=216,204)	100 (98.3 to 100)	100 (98.2 to 100)		
Anti-19A antibody, Month 11-14, ≥ 0.26(N=216,204)	100 (98.3 to 100)	100 (98.2 to 100)		
Anti-19A antibody, Month 11-14, ≥0.35(N=216,204)	100 (98.3 to 100)	100 (98.2 to 100)		
Anti-19F antibody, Month 11-14, ≥ 0.15(N=215,205)	100 (98.3 to 100)	100 (98.2 to 100)		
Anti-19F antibody, Month 11-14, ≥ 0.26(N=215,205)	100 (98.3 to 100)	100 (98.2 to 100)		
Anti-19F antibody, Month 11-14, ≥0.35(N=215,205)	100 (98.3 to 100)	100 (98.2 to 100)		
Anti-23F antibody, Month 11-14, ≥ 0.15(N=216,205)	99.5 (97.4 to 100)	100 (98.2 to 100)		
Anti-23F antibody, Month 11-14, ≥ 0.26(N=216,205)	99.5 (97.4 to 100)	100 (98.2 to 100)		
Anti-23F antibody, Month 11-14, ≥0.35(N=216,205)	98.1 (95.3 to 99.5)	100 (98.2 to 100)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects reporting any solicited local adverse events (AE).

End point title	Percentage of subjects reporting any solicited local adverse events (AE).

End point description:

Solicited local adverse events include pain, redness and swelling at injection site.

End point type	Secondary

End point timeframe:

4 days (Day 0 to Day 3) after all vaccines post-primary and post-fourth dose

End point values	HibCY Group	PedHIB Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	285	291		
Units: Percentage of subjects				
number (confidence interval 95%)				
Pain,Hib-MenCY-TT/PedvaxHIB,Dose 1(N=285, 291)	44.2 (38.4 to 50.2)	61.2 (55.3 to 66.8)		
Pain,Pediarix,Dose 1(N=285, 291)	50.5 (44.6 to 56.5)	57.4 (51.5 to 63.1)		
Pain,Prevnar 13,Dose 1(N=285, 291)	46.3 (40.4 to 52.3)	58.8 (52.9 to 64.5)		
Pain,Hib-MenCY-TT/PedvaxHIB,Dose 2(N=272, 278)	45.6 (39.6 to 51.7)	56.8 (50.8 to 62.7)		
Pain,Pediarix,Dose 2(N=272, 278)	45.2 (39.2 to 51.3)	55.8 (49.7 to 61.7)		
Pain,Prevnar 13,Dose 2(N=272, 277)	44.5 (38.5 to 50.6)	56.0 (49.9 to 61.9)		
Pain,Hib-MenCY-TT/PedvaxHIB,Dose 3(N=N=260, 0)	38.8 (32.9 to 45.1)	0 (0 to 0)		
Pain,Pediarix,Dose 3(N=262, 264)	42.7 (36.7 to 49.0)	50.8 (44.6 to 56.9)		
Pain,Prevnar 13,Dose 3(N=262, 264)	39.7 (33.7 to 45.9)	47.7 (41.6 to 53.9)		
Pain,Havrix,Dose 4(N=241,242)	44.8 (38.4 to 51.3)	50.0 (43.5 to 56.5)		
Pain,Hib-MenCY-TT/PedvaxHIB,Dose 4(N=241,242)	42.3 (36.0 to 48.8)	56.2 (49.7 to 62.5)		
Pain,Prevnar 13,Dose 4(N=241,242)	41.5 (35.2 to 48.0)	46.7 (40.3 to 53.2)		
Redness,Hib-MenCY-TT/PedvaxHIB,Dose 1(N=284,291)	21.1 (16.5 to 26.3)	35.4 (29.9 to 41.2)		
Redness,Pediarix,Dose 1(N=284,291)	27.1 (22.0 to 32.7)	25.1 (20.2 to 30.5)		
Redness,Prevnar 13,Dose 1(N=284,291)	23.6 (18.8 to 29.0)	24.4 (19.6 to 29.8)		
Redness,Hib-MenCY-TT/PedvaxHIB,Dose 2(N=271,278)	30.3 (24.8 to 36.1)	41.4 (35.5 to 47.4)		
Redness,Pediarix,Dose 2(N=271,278)	33.9 (28.3 to 39.9)	43.2 (37.3 to 49.2)		
Redness,Prevnar 13,Dose 2(N=271,277)	30.6 (25.2 to 36.5)	41.2 (35.3 to 47.2)		
Redness,Hib-MenCY-TT/PedvaxHIB,Dose 3(N=260,0)	31.5 (25.9 to 37.6)	0 (0 to 0)		
Redness,Pediarix,Dose 3(N=262,264)	38.2 (32.3 to 44.3)	50.4 (44.2 to 56.6)		
Redness,Prevnar 13,Dose 3(N=262,264)	36.3 (30.4 to 42.4)	45.8 (39.7 to 52.1)		
Redness,Havrix,Dose 4(N=241,242)	38.6 (32.4 to 45.1)	43.8 (37.5 to 50.3)		
Redness,Hib-MenCY-TT/PedvaxHIB,Dose 4(N=241,242)	38.6 (32.4 to 45.1)	50.8 (44.3 to 57.3)		
Redness,Prevnar 13,Dose 4(N=241,242)	41.1 (34.8 to 47.6)	44.6 (38.3 to 51.1)		
Swelling,Hib-MenCY-TT/PedvaxHIB,Dose 1(N=284,291)	11.3 (7.8 to 15.5)	22.0 (17.4 to 27.2)		
Swelling,Pediarix,Dose 1(N=284,291)	18.7 (14.3 to 23.7)	16.2 (12.1 to 20.9)		
Swelling,Prevnar 13,Dose 1(N=284,291)	14.8 (10.9 to 19.5)	16.2 (12.1 to 20.9)		
Swelling,Hib-MenCY-TT/PedvaxHIB,Dose 2(N=271,278)	18.5 (14.0 to 23.6)	30.6 (25.2 to 36.4)		

Swelling,Pediarix,Dose 2(N=271,278)	22.1 (17.3 to 27.6)	36.3 (30.7 to 42.3)		
Swelling,Prevnar 13,Dose 2(N=271,277)	22.5 (17.7 to 28.0)	28.9 (23.6 to 34.6)		
Swelling,Hib-MenCY-TT/PedvaxHIB,Dose 3(N=260,0)	19.2 (14.6 to 24.6)	0 (0 to 0)		
Swelling,Pediarix,Dose 3(N=262, 264)	29.4 (23.9 to 35.3)	37.9 (32.0 to 44.0)		
Swelling,Prevnar 13,Dose 3(N=262, 264)	24.4 (19.3 to 30.1)	31.4 (25.9 to 37.4)		
Swelling,Havrix,Dose 4(N=241, 242)	25.3 (19.9 to 31.3)	26.0 (20.6 to 32.0)		
Swelling,Hib-MenCY-TT/PedvaxHIB,Dose 4(N=241, 242)	22.8 (17.7 to 28.6)	34.3 (28.3 to 40.6)		
Swelling,Prevnar 13,Dose 4(N=241, 242)	26.1 (20.7 to 32.2)	27.7 (22.1 to 33.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects reporting any solicited general AEs.

End point title	Percentage of subjects reporting any solicited general AEs.

End point description:

Solicited general AEs include fever [defined as temperature ≥38.0 degrees Celsius (°C) by any method], drowsiness, irritability/fussiness and loss of appetite.

End point type	Secondary

End point timeframe:

4 days (Day 0 to Day 3) after all vaccines post-primary and post-fourth dose.

End point values	HibCY Group	PedHIB Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	285	291		
Units: Percentage of subjects				
number (confidence interval 95%)				
Any Temperature (°C), Dose 1(N=285, 291)	11.2 (7.8 to 15.5)	20.6 (16.1 to 25.7)		
Any Temperature (°C), Dose 2(N=273, 279)	19.4 (14.9 to 24.6)	29.0 (23.8 to 34.7)		
Any Temperature (°C), Dose 3(N=262, 265)	16.4 (12.1 to 21.5)	17.0 (12.7 to 22.1)		
Any Temperature (°C), Dose 4(N=242, 241)	8.7 (5.5 to 13.0)	10.4 (6.8 to 14.9)		
Irritability / Fussiness, Dose 1(N=285,291)	71.2 (65.6 to 76.4)	81.8 (76.9 to 86.0)		
Irritability / Fussiness, Dose 2(N=273,278)	70.0 (64.1 to 75.3)	83.5 (78.6 to 87.6)		
Irritability / Fussiness, Dose 3(N=262,265)	66.0 (59.9 to 71.7)	69.4 (63.5 to 74.9)		
Irritability / Fussiness, Dose 4(N=241,241)	66.0 (59.6 to 71.9)	74.3 (68.3 to 79.7)		

Loss Of Appetite, Dose 1(N=285, 291)	31.6 (26.2 to 37.3)	42.3 (36.5 to 48.2)		
Loss Of Appetite, Dose 2(N=273,278)	29.7 (24.3 to 35.5)	31.7 (26.2 to 37.5)		
Loss Of Appetite, Dose 3(N=262,265)	29.8 (24.3 to 35.7)	28.7 (23.3 to 34.5)		
Loss Of Appetite, Dose 4(N=241,241)	33.2 (27.3 to 39.5)	39.8 (33.6 to 46.3)		
Drowsiness, Dose 1(N=285, 291)	64.9 (59.1 to 70.4)	70.1 (64.5 to 75.3)		
Drowsiness, Dose 2(N=273,278)	54.2 (48.1 to 60.2)	65.1 (59.2 to 70.7)		
Drowsiness, Dose 3(N=262,265)	48.9 (42.7 to 55.1)	52.5 (46.3 to 58.6)		
Drowsiness, Dose 4(N=241,241)	44.0 (37.6 to 50.5)	48.5 (42.1 to 55.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects reporting any unsolicited AEs.

End point title	Percentage of subjects reporting any unsolicited AEs.

End point description:

Any adverse event (AE) reported in addition to those solicited during the clinical study. Also any "solicited" symptom with onset outside the specified period of follow-up for solicited symptoms were reported as an unsolicited adverse event.

End point type	Secondary

End point timeframe:

During 31 days (Day 0 to Day 30) after all vaccines post-primary (Dose 1-3) and post-fourth dose (Dose 4)

End point values	HibCY Group	PedHIB Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	297	303		
Units: Percentage of subjects				
number (confidence interval 95%)				
Dose 1-3 (N=297, 303)	60.6 (54.8 to 66.2)	56.4 (50.6 to 62.1)		
Dose 4(N=248, 250)	39.9 (33.8 to 46.3)	42.0 (35.8 to 48.4)		

Statistical analyses

No statistical analyses for this end point

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

End point title	Percentage of subjects reporting any serious adverse events

	(SAEs).

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

End point timeframe:

During the entire study period (from Day 0 to Month 17-20)

End point values	HibCY Group	PedHIB Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	297	303		
Units: Percentage of subjects				
number (confidence interval 95%)				
Any SAEs(N=297,303)	2.7 (1.2 to 5.2)	3.6 (1.8 to 6.4)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Solicited adverse events - Day 0-Day 4 Unsolicited Adverse events - Day 0- Day 31 after all vaccines post-primary and post-fourth dose. SAEs - day 0 to study end (Month 17-20)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	PedHIB group

Reporting group description:

Subjects received 3 doses of PedvaxHIB vaccine at Day 0, Month 2 and Month 10-13, 3 doses of Pediarix vaccine at Day 0, Month 2 and Month 4, 2 doses of Rotarix vaccine at Day 0 and Month 2, 4 doses of Prevnar 13 vaccine at Day 0 and Month 2, Month 4 and Month 10-13 and 2 doses of Havrix vaccine at Month 10-13 and Month 16-19.

Reporting group title	HibCY group

Reporting group description:

Subjects received 4 doses of Hib-MenCY-TT vaccine at Day 0, Month 2, Month 4 and Month 10-13 , 3 doses of Pediarix vaccine at Day 0, Month 2 and Month 4, 2 doses of Rotarix vaccine at Day 0 and Month 2, 4 doses of Prevnar 13 vaccine at Day 0 and Month 2, Month 4 and Month 10-13 and 2 doses of Havrix vaccine at Month 10-13 and Month 16-19.

Serious adverse events	PedHIB group	HibCY group	
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 303 (3.63%)	8 / 297 (2.69%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	0 / 303 (0.00%)	1 / 297 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	1 / 303 (0.33%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Kawasaki's disease			

subjects affected / exposed	1 / 303 (0.33%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 303 (0.33%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Histiocytosis haematophagic			
subjects affected / exposed	1 / 303 (0.33%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	1 / 303 (0.33%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Hypothermia			
subjects affected / exposed	1 / 303 (0.33%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden infant death syndrome			
subjects affected / exposed	0 / 303 (0.00%)	1 / 297 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Gastrointestinal disorders			
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 303 (0.00%)	1 / 297 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Apparent life threatening event			

subjects affected / exposed	1 / 303 (0.33%)	1 / 297 (0.34%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Croup infectious			
subjects affected / exposed	0 / 303 (0.00%)	1 / 297 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 303 (0.00%)	1 / 297 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 303 (0.00%)	2 / 297 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory syncytial virus bronchiolitis			
subjects affected / exposed	2 / 303 (0.66%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous abscess			
subjects affected / exposed	1 / 303 (0.33%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 303 (0.33%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	1 / 303 (0.33%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			

Failure to thrive			
subjects affected / exposed	0 / 303 (0.00%)	1 / 297 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypernatraemia			
subjects affected / exposed	1 / 303 (0.33%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ketoacidosis			
subjects affected / exposed	1 / 303 (0.33%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Type 1 diabetes mellitus			
subjects affected / exposed	1 / 303 (0.33%)	0 / 297 (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: 0 %

Non-serious adverse events	PedHIB group	HibCY group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	291 / 303 (96.04%)	282 / 297 (94.95%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Haemangioma			
subjects affected / exposed	1 / 303 (0.33%)	1 / 297 (0.34%)	
occurrences (all)	1	1	
Vascular disorders			
Flushing			
subjects affected / exposed	0 / 303 (0.00%)	1 / 297 (0.34%)	
occurrences (all)	0	1	
Pregnancy, puerperium and perinatal conditions			
Umbilical granuloma			
subjects affected / exposed	0 / 303 (0.00%)	1 / 297 (0.34%)	
occurrences (all)	0	1	
General disorders and administration			

site conditions				
Administration site haemorrhage				
subjects affected / exposed	0 / 303 (0.00%)	1 / 297 (0.34%)		
occurrences (all)	0	1		
Administration site rash				
subjects affected / exposed	1 / 303 (0.33%)	0 / 297 (0.00%)		
occurrences (all)	1	0		
Ill-defined disorder				
subjects affected / exposed	1 / 303 (0.33%)	0 / 297 (0.00%)		
occurrences (all)	1	0		
Injection site bruising				
subjects affected / exposed	3 / 303 (0.99%)	5 / 297 (1.68%)		
occurrences (all)	3	5		
Injection site erythema				
subjects affected / exposed	211 / 303 (69.64%)	189 / 297 (63.64%)		
occurrences (all)	539	442		
Injection site induration				
subjects affected / exposed	2 / 303 (0.66%)	2 / 297 (0.67%)		
occurrences (all)	2	2		
Injection site mass				
subjects affected / exposed	1 / 303 (0.33%)	0 / 297 (0.00%)		
occurrences (all)	1	0		
Injection site pain				
subjects affected / exposed	248 / 303 (81.85%)	229 / 297 (77.10%)		
occurrences (all)	648	550		
Injection site rash				
subjects affected / exposed	0 / 303 (0.00%)	1 / 297 (0.34%)		
occurrences (all)	0	1		
Injection site reaction				
subjects affected / exposed	1 / 303 (0.33%)	0 / 297 (0.00%)		
occurrences (all)	1	0		
Injection site swelling				
subjects affected / exposed	182 / 303 (60.07%)	147 / 297 (49.49%)		
occurrences (all)	413	322		
Injection site warmth				

subjects affected / exposed	1 / 303 (0.33%)	0 / 297 (0.00%)	
occurrences (all)	2	0	
Pain			
subjects affected / exposed	0 / 303 (0.00%)	1 / 297 (0.34%)	
occurrences (all)	0	1	
Peripheral swelling			
subjects affected / exposed	0 / 303 (0.00%)	1 / 297 (0.34%)	
occurrences (all)	0	1	
Pyrexia			
subjects affected / exposed	147 / 303 (48.51%)	124 / 297 (41.75%)	
occurrences (all)	235	184	
Vaccination site induration			
subjects affected / exposed	1 / 303 (0.33%)	0 / 297 (0.00%)	
occurrences (all)	2	0	
Vaccination site nodule			
subjects affected / exposed	1 / 303 (0.33%)	0 / 297 (0.00%)	
occurrences (all)	1	0	
Vaccination site reaction			
subjects affected / exposed	1 / 303 (0.33%)	0 / 297 (0.00%)	
occurrences (all)	1	0	
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 303 (0.00%)	1 / 297 (0.34%)	
occurrences (all)	0	1	
Food allergy			
subjects affected / exposed	3 / 303 (0.99%)	2 / 297 (0.67%)	
occurrences (all)	3	2	
Hypersensitivity			
subjects affected / exposed	1 / 303 (0.33%)	0 / 297 (0.00%)	
occurrences (all)	1	0	
Milk allergy			
subjects affected / exposed	0 / 303 (0.00%)	1 / 297 (0.34%)	
occurrences (all)	0	1	
Multiple allergies			
subjects affected / exposed	1 / 303 (0.33%)	0 / 297 (0.00%)	
occurrences (all)	1	0	

Seasonal allergy			
subjects affected / exposed	1 / 303 (0.33%)	0 / 297 (0.00%)	
occurrences (all)	1	0	
Reproductive system and breast disorders			
Genital labial adhesions			
subjects affected / exposed	2 / 303 (0.66%)	3 / 297 (1.01%)	
occurrences (all)	2	3	
Genital rash			
subjects affected / exposed	1 / 303 (0.33%)	0 / 297 (0.00%)	
occurrences (all)	1	0	
Penile adhesion			
subjects affected / exposed	0 / 303 (0.00%)	2 / 297 (0.67%)	
occurrences (all)	0	2	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	2 / 303 (0.66%)	1 / 297 (0.34%)	
occurrences (all)	2	1	
Bronchial hyperreactivity			
subjects affected / exposed	4 / 303 (1.32%)	5 / 297 (1.68%)	
occurrences (all)	4	5	
Cough			
subjects affected / exposed	31 / 303 (10.23%)	21 / 297 (7.07%)	
occurrences (all)	32	24	
Hiccups			
subjects affected / exposed	0 / 303 (0.00%)	1 / 297 (0.34%)	
occurrences (all)	0	1	
Increased upper airway secretion			
subjects affected / exposed	0 / 303 (0.00%)	1 / 297 (0.34%)	
occurrences (all)	0	1	
Nasal congestion			
subjects affected / exposed	15 / 303 (4.95%)	15 / 297 (5.05%)	
occurrences (all)	15	18	
Oropharyngeal pain			
subjects affected / exposed	3 / 303 (0.99%)	1 / 297 (0.34%)	
occurrences (all)	3	1	
Pneumonitis			

subjects affected / exposed	0 / 303 (0.00%)	1 / 297 (0.34%)	
occurrences (all)	0	1	
Productive cough			
subjects affected / exposed	0 / 303 (0.00%)	1 / 297 (0.34%)	
occurrences (all)	0	1	
Respiratory disorder			
subjects affected / exposed	7 / 303 (2.31%)	6 / 297 (2.02%)	
occurrences (all)	12	9	
Rhinitis allergic			
subjects affected / exposed	4 / 303 (1.32%)	4 / 297 (1.35%)	
occurrences (all)	4	5	
Rhinorrhoea			
subjects affected / exposed	19 / 303 (6.27%)	14 / 297 (4.71%)	
occurrences (all)	21	16	
Sinus disorder			
subjects affected / exposed	2 / 303 (0.66%)	0 / 297 (0.00%)	
occurrences (all)	2	0	
Sneezing			
subjects affected / exposed	1 / 303 (0.33%)	0 / 297 (0.00%)	
occurrences (all)	1	0	
Stridor			
subjects affected / exposed	1 / 303 (0.33%)	0 / 297 (0.00%)	
occurrences (all)	1	0	
Tachypnoea			
subjects affected / exposed	0 / 303 (0.00%)	1 / 297 (0.34%)	
occurrences (all)	0	1	
Upper respiratory tract congestion			
subjects affected / exposed	1 / 303 (0.33%)	1 / 297 (0.34%)	
occurrences (all)	1	1	
Wheezing			
subjects affected / exposed	0 / 303 (0.00%)	9 / 297 (3.03%)	
occurrences (all)	0	9	
Psychiatric disorders			
Communication disorder			
subjects affected / exposed	1 / 303 (0.33%)	0 / 297 (0.00%)	
occurrences (all)	1	0	

Insomnia			
subjects affected / exposed	2 / 303 (0.66%)	0 / 297 (0.00%)	
occurrences (all)	2	0	
Irritability			
subjects affected / exposed	284 / 303 (93.73%)	267 / 297 (89.90%)	
occurrences (all)	839	737	
Screaming			
subjects affected / exposed	1 / 303 (0.33%)	0 / 297 (0.00%)	
occurrences (all)	1	0	
Selective eating disorder			
subjects affected / exposed	2 / 303 (0.66%)	0 / 297 (0.00%)	
occurrences (all)	2	0	
Sleep disorder			
subjects affected / exposed	1 / 303 (0.33%)	1 / 297 (0.34%)	
occurrences (all)	1	1	
Investigations			
Body height below normal			
subjects affected / exposed	0 / 303 (0.00%)	1 / 297 (0.34%)	
occurrences (all)	0	1	
Body temperature increased			
subjects affected / exposed	1 / 303 (0.33%)	0 / 297 (0.00%)	
occurrences (all)	1	0	
Cardiac murmur			
subjects affected / exposed	1 / 303 (0.33%)	1 / 297 (0.34%)	
occurrences (all)	1	1	
Mycoplasma test positive			
subjects affected / exposed	0 / 303 (0.00%)	1 / 297 (0.34%)	
occurrences (all)	0	1	
Weight			
subjects affected / exposed	0 / 303 (0.00%)	1 / 297 (0.34%)	
occurrences (all)	0	1	
Weight decreased			
subjects affected / exposed	1 / 303 (0.33%)	0 / 297 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			

Accidental exposure to product			
subjects affected / exposed	0 / 303 (0.00%)	1 / 297 (0.34%)	
occurrences (all)	0	1	
Animal bite			
subjects affected / exposed	1 / 303 (0.33%)	0 / 297 (0.00%)	
occurrences (all)	1	0	
Arthropod bite			
subjects affected / exposed	1 / 303 (0.33%)	2 / 297 (0.67%)	
occurrences (all)	1	2	
Burns second degree			
subjects affected / exposed	1 / 303 (0.33%)	0 / 297 (0.00%)	
occurrences (all)	1	0	
Contusion			
subjects affected / exposed	3 / 303 (0.99%)	5 / 297 (1.68%)	
occurrences (all)	3	5	
Ear injury			
subjects affected / exposed	0 / 303 (0.00%)	1 / 297 (0.34%)	
occurrences (all)	0	1	
Eye injury			
subjects affected / exposed	0 / 303 (0.00%)	1 / 297 (0.34%)	
occurrences (all)	0	1	
Fall			
subjects affected / exposed	1 / 303 (0.33%)	2 / 297 (0.67%)	
occurrences (all)	1	3	
Foreign body in gastrointestinal tract			
subjects affected / exposed	2 / 303 (0.66%)	0 / 297 (0.00%)	
occurrences (all)	2	0	
Head injury			
subjects affected / exposed	1 / 303 (0.33%)	4 / 297 (1.35%)	
occurrences (all)	1	4	
Laceration			
subjects affected / exposed	2 / 303 (0.66%)	0 / 297 (0.00%)	
occurrences (all)	2	0	
Limb injury			
subjects affected / exposed	1 / 303 (0.33%)	0 / 297 (0.00%)	
occurrences (all)	1	0	

Lip injury			
subjects affected / exposed	1 / 303 (0.33%)	0 / 297 (0.00%)	
occurrences (all)	1	0	
Nail avulsion			
subjects affected / exposed	1 / 303 (0.33%)	0 / 297 (0.00%)	
occurrences (all)	1	0	
Skin injury			
subjects affected / exposed	0 / 303 (0.00%)	1 / 297 (0.34%)	
occurrences (all)	0	1	
Thermal burn			
subjects affected / exposed	1 / 303 (0.33%)	1 / 297 (0.34%)	
occurrences (all)	1	1	
Tongue injury			
subjects affected / exposed	1 / 303 (0.33%)	0 / 297 (0.00%)	
occurrences (all)	1	0	
Tooth fracture			
subjects affected / exposed	0 / 303 (0.00%)	1 / 297 (0.34%)	
occurrences (all)	0	1	
Congenital, familial and genetic disorders			
Ankyloglossia congenital			
subjects affected / exposed	0 / 303 (0.00%)	1 / 297 (0.34%)	
occurrences (all)	0	1	
Congenital torticollis			
subjects affected / exposed	1 / 303 (0.33%)	0 / 297 (0.00%)	
occurrences (all)	1	0	
Craniosynostosis			
subjects affected / exposed	1 / 303 (0.33%)	1 / 297 (0.34%)	
occurrences (all)	1	1	
Dacryostenosis congenital			
subjects affected / exposed	1 / 303 (0.33%)	0 / 297 (0.00%)	
occurrences (all)	1	0	
Developmental hip dysplasia			
subjects affected / exposed	0 / 303 (0.00%)	1 / 297 (0.34%)	
occurrences (all)	0	1	
Frenulum breve			

subjects affected / exposed	1 / 303 (0.33%)	0 / 297 (0.00%)	
occurrences (all)	1	0	
Hydrocele			
subjects affected / exposed	0 / 303 (0.00%)	1 / 297 (0.34%)	
occurrences (all)	0	1	
Laryngomalacia			
subjects affected / exposed	1 / 303 (0.33%)	0 / 297 (0.00%)	
occurrences (all)	1	0	
Macrocephaly			
subjects affected / exposed	1 / 303 (0.33%)	1 / 297 (0.34%)	
occurrences (all)	1	1	
Plagiocephaly			
subjects affected / exposed	6 / 303 (1.98%)	6 / 297 (2.02%)	
occurrences (all)	6	6	
Cardiac disorders			
Cyanosis			
subjects affected / exposed	2 / 303 (0.66%)	0 / 297 (0.00%)	
occurrences (all)	2	0	
Nervous system disorders			
Aphonia			
subjects affected / exposed	1 / 303 (0.33%)	0 / 297 (0.00%)	
occurrences (all)	1	0	
Fontanelle depressed			
subjects affected / exposed	1 / 303 (0.33%)	0 / 297 (0.00%)	
occurrences (all)	1	0	
Language disorder			
subjects affected / exposed	0 / 303 (0.00%)	1 / 297 (0.34%)	
occurrences (all)	0	1	
Lethargy			
subjects affected / exposed	0 / 303 (0.00%)	1 / 297 (0.34%)	
occurrences (all)	0	1	
Motor developmental delay			
subjects affected / exposed	0 / 303 (0.00%)	1 / 297 (0.34%)	
occurrences (all)	0	1	
Poor quality sleep			

subjects affected / exposed	0 / 303 (0.00%)	1 / 297 (0.34%)	
occurrences (all)	0	1	
Somnolence			
subjects affected / exposed	254 / 303 (83.83%)	230 / 297 (77.44%)	
occurrences (all)	641	569	
Speech disorder			
subjects affected / exposed	0 / 303 (0.00%)	1 / 297 (0.34%)	
occurrences (all)	0	1	
Speech disorder developmental			
subjects affected / exposed	1 / 303 (0.33%)	1 / 297 (0.34%)	
occurrences (all)	1	1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 303 (0.00%)	1 / 297 (0.34%)	
occurrences (all)	0	1	
Iron deficiency anaemia			
subjects affected / exposed	0 / 303 (0.00%)	1 / 297 (0.34%)	
occurrences (all)	0	1	
Leukocytosis			
subjects affected / exposed	0 / 303 (0.00%)	1 / 297 (0.34%)	
occurrences (all)	0	1	
Lymphadenopathy			
subjects affected / exposed	1 / 303 (0.33%)	1 / 297 (0.34%)	
occurrences (all)	1	1	
Ear and labyrinth disorders			
Cerumen impaction			
subjects affected / exposed	4 / 303 (1.32%)	0 / 297 (0.00%)	
occurrences (all)	4	0	
Ear pain			
subjects affected / exposed	4 / 303 (1.32%)	2 / 297 (0.67%)	
occurrences (all)	4	2	
Middle ear effusion			
subjects affected / exposed	1 / 303 (0.33%)	1 / 297 (0.34%)	
occurrences (all)	1	1	
Otorrhoea			

subjects affected / exposed	1 / 303 (0.33%)	1 / 297 (0.34%)	
occurrences (all)	1	1	
Eye disorders			
Conjunctivitis allergic			
subjects affected / exposed	0 / 303 (0.00%)	2 / 297 (0.67%)	
occurrences (all)	0	2	
Dacryostenosis acquired			
subjects affected / exposed	0 / 303 (0.00%)	2 / 297 (0.67%)	
occurrences (all)	0	2	
Eye discharge			
subjects affected / exposed	0 / 303 (0.00%)	2 / 297 (0.67%)	
occurrences (all)	0	2	
Hypermetropia			
subjects affected / exposed	0 / 303 (0.00%)	1 / 297 (0.34%)	
occurrences (all)	0	1	
Strabismus			
subjects affected / exposed	2 / 303 (0.66%)	0 / 297 (0.00%)	
occurrences (all)	2	0	
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	1 / 303 (0.33%)	1 / 297 (0.34%)	
occurrences (all)	2	1	
Abdominal pain			
subjects affected / exposed	0 / 303 (0.00%)	2 / 297 (0.67%)	
occurrences (all)	0	2	
Abdominal pain upper			
subjects affected / exposed	1 / 303 (0.33%)	1 / 297 (0.34%)	
occurrences (all)	1	1	
Abnormal faeces			
subjects affected / exposed	1 / 303 (0.33%)	0 / 297 (0.00%)	
occurrences (all)	1	0	
Aerophagia			
subjects affected / exposed	1 / 303 (0.33%)	0 / 297 (0.00%)	
occurrences (all)	1	0	
Anal fissure			

subjects affected / exposed	1 / 303 (0.33%)	1 / 297 (0.34%)	
occurrences (all)	1	1	
Constipation			
subjects affected / exposed	9 / 303 (2.97%)	13 / 297 (4.38%)	
occurrences (all)	11	13	
Diarrhoea			
subjects affected / exposed	18 / 303 (5.94%)	26 / 297 (8.75%)	
occurrences (all)	20	31	
Dysphagia			
subjects affected / exposed	0 / 303 (0.00%)	1 / 297 (0.34%)	
occurrences (all)	0	1	
Flatulence			
subjects affected / exposed	3 / 303 (0.99%)	4 / 297 (1.35%)	
occurrences (all)	3	6	
Gastrooesophageal reflux disease			
subjects affected / exposed	13 / 303 (4.29%)	6 / 297 (2.02%)	
occurrences (all)	13	6	
Gingival pain			
subjects affected / exposed	1 / 303 (0.33%)	0 / 297 (0.00%)	
occurrences (all)	1	0	
Haematochezia			
subjects affected / exposed	1 / 303 (0.33%)	1 / 297 (0.34%)	
occurrences (all)	1	1	
Inguinal hernia			
subjects affected / exposed	0 / 303 (0.00%)	2 / 297 (0.67%)	
occurrences (all)	0	2	
Nausea			
subjects affected / exposed	1 / 303 (0.33%)	0 / 297 (0.00%)	
occurrences (all)	1	0	
Oral mucosal eruption			
subjects affected / exposed	1 / 303 (0.33%)	0 / 297 (0.00%)	
occurrences (all)	1	0	
Oral pain			
subjects affected / exposed	1 / 303 (0.33%)	0 / 297 (0.00%)	
occurrences (all)	1	0	
Retching			

subjects affected / exposed	1 / 303 (0.33%)	0 / 297 (0.00%)	
occurrences (all)	1	0	
Teething			
subjects affected / exposed	13 / 303 (4.29%)	13 / 297 (4.38%)	
occurrences (all)	13	13	
Vomiting			
subjects affected / exposed	20 / 303 (6.60%)	14 / 297 (4.71%)	
occurrences (all)	24	14	
Vomiting projectile			
subjects affected / exposed	1 / 303 (0.33%)	0 / 297 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	1 / 303 (0.33%)	0 / 297 (0.00%)	
occurrences (all)	1	0	
Blister			
subjects affected / exposed	1 / 303 (0.33%)	0 / 297 (0.00%)	
occurrences (all)	1	0	
Cafe au lait spots			
subjects affected / exposed	0 / 303 (0.00%)	1 / 297 (0.34%)	
occurrences (all)	0	1	
Dermatitis			
subjects affected / exposed	2 / 303 (0.66%)	0 / 297 (0.00%)	
occurrences (all)	2	0	
Dermatitis atopic			
subjects affected / exposed	15 / 303 (4.95%)	11 / 297 (3.70%)	
occurrences (all)	15	11	
Dermatitis contact			
subjects affected / exposed	0 / 303 (0.00%)	2 / 297 (0.67%)	
occurrences (all)	0	2	
Dermatitis diaper			
subjects affected / exposed	12 / 303 (3.96%)	14 / 297 (4.71%)	
occurrences (all)	13	15	
Eczema			
subjects affected / exposed	8 / 303 (2.64%)	7 / 297 (2.36%)	
occurrences (all)	8	7	

Erythema			
subjects affected / exposed	0 / 303 (0.00%)	1 / 297 (0.34%)	
occurrences (all)	0	1	
Hyperhidrosis			
subjects affected / exposed	0 / 303 (0.00%)	1 / 297 (0.34%)	
occurrences (all)	0	1	
Ingrowing nail			
subjects affected / exposed	1 / 303 (0.33%)	0 / 297 (0.00%)	
occurrences (all)	1	0	
Keratosis pilaris			
subjects affected / exposed	1 / 303 (0.33%)	1 / 297 (0.34%)	
occurrences (all)	1	1	
Miliaria			
subjects affected / exposed	1 / 303 (0.33%)	0 / 297 (0.00%)	
occurrences (all)	1	0	
Pruritus			
subjects affected / exposed	1 / 303 (0.33%)	0 / 297 (0.00%)	
occurrences (all)	1	0	
Rash			
subjects affected / exposed	13 / 303 (4.29%)	9 / 297 (3.03%)	
occurrences (all)	14	12	
Rash erythematous			
subjects affected / exposed	1 / 303 (0.33%)	0 / 297 (0.00%)	
occurrences (all)	1	0	
Rash macular			
subjects affected / exposed	0 / 303 (0.00%)	1 / 297 (0.34%)	
occurrences (all)	0	1	
Rash maculo-papular			
subjects affected / exposed	1 / 303 (0.33%)	0 / 297 (0.00%)	
occurrences (all)	1	0	
Rash papular			
subjects affected / exposed	0 / 303 (0.00%)	2 / 297 (0.67%)	
occurrences (all)	0	2	
Seborrhoea			
subjects affected / exposed	2 / 303 (0.66%)	0 / 297 (0.00%)	
occurrences (all)	2	0	

Seborrhoeic dermatitis			
subjects affected / exposed	2 / 303 (0.66%)	1 / 297 (0.34%)	
occurrences (all)	2	1	
Skin discolouration			
subjects affected / exposed	0 / 303 (0.00%)	1 / 297 (0.34%)	
occurrences (all)	0	1	
Urticaria			
subjects affected / exposed	3 / 303 (0.99%)	3 / 297 (1.01%)	
occurrences (all)	4	3	
Renal and urinary disorders			
Pollakiuria			
subjects affected / exposed	0 / 303 (0.00%)	1 / 297 (0.34%)	
occurrences (all)	0	1	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 303 (0.00%)	1 / 297 (0.34%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	0 / 303 (0.00%)	2 / 297 (0.67%)	
occurrences (all)	0	2	
Positional plagiocephaly			
subjects affected / exposed	2 / 303 (0.66%)	1 / 297 (0.34%)	
occurrences (all)	2	1	
Torticollis			
subjects affected / exposed	5 / 303 (1.65%)	0 / 297 (0.00%)	
occurrences (all)	5	0	
Infections and infestations			
Acarodermatitis			
subjects affected / exposed	0 / 303 (0.00%)	1 / 297 (0.34%)	
occurrences (all)	0	1	
Body tinea			
subjects affected / exposed	1 / 303 (0.33%)	1 / 297 (0.34%)	
occurrences (all)	1	1	
Bronchiolitis			

subjects affected / exposed	9 / 303 (2.97%)	13 / 297 (4.38%)	
occurrences (all)	9	13	
Bronchitis			
subjects affected / exposed	1 / 303 (0.33%)	0 / 297 (0.00%)	
occurrences (all)	1	0	
Candida infection			
subjects affected / exposed	4 / 303 (1.32%)	3 / 297 (1.01%)	
occurrences (all)	4	3	
Candida nappy rash			
subjects affected / exposed	4 / 303 (1.32%)	1 / 297 (0.34%)	
occurrences (all)	4	1	
Cellulitis			
subjects affected / exposed	1 / 303 (0.33%)	0 / 297 (0.00%)	
occurrences (all)	1	0	
Conjunctivitis			
subjects affected / exposed	16 / 303 (5.28%)	11 / 297 (3.70%)	
occurrences (all)	17	11	
Conjunctivitis bacterial			
subjects affected / exposed	1 / 303 (0.33%)	1 / 297 (0.34%)	
occurrences (all)	1	1	
Coxsackie viral infection			
subjects affected / exposed	0 / 303 (0.00%)	1 / 297 (0.34%)	
occurrences (all)	0	1	
Croup infectious			
subjects affected / exposed	10 / 303 (3.30%)	1 / 297 (0.34%)	
occurrences (all)	10	1	
Dacryocystitis			
subjects affected / exposed	1 / 303 (0.33%)	1 / 297 (0.34%)	
occurrences (all)	1	1	
Ear infection			
subjects affected / exposed	5 / 303 (1.65%)	6 / 297 (2.02%)	
occurrences (all)	9	9	
Erythema infectiosum			
subjects affected / exposed	1 / 303 (0.33%)	1 / 297 (0.34%)	
occurrences (all)	1	1	
Exanthema subitum			

subjects affected / exposed	0 / 303 (0.00%)	1 / 297 (0.34%)	
occurrences (all)	0	1	
Eye infection			
subjects affected / exposed	1 / 303 (0.33%)	0 / 297 (0.00%)	
occurrences (all)	1	0	
Fungal infection			
subjects affected / exposed	4 / 303 (1.32%)	0 / 297 (0.00%)	
occurrences (all)	4	0	
Fungal skin infection			
subjects affected / exposed	1 / 303 (0.33%)	1 / 297 (0.34%)	
occurrences (all)	1	1	
Furuncle			
subjects affected / exposed	0 / 303 (0.00%)	1 / 297 (0.34%)	
occurrences (all)	0	1	
Gastroenteritis			
subjects affected / exposed	12 / 303 (3.96%)	7 / 297 (2.36%)	
occurrences (all)	12	7	
Gastroenteritis viral			
subjects affected / exposed	1 / 303 (0.33%)	0 / 297 (0.00%)	
occurrences (all)	1	0	
Hand-foot-and-mouth disease			
subjects affected / exposed	4 / 303 (1.32%)	3 / 297 (1.01%)	
occurrences (all)	4	3	
Herpangina			
subjects affected / exposed	1 / 303 (0.33%)	1 / 297 (0.34%)	
occurrences (all)	1	1	
Impetigo			
subjects affected / exposed	0 / 303 (0.00%)	1 / 297 (0.34%)	
occurrences (all)	0	1	
Influenza			
subjects affected / exposed	1 / 303 (0.33%)	1 / 297 (0.34%)	
occurrences (all)	1	1	
Laryngitis			
subjects affected / exposed	1 / 303 (0.33%)	0 / 297 (0.00%)	
occurrences (all)	1	0	
Molluscum contagiosum			

subjects affected / exposed	1 / 303 (0.33%)	2 / 297 (0.67%)	
occurrences (all)	1	3	
Mycoplasma infection			
subjects affected / exposed	1 / 303 (0.33%)	1 / 297 (0.34%)	
occurrences (all)	1	1	
Nasopharyngitis			
subjects affected / exposed	12 / 303 (3.96%)	16 / 297 (5.39%)	
occurrences (all)	14	17	
Oral candidiasis			
subjects affected / exposed	2 / 303 (0.66%)	3 / 297 (1.01%)	
occurrences (all)	2	3	
Oropharyngeal candidiasis			
subjects affected / exposed	1 / 303 (0.33%)	0 / 297 (0.00%)	
occurrences (all)	1	0	
Otitis externa			
subjects affected / exposed	1 / 303 (0.33%)	0 / 297 (0.00%)	
occurrences (all)	1	0	
Otitis media			
subjects affected / exposed	41 / 303 (13.53%)	43 / 297 (14.48%)	
occurrences (all)	49	48	
Otitis media acute			
subjects affected / exposed	5 / 303 (1.65%)	6 / 297 (2.02%)	
occurrences (all)	6	6	
Paronychia			
subjects affected / exposed	1 / 303 (0.33%)	0 / 297 (0.00%)	
occurrences (all)	1	0	
Periorbital cellulitis			
subjects affected / exposed	1 / 303 (0.33%)	0 / 297 (0.00%)	
occurrences (all)	1	0	
Pharyngitis			
subjects affected / exposed	6 / 303 (1.98%)	5 / 297 (1.68%)	
occurrences (all)	7	5	
Pneumonia			
subjects affected / exposed	1 / 303 (0.33%)	3 / 297 (1.01%)	
occurrences (all)	1	3	
Pneumonia bacterial			

subjects affected / exposed	0 / 303 (0.00%)	1 / 297 (0.34%)	
occurrences (all)	0	1	
Pneumonia streptococcal			
subjects affected / exposed	1 / 303 (0.33%)	0 / 297 (0.00%)	
occurrences (all)	1	0	
Pneumonia viral			
subjects affected / exposed	0 / 303 (0.00%)	1 / 297 (0.34%)	
occurrences (all)	0	1	
Pyelonephritis			
subjects affected / exposed	0 / 303 (0.00%)	1 / 297 (0.34%)	
occurrences (all)	0	1	
Respiratory syncytial virus bronchiolitis			
subjects affected / exposed	1 / 303 (0.33%)	0 / 297 (0.00%)	
occurrences (all)	1	0	
Respiratory syncytial virus infection			
subjects affected / exposed	0 / 303 (0.00%)	1 / 297 (0.34%)	
occurrences (all)	0	1	
Respiratory tract infection			
subjects affected / exposed	0 / 303 (0.00%)	1 / 297 (0.34%)	
occurrences (all)	0	1	
Respiratory tract infection viral			
subjects affected / exposed	0 / 303 (0.00%)	1 / 297 (0.34%)	
occurrences (all)	0	1	
Rhinitis			
subjects affected / exposed	0 / 303 (0.00%)	1 / 297 (0.34%)	
occurrences (all)	0	1	
Roseola			
subjects affected / exposed	1 / 303 (0.33%)	2 / 297 (0.67%)	
occurrences (all)	1	2	
Sinusitis			
subjects affected / exposed	2 / 303 (0.66%)	5 / 297 (1.68%)	
occurrences (all)	2	5	
Skin candida			
subjects affected / exposed	1 / 303 (0.33%)	1 / 297 (0.34%)	
occurrences (all)	1	1	

Staphylococcal infection			
subjects affected / exposed	0 / 303 (0.00%)	1 / 297 (0.34%)	
occurrences (all)	0	1	
Tonsillitis			
subjects affected / exposed	1 / 303 (0.33%)	0 / 297 (0.00%)	
occurrences (all)	1	0	
Upper respiratory tract infection			
subjects affected / exposed	35 / 303 (11.55%)	62 / 297 (20.88%)	
occurrences (all)	40	78	
Urinary tract infection			
subjects affected / exposed	1 / 303 (0.33%)	0 / 297 (0.00%)	
occurrences (all)	1	0	
Vaginal infection			
subjects affected / exposed	0 / 303 (0.00%)	1 / 297 (0.34%)	
occurrences (all)	0	1	
Viral infection			
subjects affected / exposed	9 / 303 (2.97%)	8 / 297 (2.69%)	
occurrences (all)	9	8	
Viral rash			
subjects affected / exposed	4 / 303 (1.32%)	5 / 297 (1.68%)	
occurrences (all)	5	5	
Viral tonsillitis			
subjects affected / exposed	0 / 303 (0.00%)	1 / 297 (0.34%)	
occurrences (all)	0	1	
Viral upper respiratory tract infection			
subjects affected / exposed	5 / 303 (1.65%)	0 / 297 (0.00%)	
occurrences (all)	5	0	
Vulvovaginal candidiasis			
subjects affected / exposed	1 / 303 (0.33%)	1 / 297 (0.34%)	
occurrences (all)	1	1	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	200 / 303 (66.01%)	177 / 297 (59.60%)	
occurrences (all)	384	331	
Failure to thrive			

subjects affected / exposed	1 / 303 (0.33%)	2 / 297 (0.67%)	
occurrences (all)	1	2	
Feeding disorder			
subjects affected / exposed	0 / 303 (0.00%)	2 / 297 (0.67%)	
occurrences (all)	0	2	
Increased appetite			
subjects affected / exposed	1 / 303 (0.33%)	0 / 297 (0.00%)	
occurrences (all)	1	0	
Lactose intolerance			
subjects affected / exposed	0 / 303 (0.00%)	1 / 297 (0.34%)	
occurrences (all)	0	1	
Poor feeding infant			
subjects affected / exposed	1 / 303 (0.33%)	1 / 297 (0.34%)	
occurrences (all)	1	1	
Underweight			
subjects affected / exposed	1 / 303 (0.33%)	1 / 297 (0.34%)	
occurrences (all)	1	1	
Weight gain poor			
subjects affected / exposed	2 / 303 (0.66%)	1 / 297 (0.34%)	
occurrences (all)	2	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 September 2013	Since Havrix and Rotarix are administered in this study, the study falls under Article 46 and per our GUI-BIO-RA-9024 v01 a EudraCT number is needed for trials part of an agreed PIP and for paediatric trials falling into to scope of the Regulation (EC) No. 1901/2006 Article 41 - 45 and 46 no matter where the trial is performed.. Therefore, a Eudract number has been issued for this study and included in this Protocol. Additionally, two typographical errors were identified within the body of the Protocol and corrected: 1) The presentation of Rotarix in the vial was erroneously typed in as a white liquid rather than a powder. 2) The site of administration of the 4th dose of Prevnar 13 was erroneously typed in as in the upper thigh rather than the lower thigh. 3) The product information for the vaccines has been updated to be consistent with the vaccine dictionary definitions.
16 May 2014	In order to provide the opportunity for subjects in the control group to receive a meningococcal vaccine, which is not routinely administered in the US to this age group, the protocol has been amended to state that: "...a parent(s)/LAR(s) of a child in the PedvaxHIB control group will be offered the opportunity for their child to be vaccinated with a licensed meningococcal vaccine, which will be provided by the study sponsor, after study end as these subjects did not have the benefit of receiving any meningococcal vaccination during the study. Additionally, Distribution of a diary card for recording of medications/vaccinations post dose 2 of Havrix has been added. Treatment allocation is by component rather than dose. Text mentioning that subjects who do not continue in the booster phase will be contacted for safety information via a phone script at the ESFU timepoint has been added.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported